Cholesterol Ester Transfer Protein Inhibitor Review

Jerry Hu¹ and Scot Walker²

Abstract

Treatment of blood cholesterol is part of a strategy to lower atherosclerotic cardiovascular (ASCVD) risk. While use of HMG-CoA reductase inhibitors to modify cholesterol levels is the primary means of lowering the risk of an ASCVD event, residual risk remains. A new strategy being investigated is the use of cholesterol ester transfer protein (CETP) inhibitors to raise the levels of high-density lipoprotein cholesterol (HDL-C) and lower low-density lipoprotein cholesterol (LDL-C). While initial large-scale studies demonstrated no reduction of cardiovascular events, one CETP inhibitor, anacetrapib, has demonstrated a reduction in cardiovascular events in the REVEAL trial.

Keywords

investigational drugs, drug information, formulary management/P&T, cardiovascular

Epidemiology

Many meta-analyses have identified a correlation between blood cholesterol levels and cardiovascular risk. Specifically, decreasing low-density lipoprotein cholesterol (LDL-C), decreasing triglycerides, and increasing high-density lipoprotein cholesterol (HDL-C) have been associated with reduced risk for atherosclerotic cardiovascular events. Thus, many drugs target these biomarkers to prevent atherosclerotic cardiovascular events.¹

Current Treatment

HMG-CoA reductase inhibitors, also known as statins, lower LDL-C and have demonstrated significant reduction in reducing cardiovascular events.¹ Guidelines from the American College of Cardiology and the American Heart Association on treating hyperlipidemia to reduce cardiovascular risk recommend initiating a statin depending on a patient's risk factors and the 10-year risk for atherosclerotic cardiovascular disease events.² This initial strategy was reiterated in a recent commentary discussing new research and therapies. Despite statins' efficacy, residual risk remains. As statins' effect on non-LDL-C levels is limited, drugs targeting non-LDL-C levels may complement statins' benefit and further reduce cardiovascular risk.¹

New Treatment Options

Cholesterol ester transfer protein (CETP) inhibitors are a class of drugs in the development pipeline which increase HDL-C

with the goal of reducing residual risk of cardiovascular events in high-risk patients on statins. CETP inhibitors mediate the transfer of esterified cholesterol from HDL-C to atherogenic lipoprotein particles, such as LDL-C, thereby raising HDL-C and lowering LDL-C.³⁻⁵

Four CETP inhibitors have been studied in large phase III prospective randomized control trials: torcetrapib, dalcetrapib, evacetrapib, and anacetrapib. Trials selected adult patients with elevated cardiovascular risk, particularly those with a history of atherosclerotic vascular disease. The treatment arm (CETP inhibitor + statin) was compared with a control arm (placebo + statin). The primary outcomes were a composite of major vascular events.⁴⁻⁶

Three of the 4 pivotal trials have finished. All of these trials found that CETP inhibitors displayed significant capacity to raise HDL-C levels, ranging from an increase of 30% with dalcetrapib to over 130% with evacetrapib. In spite of these findings, the CETP inhibitors did not demonstrate a reduction in cardiovascular events compared with placebo.⁴⁻⁶ Due to the failure to demonstrate efficacy in cardiovascular risk reduction, development of torcetrapib, dalcetrapib, and evacetrapib has ceased.

¹St. Louis College of Pharmacy, MO, USA

²Prescribe Right, LLC, Wildwood, MO, USA

Corresponding Author:

Scot Walker, Chief Executive Officer, Prescribe Right, LLC, 1602 Westglen Farms Dr, Wildwood, MO 63011, USA.
Email: scot.walker@prescriberight.com

Table 1. Cholesterol Ester Transfer Protein Inhibitors

Drug	Sponsor	Trial name	Trial size (to nearest 1000)	Trial end year	Comment
Torcetrapib	Pfizer	ILLUMINATE	15 000	2006	Statistically significant increase in mortality was seen with torcetrapib. Torcetrapib increased HDL by 72%, decreased LDL by 25%, and decreased triglycerides by 9%. Off-target effects, such as increased blood pressure and mineralocorticoid excess, may have offset the benefit from an improved blood cholesterol profile. ⁴
Dalcetrapib ³	Hoffmann-La Roche	dal-OUTCOMES	16 000	2010	Study terminated early due to futility. For the primary outcome of composite major cardiovascular events, 95% confidence interval of hazard ratio of dalcetrapib was 0.93 to 1.16. Average increase of HDL while on dalcetrapib was around 35%. No significant effect on LDL was seen. Off-target effects were deemed clinically insignificant. It was suggested that future CETP inhibitors with greater effects on HDL-C and LDL-C may have clinical effects different from dalcetrapib. ⁵
Evacetrapib ⁴	Eli Lilly and Company	ACCELERATE	12 000	2015	Study terminated early due to futility. For the primary outcome of composite major cardiovascular events, 95% confidence interval of hazard ratio of evacetrapib was 0.91 to 1.11. Evacetrapib patients saw an average 130% increase of HDL-C and a 30% decrease of LDL-C. ⁶
Anacetrapib	Merck & Co	REVEAL	31 000	Ongoing	Anacetrapib reduced a composite endpoint of coronary death, acute myocardial infarction and coronary revascularization, by 9% compared to placebo in patients already receiving atorvastatin. ⁷

Source. Information adapted from the Prescribe Right Pharmaceutical Pipeline Tracker database.⁹

Note. ILLUMINATE = Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; dal-OUTCOMES = The Effects of the Cholesterol Ester Transfer Protein Inhibitor Dalcetrapib in Patients with Recent Acute Coronary Syndrome; CETP = cholesterol ester transfer protein; ACCELERATE = Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes; REVEAL = Randomized EVALuation of the Effects of Anacetrapib through Lipid-modification.

In the REVEAL trial, anacetrapib reduced cardiovascular events, but not mortality compared to placebo.⁷ A separate study of how the variants in genes associated with CETP inhibitors and statins affect lipoproteins levels and cardiovascular risk suggested that a decrease in apolipoprotein B may be more predictive of cardiovascular risk than LDL levels.⁸ Additional studies are needed to determine if CETP inhibitors have a place as add-on therapy or an alternative in statin-intolerant patients.

Authors' Note

Information is summarized from selected materials; additional information may be available from other sources. Due to the preapproval nature of the information, non-peer-reviewed data may be utilized. The information provided is meant to provide a way to assess the development status of a new drug and should not be used in making patient care decisions.

Declaration of Conflicts of Interest

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