CORONARY HEART DISEASE

New hope for CETP inhibitors

The cholesteryl ester transfer protein (CETP) inhibitor anacetrapib reduces LDL-cholesterol levels by nearly 40% and more than doubles HDL-cholesterol levels in patients with, or at high risk of, coronary heart disease. Furthermore, unlike torcetrapib—the first of the CETP inhibitors to be developed—anacetrapib has an acceptable safety profile. These findings from the DEFINE trial show great promise for this new agent. "There are very few drugs available to treat low levels of good cholesterol," says senior investigator Christopher Cannon, "anacetrapib is four to ten times more effective in raising good cholesterol compared with current therapies."

Inhibitors of CETP prevent the transport of cholesterol from HDL to LDL particles, thereby increasing levels of HDL cholesterol and reducing levels of LDL cholesterol. However, the early potential of this class of drugs was undermined in 2007 by the results of ILLUMINATE. After much anticipation of practice-changing results, this study showed that torcetrapib substantially increased the risk of mortality and cardiovascular events, and increased blood pressure and levels of aldosterone. The development of torcetrapib was discontinued and the future of CETP inhibitors seemed bleak, but anacetrapib was waiting in the wings. Early clinical studies of this new drug showed that it had none of the adverse effects of torcetrapib, indicating that these safety issues were not a class effect of CETP inhibitors, but perhaps unique to torcetrapib and unrelated to the primary mechanism of action.

The DEFINE trial was established to test the safety of anacetrapib in patients at high risk of cardiovascular events. Enrollment criteria included age between 18 and 80 years, known cardiovascular disease or a Framingham Risk Score of >20% per 10 years, and an LDL-cholesterol level 1.3–2.6 mmol/l whilst receiving statin therapy. After a 2-week run-in phase, 1,623 patients were randomly assigned to 100 mg per day of anacetrapib or placebo. Participants were also instructed to adhere to a cholesterol-lowering diet. The study drug was ceased if a patient's LDL-cholesterol level fell below 0.6 mmol/l at two consecutive measurements.

After 24 weeks of treatment, anacetrapib was associated with a 39.8% reduction in LDL cholesterol and a 138.1% increase in HDL cholesterol compared with placebo (P<0.001 for both). Dr Cannon highlights that "these changes are striking because virtually all the patients in the study were already taking cholesterol-lowering drugs." Levels of non-HDL cholesterol, triglycerides, and apolipoprotein B were also decreased among patients in the anacetrapib group when compared with placebo. Treatment with anacetrapib did not increase blood pressure or modify serum electrolyte balance, and was not associated with an increase in the risk of cardiovascular events or mortality.

Although the DEFINE trial was not powered to test the efficacy of anacetrapib in terms of hard clinical end points, it paves the way for further research on this and other CETP inhibitors. Dr Cannon is confident that "if the cardiovascular effects are borne out by future research ... we may have a new kind of drug to fight cardiovascular disease." One such study is the global REVEAL trial, which commences in 2011 and will test whether anacetrapib reduces death and cardiac morbidity in a population of 30,000 patients with cardiovascular disease.

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Original article Cannon, C. P. *et al.* for the DEFINE investigators. Safety of anacetrapib in patients with or at high risk for coronary heart disease. *N. Engl. J. Med.* doi:10.1056/NEJMoa1009744