TRIAL WATCH

Atherosclerosis drug fails to meet Phase III trial end point

A clinical trial published in the *Journal of the American Medical Association* has shown that a drug targeting acyl-CoA:cholesterol acyltransferase (ACAT), an enzyme involved in cholesterol accumulation within cells, does not slow the progression of atherosclerosis. Moreover, the drug was associated with an increased risk of major cardiovascular events.

The CAPTIVATE trial (Carotid Atherosclerosis Progression Trial Investigating Vascular ACAT Inhibition Treatment Effects) assessed the efficacy of the ACAT1 and ACAT2 inhibitor pactimibe (Daiichi Sankyo). ACAT is principally responsible for esterifying intracellular free cholesterol in cells, including macrophages and cells of the arterial wall, and is key to controlling the accumulation of low-density lipoprotein (LDL) cholesterol.

Patients with familial hypercholesterolaemia, a genetic disorder characterized by high serum levels of LDL cholesterol, received either 100 mg per day of pactimibe (n = 443) or placebo (n = 438) in addition to standard lipid-lowering therapy (that is, statins). The assessment was based on changes in carotid intima-media thickness (IMT), a surrogate marker for vascular disease, measured with an ultrasound-based imaging technique. After a mean duration of 15 months of drug therapy, maximum carotid IMT measurements did not show a treatment effect, and mean carotid IMT actually increased. This study was terminated prematurely after another study (ACTIVATE, ACAT Intravascular Atherosclerosis Treatment Evaluation) of the drug also failed to meet its primary end point. The reasons for these disappointing results are not clear; one of several hypotheses is that ACAT inhibition can lead to toxic levels of free cholesterol in cells.

Although the efficacy outcome of the trial was negative, it highlights the value of imaging techniques for assessing the effects of therapy on atherosclerotic disease. "Both carotid IMT and intravascular ultrasound studies are increasingly recognized to provide very important information, also with regards to the negative consequences of novel therapeutics," notes John Kastelein, Professor of Medicine, Chairman of the Department of Vascular Medicine at the Academic Medical Centre, Amsterdam, The Netherlands, and one of the investigators in the study.

"Even modestly sized carotid IMT studies such as this one and the RADIANCE trials [Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor (torcetrapib)] have highlighted that when the intervention arm shows more disease progression and an increase in cardiovascular side effects, it is clear the novel therapeutic confers harm."

Furthermore, there are lessons from this study that could be applied to future trials. "Small and relatively short-term imaging trials can be used to de-risk a development programme before the major decision has to be taken to invest in a large mortality and morbidity study," concludes Kastelein.

FURTHER READING Meuwese, M. C. *et al.* ACAT inhibition and progression of carotid atherosclerosis in patients with familial hypercholesterolemia: the CAPTIVATE randomized trial. *J. Amer. Med. Assoc.* **301**, 1131–1139 (2009)