Invited commentary

Another clinical evidence straw on the $4 billion ezetimibe camel’s back

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The clinical use of ezetimibe began in 2002 when the United States Food and Drug Administration licensed the compound for the reduction of LDL-C either alone or in combination with a statin medication. Since then, clinical use of ezetimibe has grown to levels exceeding annual sales of $4 billion, in parallel with efforts to broadly market the drug to clinicians despite the absence of definitive data on its net benefit on clinical cardiovascular outcomes [1]. Licensing of ezetimibe came under the Prescription Drug User Fee Act program (PDUFA), which required the conduct of clinical trials following licensing [2]. Disturbingly, over the past 9 years, no clinical trials yet support the incremental value of ezetimibe, amid growing concerns over its mechanism of action, and reports of bewildering effects on surrogates of clinical cardiovascular outcomes.

The firestorm over ezetimibe began in earnest with the publication of the ENHANCE trial showing no benefit of the drug on carotid intima media thickness (CIMT) in patients with familial hypercholesterolemia [3]. Criticisms of that trial centered on the selection of a trial population consisting of individuals previously treated with statins, and including some without advanced atherosclerosis. In this issue of the journal Atherosclerosis, West and colleagues, from the University of Virginia, report their findings on the incremental effect of ezetimibe treatment in statin naïve patients with advanced atherosclerosis of the peripheral arteries. The researchers enrolled 67 subjects in 2 different studies: (1) a group of statin naïve patients were randomized to double blind treatment with either statin monotherapy or combination treatment with a statin and ezetimibe; (2) A subset of patients already treated with statin monotherapy received the addition of ezetimibe. All subjects were followed with advanced atherosclerosis imaging of the superficial femoral artery using 1.5 T MRI. In short, they found that ezetimibe showed no benefit when combined with statin monotherapy for the primary endpoint of plaque volume of the superficial femoral artery. In patients already treated with statin, the researchers found evidence of an off-target effect with paradoxically greater progression of atherosclerosis in the setting of greater ezetimibe-induced LDL-C reductions. These data amplify findings from recent atherosclerosis imaging trials of ezetimibe showing no clinical effect of the drug beyond LDL-C reduction [3], and potentially off-target effects [4].

West’s study has important strengths and limitations. The endpoint utilized, peripheral arterial MRI, provides a volumetric assessment of atherosclerosis, which appears highly reproducible, however it must be noted that this method, and particularly its use in the superficial femoral artery, has not been validated as a surrogate of clinical cardiovascular outcomes. However, responsiveness of the femoral artery to statin treatment appears comparable to other arterial beds [5,6]. The reproducibility of the imaging technique enabled a small sample size, however this came at a cost of limited statistical power, inability to analyze subgroups for internal consistency of the findings, inability to conduct multivariable adjustment, and the potential confounding from imbalance of baseline or on-treatment variables. As such, MRI imaging micro-trials provide a “demonstration of concept” approach, but their primary strength may lie in their ability to investigate for ancillary atherosclerosis or plaque characteristics. In direct repudiation of the ENHANCE criticism, the authors studied statin naïve subjects with advanced atherosclerosis, and clearly patients with peripheral arterial disease are relevant to the question of therapeutic lipid treatment intensification. Lastly, although the authors provide us with an important evaluation in statin naïve patients, patients previously on statin treatment received ezetimibe in an observational, uncontrolled manner.

In the broader sense, the present study adds to a disturbingly growing list of investigations, which demonstrate bewildering results for a putatively simple drug that modestly lowers LDL-C. A full evaluation of the available literature shows a growing pattern suggesting that there is more to ezetimibe than meets the eye. Eze-

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−0.38, matches closely and corroborates a similar exploratory finding initially observed in ARBITER 6 (r = −0.31). This effect remains counterintuitive to the prevailing understanding that greater reduction in LDL-C yields superior clinical efficacy, and requires explanation. Could the extent to which ezetimibe inhibits SRB1-related cholesterol absorption [33], reflected in the measurable extent of LDL-C reduction, be more than offset by an immeasurable ezetimibe-induced inhibition of other transport mechanisms known to be important in HDL-related reverse cholesterol transport? Which other off-target mechanisms may contribute? Torcetrapib stands as the most recent reminder that the net effects of a lipid drug, and particularly a cholesterol transport inhibitor, cannot be measured solely through its effects on cholesterol concentrations.

Whereas the investigation by West provides no definitive answers, it adds to a growing body of evidence squarely questioning ezetimibe's efficacy, placing another evidence straw on the US $4 billion ezetimibe camel's back. Although a decrease in the use of ezetimibe following negative research reports reflects clinicians' understanding of this controversy, one should reasonably question whether the continued level of use of ezetimibe, a drug with considerable uncertainty awaiting clinical trial evidence development, represents a justifiable allocation of healthcare expenditures. Clinician's should remain open to all possibilities pending completion an ongoing study (www.clinicaltrials.gov; NCT00202878). But, the process of evidence development does not represent evidence. The ongoing trial has significant limitations having been altered several times while in progress including upwards adjustment of the sample size (from 10,000 to >18,000) powering the trial to detect a small as a 9% relative risk reduction (and with it, a minor absolute risk reduction), and what appears to be a broadening of the trial primary endpoints to include soft revascularization events [34]. Most importantly, clinicians will ultimately face significant uncertainty in generalizing results of this trial given its performance in patients with recent acute coronary syndrome, which does not match the majority of clinical scenarios in which ezetimibe use presently occurs. In the interim, regulatory officials in several European Union countries, conscious of rising health care costs and unwilling to accept an uncertain return on investment for an unproven therapy, have sensibly downgraded their recommendations regarding use of ezetimibe in prudent clinical practice.

Conflict of interest

The author reports receiving honoraria from Abbott Laboratories.

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