Ezetimibe, cardiovascular risk and atherogenic dyslipidaemia

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Submitted: 24 February 2010
Accepted: 25 February 2010

Arch Med Sci 2011; 7, 1: 5-7
DOI: 10.5114/aoms.2011.20597

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Abstract

Ezetimibe is a selective cholesterol absorption inhibitor with an excellent side-effect profile, able to reduce low-density lipoprotein (LDL) cholesterol by 15-25% from baseline in monotherapy and on top of statins and fibrates. Yet, it seems that ezetimibe produces quantitative rather than qualitative changes in LDL, with small net effects on atherogenic dyslipidaemia. This is supported by findings from the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study on atherosclerosis progression, where the addition of ezetimibe to simvastatin in patients with heterozygous familial hypercholesterolaemia did not affect the mean change in carotid intima-media thickness, although a significant reduction in LDL cholesterol levels was observed. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study has further shown that combination treatment with simvastatin significantly reduced LDL cholesterol levels in patients with aortic stenosis, but did not affect the primary end point of aortic valve and cardiovascular events, although a significant reduction in the risk of ischaemic events was reported. Formal cardiovascular outcome trials are underway and these will provide additional insights into the long-term effects of ezetimibe on clinical events as well as on atherogenic dyslipidaemia, beyond LDL cholesterol levels.

Key words: ezetimibe, cardiovascular risk, atherosclerosis, dyslipidaemia.

Ezetimibe represents the first of a new class of agents, the cholesterol absorption inhibitors, able to reduce low-density lipoprotein (LDL) cholesterol by 15-25% from baseline in monotherapy and on top of statins and fibrates [1]. The combination with simvastatin represents the most common combined therapy, due to the fact that ezetimibe can add an extra 20% reduction in LDL cholesterol to that seen with statins alone [2]. Also, ezetimibe is proved to be effective in conditions associated with dyslipidaemia [3-6].

Yet, it seems that ezetimibe produces quantitative rather than qualitative changes in LDL, with small net effects on atherogenic dyslipidaemia. This is supported by findings from the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study on atherosclerosis progression, where the addition of ezetimibe to simvastatin in patients with heterozygous familial hypercholesterolaemia did not affect the mean change in carotid intima-media thickness, although a significant reduction in LDL cholesterol levels was observed [7]. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study [8] has further shown that combination treatment with simvastatin

Table I. Effects of ezetimibe in monotherapy on LDL size and subclasses in hypercholesterolaemic patients (modified from [9])

Authors	Year	Dose [mg/day]	Duration [weeks]	Patients (*n*)	Selection criteria	Benefit
Farnier *et al.* Tribble *et al.*	2005 2008	10	12	165	mixed hyperlipidaemia without CHD	partial
Geiss *et al.*	2006	10	5	20	severe hyperlipoproteinaemia and CHD	no
Kalogirou *et al.*	2007	10	16	50	primary dyslipidaemia	no
Ose *et al.*	2007	10	12	138	primary hypercholesterolaemia	no
Nakou *et al.*	2008	10	24	86	overweight and obese subjects with hypercholesterolaemia	yes

CHD – coronary heart disease

significantly reduced LDL cholesterol levels in patients with aortic stenosis, but did not affect the primary end point of aortic valve and cardiovascular events, although a significant reduction in the risk of ischaemic events was reported.

Since these negative findings were obtained despite a significant reduction in LDL cholesterol levels, we have recently suggested that ezetimibe treats mainly LDL cholesterol and not the underlying dyslipidaemia [9]. In fact, several sources of evidence suggest that the "quality" rather than only the "quantity" of LDL exerts a direct influence on cardiovascular risk: LDL comprise multiple distinct subclasses that differ in size, density, physicochemical composition, metabolic behaviour and atherogenicity [10, 11]. We have recently shown that small, dense LDL are associated with a greater cardiovascular risk [12, 13].

Few studies have so far assessed the effects of ezetimibe on LDL size or their subclass distribution in patients with hypercholesterolaemia, and those in monotherapy are summarized in Table I. Overall, ezetimibe showed a limited role in reducing atherogenic small, dense LDL; yet, since most of these trials included patients at higher cardiovascular risk (due to the concomitant presence of obesity, diabetes and the metabolic syndrome), it cannot be fully excluded that this may have affected the results of these studies.

Therefore, available data so far suggest that treatment with ezetimibe, as monotherapy or in combination with simvastatin, significantly reduces LDL cholesterol concentrations but can be associated with the development of a pro-atherogenic LDL subclass profile. This is directly linked to the observation that end-point studies so far have consistently failed to show that the LDL-lowering effect of ezetimibe directly transfers into a corresponding reduction in cardiovascular events. Further, it has recently been highlighted that ezetimibe and its combination with simvastatin still generate 4 billion dollars per year with no evidence of clinical benefit [14].

Future prospective studies are needed to clarify to what extent ezetimibe is able to reduce atherogenic dyslipidaemia, beyond LDL cholesterol levels. Formal cardiovascular outcome trials are underway and these will provide additional insights into the long-term effects of ezetimibe. For instance, the effect of the combination with statins compared to statin monotherapy on cardiovascular end points is currently being examined by the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), which aims to recruit a very large cohort of patients with acute coronary syndromes with a follow-up period of at least 2.5 years [15].

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