



Synopsis

Ezetimibe: a review

Ezetimibe belongs to a new class of antihyperlipidaemic agents that inhibit the absorption of cholesterol by inhibiting the cholesterol transport system located within intestinal cell walls.¹ The principal benefit appears to be a reduction in low-density lipoprotein cholesterol (LDLC). Triglycerides fall moderately and a modest rise in high-density lipoprotein cholesterol (HDLC) has been consistently observed in groups of treated patients.

Mauro *et al.*¹ showed that ezetimibe reduced cholesterol absorption by >50%. Ezetimibe 10 mg/d reduced LDLC by approximately 18% and further enhanced the LDLC-lowering effect of statin medications by an additional 15 - 20%. In addition, ezetimibe lowered triglycerides by about 5% and increased HDLC approximately 3%. Ezetimibe was found to be well tolerated and so far no serious adverse effects have been directly attributable to ezetimibe.

Mauro and his co-workers concluded that ezetimibe appears to have a potential role in the treatment of primary hypercholesterolaemia. However, further data are needed to determine its long-term tolerability and efficacy.

The potential roles for ezetimibe include its concurrent use with a statin to further enhance the lowering of LDLC. This may permit a lowering of statin dosage to avoid statin-related complications or its use as monotherapy to treat hypercholesterolaemia when statin use cannot be tolerated or is contraindicated.

An article reporting specific research appeared in *Circulation* in May 2003.² In this study, Ballantyne

and colleagues investigated ezetimibe in combination with atorvastatin.

They conducted a double-blind study on 628 patients with baseline LDLC of 3.8 - 6.4 mmol/l and triglycerides

9.1 mmol/l who were randomly assigned to receive either ezetimibe 10 mg/d alone, or combinations of ezetimibe 10 mg with various strengths of atorvastatin, or placebo for 12 weeks.

Ezetimibe plus atorvastatin significantly improved LDLC, HDLC, triglycerides, total cholesterol, and high-sensitivity C-reactive protein (hs-CRP) compared with atorvastatin alone. Coadministration of ezetimibe provided a significant additional 12% LDLC reduction, 3% HDLC increase, 8% triglyceride reduction, and 10% hs-CRP reduction versus atorvastatin alone. Ezetimibe plus atorvastatin provided LDLC reductions of 50 - 60%, triglyceride reductions of 30 - 40%, and HDLC increases of 5 - 9%, depending on atorvastatin dose. LDLC reductions with ezetimibe plus 10 mg atorvastatin (50%) and 80 mg atorvastatin alone (51%) were similar. Ezetimibe plus atorvastatin was well tolerated, with a safety profile similar to atorvastatin alone and to placebo.

The workers concluded that coadministration of ezetimibe and atorvastatin offers a well-tolerated and highly efficacious new treatment option for patients with hypercholesterolaemia.

Melani *et al.*³ evaluated the efficacy and safety of ezetimibe 10 mg administered with pravastatin in patients with primary hypercholesterolaemia.

The study consisted of a 2-12 week screening/washout period, followed by a 4-week, single-blind, placebo lead-in period, during which 538 patients with baseline LDLC between 3.8 and 6.5 mmol/l and TG <=4.0

mmol/l were randomised to one of eight possible daily treatments for 12 weeks consisting of ezetimibe 10 mg alone, pravastatin 10, 20, or 40 mg alone or ezetimibe 10 mg plus pravastatin 10, 20, or 40 mg, or placebo. The primary endpoint was percentage reduction in LDLC for ezetimibe 10 mg plus pravastatin compared with pravastatin alone and ezetimibe alone. The combination of ezetimibe and pravastatin resulted in significant incremental reductions in LDLC and TG compared with pooled pravastatin alone.

The combined regimen was well tolerated, with a safety profile similar to pravastatin alone and placebo. The investigators concluded that when coadministered with pravastatin, ezetimibe provided significant reductions in LDLC and TG and was well tolerated with a safety profile similar to pravastatin alone.

Professor David Marais of the UCT Lipid Clinic says that they have been conducting trials of ezetimibe for a few years now. He says that its place will probably be as an add-on to the statins, or where statins have been contraindicated or in patients with familial hypercholesterolaemia who are not responding to statin therapy.

Cost is another factor which must be considered. In the USA, the cost of ezetimibe is about \$85 per month, which is more than that of statins. In refractory cases it may be more cost-effective to double the statin dose. South African prices are not available as the drug is not yet registered, but a statin-ezetimibe combination is currently being developed.

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1. Mauro VF, *et al. Pharmacother* 2003; 37: 839-848

2. Ballantyne CM, *et al. Circulation* 2003; 107: 2409-2415.

3. Melani L, *et al. Eur Heart J.* 2003; 24: 717-728.