Ezetimibe

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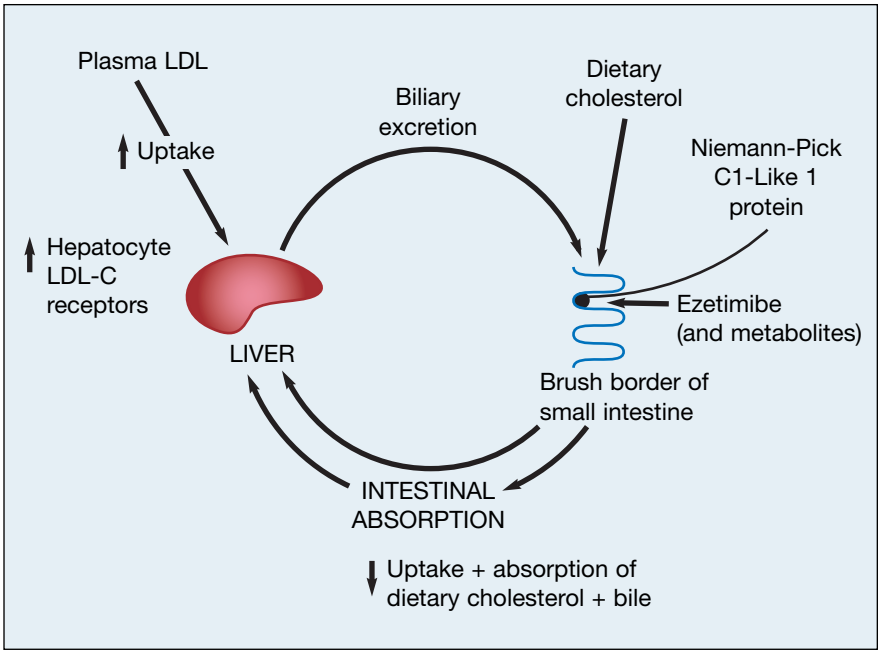
Introduction

Reducing plasma cholesterol, especially low-density lipoprotein cholesterol (LDL-C), reduces vascular events and mortality. This effect is greater the lower the cholesterol/LDL-C. Despite the widespread acceptance of the role of statins and/or fibrates, many high-risk patients still have levels of cholesterol/LDL-C that expose them to increased vascular risk. Ezetimibe, the first selective cholesterol absorption inhibitor, offers an alternative therapy to those patients intolerant of statins or add-on therapy when targets are not reached. This is of relevance to those with increased vascular risk, including patients with diabetes.

Pharmacology

Figure 1 outlines the pharmacological action of ezetimibe. Plasma cholesterol concentration is dependent upon the balance between endogenous and exogenous cholesterol metabolism. Ezetimibe has a unique mode of action by targeting the exogenous pathway. Humans ingest an average of 300mg of cholesterol per day and an additional 1g of cholesterol is secreted into the gut as bile. Ezetimibe and its glucuronide metabolite localise at the brush border of enterocytes where they bind to the Niemann-Pick C1-Like 1 (NPC1L1) protein of the enterocyte, inhibiting the uptake and absorption of dietary cholesterol and bile. The quantity of cholesterol reaching the liver is reduced with resultant up-regulation of hepatocyte LDL-C receptors, thus increasing hepatic uptake of LDL-C from plasma. This local mode of action allows ezetimibe to remain within the enterohepatic circulation, reducing systemic side effects and allowing repeated circulation and action on subsequent meals. Its half life of 22 hours allows the drug to be prescribed once daily.

Figure 1. Pharmacological action of ezetimibe



Trials of safety and efficacy

Monotherapy

In a double-blind, placebo controlled, parallel-group study to assess the safety and efficacy of ezetimibe as a cholesterol lowering agent in patients with primary hypercholesterolaemia, 827 patients with LDL-C of ≥3.36mmol/L (130mg/dl) to <6.47mmol/L (250mg/dl) and triglycerides of <3.95mmol/L (350mg/dl) were randomised in a 3:1 ratio and given either ezetimibe 10mg or placebo once daily for 12 weeks.[1] In the ezetimibe group there was a mean reduction in LDL-C of 17.7% compared to an increased mean LDL-C of 0.8% in the placebo group. Ezetimibe was also found to significantly reduce plasma total cholesterol, apolipoprotein B, high-density lipoprotein(2)-cholesterol and lipoprotein(a). A trend towards lower triglyceride levels was noted. Serum concentrations of lipid-soluble vitamins and baseline or stimulated cortisol levels were not significantly affected by ezetimibe. The drug was well tolerated, with reported side effects being similar to those of the placebo group.

Dual therapy

In a double-blind, multi-centre trial, 668 patients were randomised into one of 10 groups: ezetimibe alone, simvastatin alone at four different doses, fixed-dose ezetimibe in combination with four different doses of simvastatin, and placebo.[2] Following a two- to 12-week washout period, patients received 12 consecutive weeks of medication. Patients were required to follow a strict diet

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throughout the study. Plasma lipid profiles were sampled at weeks two, four, eight and 12.

Dual therapy was significantly more effective than monotherapy with ezetimibe or low-dose simvastatin alone. Pooled results across all dose ranges found co-administration to reduce LDL-C by a further 13.8% compared to simvastatin alone (-36.1% to -49.9%), and a further 31.8% as compared to ezetimibe monotherapy (-18.1% to -49.9%). Dose-specific reduction in plasma LDL-C ranged from -44% to -57% for dual therapy, compared to -27% to -44% for simvastatin monotherapy. Ezetimibe 10mg co-administered with simvastatin 10mg achieved a mean reduction in LDL-C of -44%, comparable to that achieved by simvastatin 80mg alone (also -44%). Fifty-nine percent of patients receiving dual therapy achieved >50% reduction in plasma LDL-C concentration compared with just 15% of patients receiving simvastatin monotherapy. Seventy-seven percent of patients receiving dual therapy achieved LDL-C concentrations <2.56mmol/L (<100mg/dl, the NCEP ATP III – National Cholesterol Education Program Adult Treatment Panel III target) compared to just 64% of those receiving monotherapy. Adverse effects were similar across treatment groups.

Specific evidence for use in diabetes

The largest study looking at the use of ezetimibe in patients with diabetes involved 1229 patients recruited into the VYTAL study comparing ezetimibe/simvastatin combination to atorvastatin in patients with type 2 diabetes.[3] All patients had an LDL-C >2.56mmol/L (>100mg/dl) following a three- to five-week washout period (mean baseline LDL-C 3.72mmol/L [145mg/dl]) and were randomised into four treatment groups: ezetimibe 10mg + simvastatin 20mg *vs* atorvastatin 10 or 20mg; ezetimibe 10mg + simvastatin 40mg *vs* atorvastatin 40mg. Treatment duration was six weeks.

Dual therapy with lower-dose simvastatin was found to significantly reduce LDL-C from the baseline (-53.6%) compared to monotherapy with atorvastatin 10 and 20mg (-38.3% and -44.6% respectively). Dual therapy of ezetimibe and simvastatin continued to be more effective than atorvastatin alone at higher doses (-57.6% for ezetimibe 10mg/simvastatin 40mg, -50.9% for atorvastatin 40mg). A total of 59.7% of patients in the ezetimibe/simvastatin 10/20mg group achieved LDL-C <1.79mmol/L (<70mg/dl); this compares to just 21.5% and 35% in the atorvastatin 10mg and 20mg groups respectively. In all, 74.4% of ezetimibe/simvastatin 10/40mg attained LDL-C <1.79mmol/L (<70mg/dl) compared with 52.2% of patients taking atorvastatin 40mg. In addition to reduction in LDL-C, the dual therapy was superior at increasing HDL-C levels from baseline at all doses.

Discussion

Although lifestyle modification and tight glucose control have been shown to improve general lipid profiles, most patients require the addition of a pharmacological agent to reduce LDL-C. The Heart Protection Study linked substantial reductions in LDL-C to significant reduction in major adverse coronary events. The NCEP ATP III in the United States has a target of LDL-C <1.79mmol/L (<70mg/dl) for high-risk patients, including those with diabetes. JBS 2, the Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice, recommends a target LDL-C of <2mmol/L for those at high risk, including patients with diabetes. These targets are difficult to achieve. From the available evidence, monotherapy with ezetimibe is unlikely to achieve these targets but may have a role in those intolerant of statins. All of the combination studies have shown ezetimibe to enhance the effects of statins without the addition of significant side effects. Given that the VYTAL study showed 74.4% of patients receiving ezetimibe in combination with 40mg simvastatin attaining endpoint cholesterol of <1.79mmol/L (<70mg/dl), the use of combination treatment should be considered in those patients at high risk of vascular events who are not achieving LDL-C targets. However, it should be noted that there has been no direct comparison with 80mg of atorvastatin recommended elsewhere for high-risk patients and at present there are no morbidity/mortality outcomes data for ezetimibe. There are ongoing morbidity/mortality studies including the IMPROVE-IT study in patients with acute coronary syndromes and the results are awaited with considerable interest. This is particularly so given that Merck and Schering-Plough Pharmaceuticals, manufacturers of ezetimibe, posted results on their websites in January 2008 showing that 356 people treated with ezetimibe (10mg) plus simvastatin (80mg) fared no better than the 360 who had received simvastatin alone when using the surrogate marker of change in carotid intima media thickness over a period of two years as the primary endpoint.

Key points

- Ezetimibe lowers cholesterol by reducing its absorption in the small intestine
- Ezetimibe can be used for the management of hypercholesterolaemia in patients, including those with diabetes, intolerant of statins or where lipid lowering targets have not been achieved on statin alone
- Unlike statins there are no endpoint data to show improved morbidity/mortality for the established lipid lowering effects of ezetimibe, but these studies are ongoing

Conflict of interest statement

Dr Nelson and Dr McKay have no conflicts of interest to declare. Dr Fisher has received lecture fees from and has worked as an advisor to Merck Sharp & Dohme/Schering-Plough.

References

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