The place of ezetimibe in clinical practice

Clive Weston

Ezetimibe is the first selective cholesterol absorption inhibitor to be licenced in the UK. It interferes both with dietary cholesterol absorption and the enterohepatic circulation of cholesterol synthesized by the liver. As monotherapy it leads to modest reductions in plasma low-density lipoprotein cholesterol levels, but has synergistic effects when used with statins.

Atherosclerosis remains a major cause of death and illness in the UK. High concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) are associated with an increased risk of cardiovascular events, while high concentrations of high-density lipoprotein cholesterol (HDL-C) provide some protection (Castelli et al, 1986; Assmann et al, 1998). The identification and management of hyperlipidaemia in patients at risk of future vascular events is a priority in hospital practice and primary care.

Optimization of the lipid profile (predominantly lowering TC and LDL-C levels, but also reducing TG, increasing HDL-C and effecting compositional changes within lipid particles) has been shown to reduce the risk of coronary heart disease, both in those with manifest atherosclerosis (Sacks et al, 1996) and in those asymptomatic individuals at high risk (Heart Protection Study Collaborative Group, 2002). Most of the evidence for this risk reduction has been obtained from studies using hydroxy methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors ('statins'), although similar data exist for a variety of other approaches, including dietary change (de Lorgeril et al, 1994), surgical intervention (Buchwald et al, 1998), bile acid sequestrants (Lipid Research Clinics Program, 1984), nicotinic acid (Canner et al, 1986) and fibrates (Rubins and Robins, 2000). Thus, while there is debate regarding the added contribution of anti-inflammatory, and other pleiotropic, effects of statins (Ridker et al, 2001), it seems likely that cholesterol lowering, by whatever means, should be beneficial to those at risk of cardiovascular events (Gould et al, 1998).

TARGETS AND THEIR ATTAINMENT

Various organizations have developed different guidance on thresholds for initiation of lipid-modifying treatment and targets to be achieved by such therapies (Feher, 2003). In the UK the Joint British Societies (Wood et al, 1998) advise a reduction in TC to below 5 mmol/litre and LDL-C to below 3 mmol/litre. Such recommendations were incorporated into the National Service Framework for Coronary Artery Disease (Department of Health, 2000), the Welsh implementation document and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines, with added provisos, for example that percentage reductions of TC and LDL-C should be 25% and 30% respectively, or that a reduction in TC of at least 1 mmol/litre be achieved. More stringent targets may be introduced in the UK, in keeping with those advised by the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) in America (LDL-C <2.6 mmol/litre), and the Canadian Working Group on Hypercholesterolemia (Fodor et al, 2000) (LDL-C <2.5 mmol/litre and TC:HDL-C ratio <4.0).

Existing targets have proved difficult to achieve. Data from the 1998 Health Survey for England showed that 30% of those with a history of coronary heart disease were taking lipid-lowering drugs, of which 44% were attaining a TC of below 5 mmol/litre (Primatesta and Poulter, 2000). A cross-sectional survey of 17 general practices, in 2001, reported 54.8% of patients receiving lipid-lowering therapy attaining a TC of 5 mmol/litre or below (Hippisley-Cox et al, 2003). Further, the authors of this study discovered that the initial serum cholesterol concentrations of their study population tended to be higher than those for patients in clinical trials, and that the absolute reduction needed to meet the target was therefore greater than suggested in such trials.

Another explanation for failure to achieve targets is the recognition that clinicians tend to

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start statin therapy at low doses and frequently fail to increase the dose if LDL-C and/or TC remains elevated. Except for more potent statins, such low doses are unlikely to be sufficient (Brown et al, 1998). The problem with dose is compounded by the 'rule of six', whereby a doubling of the dose of a statin results in only an extra 6% reduction in LDL-C concentration (Knopp, 1999). Moreover long-term treatment with statins have been associated with a slow increase in LDL-C level – the 'escape phenomenon' (Rubinstein and Weintraub, 1995) – although whether this reflects a biological change or worsening adherence to dietary advice and drug prescription is uncertain.

COMBINATION THERAPY

Whereas in the management of hypertension, clinicians are comfortable using combinations of drugs to reach blood pressure targets, the same is not true when it comes to lipid management. This is in spite of evidence that combinations of different classes of lipid-lowering agents, with complementary actions, often lead to better lipid profiles compared with high-dose statin monotherapy (Kastelein and van Dam, 2001). This reluctance is fuelled by the slight increase in risk of myotoxicity observed with the use of statin–fibrate combination therapy. Yet if more stringent lipid targets are to be reached, it seems likely that combination therapy may be needed (Davidson, 2002; Xydakis and Ballantyne, 2002).

PATHWAYS OF CHOLESTEROL METABOLISM

Plasma cholesterol concentration is determined by a balance of biosynthesis – predominantly in the liver from acetyl CoA substrates through the action of enzymes including HMG-CoA reductase – and dietary cholesterol uptake from the intestine. Thus there are two pathways of cholesterol metabolism, the endogenous (synthesis) and exogenous (absorption). While dietary intake is typically 300–700 mg per day, a further 1000 mg is secreted into the intestinal lumen within the bile, and virtually all of this is reabsorbed as part of the 'enterohepatic circulation'. Intestinal absorption of cholesterol (or its blockade) will therefore have effects on plasma cholesterol that are greater than dietary restriction alone. In fact low-cholesterol diets have only a minor effect on plasma cholesterol concentration (Knopp et al, 1997).

Feedback mechanisms allow for alterations in activity of both pathways; reduced intestinal cholesterol absorption leads to increased HMG-CoA activity and greater synthesis of cholesterol is associated with lower cholesterol absorption (Miettinen, 2001). It is also likely that individuals vary in the relative contributions of the endogenous and exogenous pathways to plasma cholesterol concentrations.

INHIBITION OF CHOLESTEROL ABSORPTION

Bile acid sequestrants such as cholestyramine and colestipol indirectly interfere with intestinal cholesterol absorption by binding bile acids in the intestinal lumen. Lipid modification using these agents has been shown to be of benefit, and combinations of such agents with, for example, statins, do improve lipid profiles and clinical outcomes. However, tolerability is a major problem, and TG concentration may increase in susceptible individuals. Statins themselves may indirectly play a part. High dose statins can reduce cholesterol excretion into bile (Mitchell et al, 1991).

Orlistat, used for the promotion of weight loss, inhibits lipase activity in the intestine, resulting in reduced cholesterol absorption. In combination with a hypocalorific diet, orlistat is associated with significant weight loss and an independent reduction of both TC (11% orlistat *vs* 3% placebo) and LDL-C (14% orlistat *vs* 4% placebo) (Broom et al, 2002). While such treatment can also improve TG levels and glycaemia, HDL-C concentrations are not significantly altered. Moreover absorption of fat-soluble vitamins is also affected, and troublesome diarrhoea is common.

Cholesterol absorption is inhibited by ingestion of naturally-occurring plant sterols and plant stanols, perhaps by competing with cholesterol for solubilization into absorbable micelles (Minhas, 2003). Esterified stanols have formed the basis for a variety of 'functional foods', predominantly margarines, which can be used to achieve reductions in TC by 10% and LDL-C by 15%. When used in combination with a statin, an extra 15% LDL-C lowering effect was observed (Gylling et al, 1997). Again absorption of other fat-soluble substances is affected (Miettinen and Gylling, 1999).

EZETIMIBE: SELECTIVE CHOLESTEROL ABSORPTION INHIBITION

Ezetimibe (Ezetrol, Schering-Plough, Welwyn Garden City; Merck Sharp & Dohme, Hoddesdon) is a cholesterol absorption inhibitor that interferes with intestinal absorption of both dietary and biliary-derived cholesterol, as well

as non-cholesterol sterols (sitosterol and campesterol), without altering uptake of fatty acids and fat-soluble vitamins. It is rapidly glucuronidated in the enterocyte, transported within the portal veins, and takes advantage of recirculation within the enterohepatic circulation, predominantly being found in the gall bladder, biliary tract and at the brush border of the enterocyte (Kastelein and van Dam, 2001; Farnier, 2002). Because of this recirculation, ezetimibe is effective in 'mg' doses and is less affected by occasional forgotten doses (unlike bile acid sequestrants that require 'g' doses and are highly dose-dependent). It is not metabolized by the cytochrome P450 system, which should limit potential drug interactions, and does not interfere with the pharmacokinetics of co-administered statins (which should equate with no increased risk of statin side effects) (Kosoglou et al, 2002).

Ezetimibe is available as a 10 mg tablet taken once daily, administered at any time of day. It is licenced:

- For co-administration with a statin in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not otherwise adequately controlled
- As monotherapy (with diet) in patients with primary hypercholesterolaemia in whom statins are not tolerated or considered inappropriate
- For co-administration with a statin in patients with homozygous familial hypercholesterolaemia
- As adjunctive therapy to diet in patients with homozygous sitosterolaemia (a rare inherited condition characterized by increased plasma levels of plant sterols and premature atherosclerosis without elevated LDL-C).

EFFICACY OF EZETIMIBE

Monotherapy

As monotherapy, ezetimibe works rapidly. A randomized, double-blind, placebo-controlled crossover study in 18 patients with mild to moderate hypercholesterolaemia demonstrated a 54% relative reduction in cholesterol absorption (fractional cholesterol absorption averaged 49.8% on placebo *vs* 22.7% on ezetimibe 10 mg/day) after 2 weeks (Sudhop et al, 2002). There was obvious variation in effect between individuals. The reduction in absorption was associated with an increase in cholesterol and bile acid synthesis, leading to a short-term lowering of TC by 15% and of LDL-C by 20%. The beneficial effects appear unaffected by the dietary fat content (Dujovne et al, 2002b).

Larger, although still short-lasting (12 weeks) studies, have confirmed these effects of monotherapy. Directly-measured plasma LDL-C was lowered by 17.7% with ezetimibe compared with an increase of 0.8% with placebo in a study of 827 patients (Knopp et al, 2003), and by 16.9% with ezetimibe compared with an increase of 0.4% with placebo in a study of 892 patients (Dujovne et al, 2002a). TC fell by approximately 12% and there were small but statistically significant increases in HDL-C (approximately 2%) in both studies. The level of TG was also reduced. The effects were seen at 2 weeks, but persisted for the remainder of the study.

Combination therapy

When ezetimibe is started simultaneously with statins or used as 'add-on' therapy to statins, the combination leads to significantly greater reductions in TC and LDL-C than that achieved by statins alone. A placebo-controlled trial of additional ezetimibe 10 mg/day in 769 patients taking a variety of statins at varying doses reported a further 21.4% reduction of LDL-C, from a mean 138 mg/dl (3.6 mmol/litre) (Gagne et al, 2002b). The improvement achieved by the combination appeared with all the statins and across a range of doses. Moreover there was a significant additional increase (1.7%) in HDL-C and 11% reduction in TG.

A number of studies of statin/ezetimibe combination therapy have been organized by the Ezetimibe Study Group (which includes members of the Schering-Plough Research Institute) and have been presented at major international meetings and published in peer-reviewed journals. Twelve weeks co-administration of ezetimibe 10 mg with pravastatin (10, 20 or 40 mg), to individuals with LDL-C between 3.8 and 6.5 mmol/litre, reduced LDL-C by 34–41%, TG by 21–23% and increased HDL-C by 7.8–8.4% depending on the dose of pravastatin (Melani et al, 2003).

A similar trial of ezetimibe and lovastatin reported an additional 14% LDL-C decrease, 5% HDL-C increase and 10% TG decrease compared with 'pooled' lovastatin alone (Kerzner et al, 2003). The addition of ezetimibe 10 mg to simvastatin 20 mg/day achieved a greater reduction in LDL-C (24.5%) than doubling the dose of simvastatin (11.1%) (Dobs et al, 2003).

Twelve weeks of ezetimibe 10 mg combined with lower dose statin treatment – 10 mg of simvastatin, lovastatin, pravastatin or atorvastatin – caused similar reductions in LDL-C as

achieved by high-dose statin treatment alone – simvastatin 80 mg, lovastatin 40 mg, pravastatin 40 mg or atorvastatin 80 mg (Sagar et al, 2003).

This was confirmed in a large placebo-controlled study (628 patients with LDL-C 145–250 mg/dl (3.7–6.5 mmol/litre)) comparing ezetimibe 10 mg, atorvastatin 10, 20, 40 or 80 mg, with the combination of both agents. The reduction in LDL-C achieved by ezetimibe with atorvastatin 10 mg was similar to that achieved by atorvastatin 80 mg alone (50% *vs* 51%), although there was a still greater effect when ezetimibe was combined with atorvastatin 80 mg (60% LDL-C reduction) (Ballantyne et al, 2003). As in other studies, higher doses of atorvastatin were associated with an attenuation of the increase in HDL-C (6% increase with 10 mg, 3% increase with 80 mg).

There was a trend towards a similar attenuation of response using the combination, although the increases in HDL-C remained superior when the combination was used (9% increase with ezetimibe 10 mg and atorvastatin 10 mg, 7% increase with ezetimibe 10 mg and atorvastatin 80 mg). Across all doses of atorvastatin, coadministration of ezetimibe was associated with an extra 12% LDL-C reduction, 9% TC reduction, 3% HDL-C increase, 8% TG reduction and 10% fall in TC:HDL-C ratio.

The same study allowed an assessment of changes in C-reactive protein measured by high-sensitivity techniques (hs-CRP). Reductions in hs-CRP have been used to support the theory of non-lipid, beneficial anti-inflammatory effects of statins. In the placebo group there was a 7% increase over 12 weeks. In those taking ezetimibe alone there was no change from median baseline values. However, at all doses of atorvastatin above 10 mg the coadministration of ezetimibe was associated with a significant added reduction in hs-CRP, e.g. 43% reduction with atorvastatin 80 mg and 62% reduction with the addition of ezetimibe.

In one short (2-week) study of combination therapy with fibrates in hospitalized patients, coadministration of ezetimibe 10 mg with fenofibrate 200 mg resulted in a significant reduction in LDL-C (36.3%) compared with ezetimibe alone (13.5%), fenofibrate alone (22.3%) or placebo (10.1%). Surprisingly HDL-C fell in all groups, possibly as a result of hospitalization, but by only 2.0% with combination therapy compared with 6.1% with fenofibrate, 13.3% with ezetimibe and 14.1% with placebo (Kosoglou et al, 2001). At present the combination of ezetimibe and fibrates is not recommended (see below).

Studies of combinations of ezetimibe and bile acid sequestrants have not been published, although unpublished data suggest that such resins reduce the plasma levels of ezetimibe by 55% and may attenuate the LDL-C lowering effects. If both agents are to be used it is recommended that ezetimibe ingestion takes place at least 2 hours before or 4 hours after administration of the resin.

ACHIEVING TARGETS

In the study by Ballantyne et al (2003), of ezetimibe, atorvastatin or both, coadministration also allowed significantly more individuals to attain the strict US Adult Treatment Panel III target cholesterol – 85% with combination therapy compared with 73% with atorvastatin alone (Ballantyne et al, 2003). Achievement of strict targets (LDL-C of 100 mg/dl or less, 2.6 mmol/litre) was the endpoint of a study of 621 patients with familial hypercholesterolaemia, coronary heart disease or multiple cardiovascular risk factors whose LDL-C remained above 129 mg/dl (3.3 mmol/litre) in spite of atorvastatin 10 mg per day. They were randomly assigned to either ezetimibe 10 mg or additional atorvastatin 10 mg.

After 4 weeks and 9 weeks the dose of atorvastatin could be doubled in order to achieve target LDL-C. After 14 weeks, in those on combination therapy the mean LDL-C reduction from baseline was 31.2%, 60% were taking ezetimibe 10 mg with atorvastatin 40 mg, and 67 of 305 (22%) attained target LDL-C. In those taking atorvastatin alone, the mean LDL-C reduction from baseline was 18.9%, 85% were taking atorvastatin 80 mg and 23 of 316 (8.6%) attained target LDL-C (Stein et al, 2003).

SPECIAL GROUPS

Homozygous familial hypercholesterolaemia

A double-blind, randomized trial involved 50 patients with homozygous familial hypercholesterolaemia who were already on strict diets and receiving 40 mg of either atorvastatin or simvastatin (with or without LDL-apheresis). Patients were randomized to 12 weeks' treatment with either a doubling of the existing statin dose, the addition of ezetimibe 10 mg to the existing statin dose or the addition of ezetimibe 10 mg to a double dose of statin. The mean percentage reduction in LDL-C from baseline was 7% (from 9.7 to 9.1 mmol/litre) in those receiving 80 mg statin alone and

27.5% in those receiving the combination of ezetimibe and 80 mg statin. A reduction in LDL-C of 15% or more was achieved in 18% of those taking 80 mg statin alone, 58% in all those taking ezetimibe and 76% in those taking ezetimibe and highest dose statin (Gagne et al, 2002a).

Homozygous sitosterolaemia

A double-blind, placebo-controlled trial (G Salen, unpublished data, 2002) of 8 weeks' treatment with ezetimibe 10 mg in 37 patients with homozygous sitosterolaemia showed treatment associated with a significant 25% reduction in plasma sitosterol levels and 27.5% reduction in plasma campesterol concentrations. Clinical outcomes were not assessed.

CLINICAL OUTCOMES

New drugs suffer when compared with existing treatments because of their inability to produce 'outcome' data in the form of clinically meaningful reductions in cardiovascular events. As discussed above, it seems likely that cholesterol lowering, regardless of the method, should have beneficial effects (Gould et al, 1998). Moreover, animal studies have demonstrated significant reductions in atherosclerotic lesions associated with ezetimibe treatment (Davis et al, 2001). A variety of clinical trials are planned, or are in progress, which should provide some measurable outcomes, and further safety data regarding longer-term use. These include studies assessing the impact of ezetimibe on carotid artery arteriosclerosis, cardiovascular morbidity in patients with aortic stenosis, and vascular disease in patients with chronic renal disease.

SAFETY PROFILE

Short-term clinical trials of ezetimibe suggest that it is a well-tolerated drug, with an adverse event rate no different to placebo when used as monotherapy, and a side-effect profile no different to statin therapy alone when coadministered with statins (Ballantyne, 2002). Elevation of liver or skeletal muscle enzymes is rare. Rhabdomyolysis has not been reported with statin–ezetimibe combination therapy, although this is such a rare complication that many more patients would be required in order to prove the absence of small increases in incidence with combination therapy.

In the dog, ezetimibe results in an increased cholesterol concentration in the bile, although even at supra-therapeutic doses for up to a year, no gall-stones were detected. Because fibrates also increase cholesterol excretion into the bile, and increase the plasma ezetimibe concentration, there are concerns that long-term coadministration with ezetimibe and fibrates could be lithogenic, and should be avoided.

No dosage adjustment is recommended in the elderly, nor in those with renal insufficiency. Ezetimibe is best avoided in patients with moderate to severe liver disease.

COST

As of June 1 2003, the cost of 28 days of ezetimibe is £26.31. This compares with £18.03 for atorvastatin 10 mg, and £29.69 for simvastatin 40 mg.

CONCLUSION

Ezetimibe is a novel agent that interferes with the intestinal absorption of cholesterol and plant sterols. It is safe, at least in short-term (up to 12 weeks) trials, and is well tolerated. Post-marketing surveillance will be important to alert clinicians to any adverse effects of long-term use. It appears free of significant interactions with other drugs. Although licenced for use as monotherapy, it will normally form part of a combination of lipid-lowering agents, where it will commonly be used with existing statin treatment. It is likely that fixed-dose combination tablets containing ezetimibe and simvastatin will become available soon. Until then, combination therapy will increase direct drug costs. Its use will allow more patients to reach target LDL-C concentrations, which should lead to improved outcomes. HM

Conflict of interest: Dr Weston received an honorarium for participating in the UK launch meeting for Ezetrol, and was a member of an advisory board to Schering Plough/MSD, who co-promote Ezetrol in the UK.

KEY POINTS

- Lowering total and low-density lipoprotein-cholesterol, usually using statin treatment, reduces the risk of cardiovascular events.
- There are two pathways of cholesterol metabolism – endogenous synthesis and exogenous absorption of dietary and biliary cholesterol
- Ezetimibe selectively interferes with intestinal cholesterol absorption, while statins reduce cholesterol synthesis; the effects of these two agents are synergistic.
- If stringent cholesterol targets are to be achieved, combinations of lipid-lowering agents may be needed.

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