Expert Perspective

Ezetimibe: A New Class of Cholesterol Lowering Drugs

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There is an increasing amount of evidence to show that we need to reduce low density lipoprotein cholesterol (LDL-C) levels to 70 mg/dl (1.8 mmol/l) in very high-risk patients.[1] This fact has been recognised by the revised National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines.[1] How are we to achieve this strict target, or even the previously defined LDL-C goals for high-risk patients (100 mg/dl; 2.6 mmol/l, NCEP ATP III; 96 mg/dl; 2.5 mmol/l, European guidelines)?[2,3] Monotherapy with evidence-based statins remains the ideal solution. However, this option will not always be successful, as can be seen from the studies described below. This problem leads to the need for combination therapy (for a review, see reference 4). Among several options open to clinicians is the addition of ezetimibe to a statin. In this brief overview, we discuss the place of ezetimibe in clinical practice.

Mode of action of ezetimibe

Ezetimibe is a selective cholesterol transport inhibitor that works in the small bowel.[5-9] It is not widely appreciated that endogenous cholesterol production and its recirculation to the liver is a major determinant of plasma LDL-C levels.[5-9] It follows that the inhibition of this process, together with a decrease in the absorption of dietary cholesterol, will help reduce the circulating concentration of LDL-C.[5-9]

A detailed description of the mechanism of action of ezetimibe is beyond the scope of this brief overview. However, it is of interest that the intestinal transport protein responsible for cholesterol transport has been tentatively identified.[8]

Ezetimibe has been reported to reduce intestinal cholesterol absorption by 54% from baseline in association with a compensatory increase in endogenous cholesterol synthesis.[9]

Effectiveness of ezetimibe in lowering LDL-C levels

A large number of dose ranging studies have assessed the effect of ezetimibe, used alone or in combination with statins, on plasma LDL-C levels.[9-22] These studies showed a decrease in LDL-C of the order of 12-23%. Such a reduction may initially appear to be relatively unimpressive. However, it has to be considered in relation to the 6-7% fall in LDL-C that is expected after doubling the initial dose of any statin. Thus, in many of these studies, the initial dose of a statin (e.g. atorvastatin or simvastatin 10 mg/day) together with ezetimibe 10 mg/day (the only dose of ezetimibe used in clinical practice) resulted in a similar decrease in LDL-C to that seen with the maximal dose of the statin (i.e. 80 mg/day) used alone.[13,16,21,22]

In a more recent (but yet unpublished study) the capacity of ezetimibe to achieve the NCEP ATP III target when added to a statin was assessed. In this study (Eze-

timibe Add-on to Statin for Effectiveness, EASE; n = 3,030), the net reduction (compared to placebo + statin) in LDL-C achieved with ezetimibe + statin was greater (of the order of 23%, depending on the patient subgroup) than that reported in the dose ranging studies. In the EASE study, the percentage of coronary heart disease (CHD) or CHD equivalent patients that reached the NCEP ATP III target was 70% in the ezetimibe + statin group and 17.3% in the placebo + statin group.

Based on our own experience, the reduction in LDL-C in three patient categories is:

(i) Those who cannot tolerate a statin: 27.8 ± 12.2%, n = 18, p<0.0001
(ii) Those who cannot tolerate a higher dose of a statin: 24.2 ± 12.2%, n = 6, p<0.0001
(iii) Those who cannot achieve the LDL-C target despite taking a statin: 33.2 ± 12.6%, n = 33, p<0.0001. In this group, 66.7% of these high-risk patients reached the NCEP ATP III goal (100 mg/dl; 2.6 mmol/l) after the addition of ezetimibe to their statin.

None of these patients had any change in their treatment, body weight (>5%), thyroid function or smoking status during the two month follow-up period (unpublished results: Daskalopoulou SS, Nair DR and Mikhailidis DP).

The side effect profile of ezetimibe is very good, with most trials showing equivalent results in the placebo and active treatment arms.[9-22]

There are as yet no extensive trials that have evaluated the use of ezetimibe together with fibrates. This will be an important category to establish, because the weakness of fibrates is their lack of LDL-C-lowering power.[23] However, fibrates are superior to statins in their capacity to raise high density lipoprotein cholesterol (HDL-C) and lower triglyceride levels.[23]

Other actions of ezetimibe

In addition to decreasing LDL-C, ezetimibe also raises the plasma HDL-C and lowers triglyceride levels by about 1.7-5% and 7.5-11.1%, respectively.[13,15,16,18] Although these changes are small, the associated gain in risk reduction, especially as a result of the rise in HDL-C levels is likely to be appreciable (of the order of 6%).[23]

There is also evidence showing that the use of ezetimibe in conjunction with a statin extends the reduction in serum high-sensitivity C-reactive protein (hs-CRP) levels. For example, ezetimibe plus simvastatin significantly reduced median hs-CRP levels compared with simvastatin monotherapy (-34.8% vs. -18.2%, p<0.01); incremental reductions were observed at each simvastatin dose level.[24] Co-administration of ezetimibe with atorvastatin provided a significant additional 10% reduction in hs-CRP compared with atorvastatin alone (p<0.01).[13] These findings may be relevant since CRP levels are considered as predictors of vascular risk.[13,24] These reductions do not seem to be linearly related to the fall in LDL-C achieved.[13,24]

Ezetimibe can also be used to treat rare lipid disorders such as sitosterolaemia.[25,26]

Recent trials supporting the benefits of aggressive LDL-C lowering

Two recently published key trials[27,28] comparing pravastatin (40 mg) with atorvastatin (80 mg) clearly showed the benefit of lowering LDL-C aggressively. The REVERSAL (Reversing Atherosclerosis with Aggressive Lipid Lowering) trial[27] in CHD patients (n=654) showed that those taking atorvastatin had significantly less atheroma burden as assessed by intravascular ultrasound of the coronary arteries after 18 months.

In the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22) trial[28] (n=4,162), atorvastatin significantly reduced the incidence of primary endpoints (relative risk reduction 16%; p=0.005) in patients post acute coronary syndrome after 24 months.

The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study[29] (n=1,600) showed the benefit of aggressive treatment (for 3 years) with atorvastatin to achieve the LDL-C target (< 100 mg/dl; 2.6 mmol/l) when compared with 'usual care' in CHD patients.

In the Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm (ASCOT-LLA) primary prevention trial[30] (n=10,305), comparing atorvastatin 10 mg with placebo, the mean LDL-C achieved in the treatment arm was 2.3 mmol/l (89 mg/dl). This was associated with significant benefits in several clinically relevant endpoints after 3.3 years of treatment.

The "lower is better for cholesterol reduction" topic has been reviewed in a previous issue of this journal.[31]

Concluding comments

With the introduction of stricter LDL-C goals for high-risk and very high-risk patients,[1-3] there is a

need for either more efficacious monotherapy or combination therapy. We have gone down this path many times before in medicine; for example, in the treatment of hypertension, cancer and infections.

How can we justify the use of ezetimibe, since we practice evidence based medicine and this drug does not yet have endpoint trials? Firstly, the side effect profile of ezetimibe is satisfactory. This has been demonstrated in many studies[9-22,24-26] and there have been no major scares despite its widespread use in many countries for the past two years. This situation differs from that of rosuvastatin where there have been some reservations expressed regarding its use, especially at higher doses.[32,33] Secondly, in high-risk patients prescribers will often have a choice: to reduce LDL-C levels further or to accept what has been achieved by statin monotherapy. In the light of the recent evidence,[27-30] it would appear that we should strive to achieve an LDL-C of 70 mg/dl (1.8 mmol/l), especially in very high-risk patients. Nevertheless, until event-based trials are available, the decision to add ezetimibe must remain within the discretion of the prescribing physician.

Finally, we have to consider the minority of patients who cannot tolerate statins or who develop adverse effects at higher doses of statins. As the use of statins increases, the number of patients that fall into this category (estimated as 5% of those started on a statin)[34] will rise. One treatment option for this minority group will be ezetimibe.

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