Ezetimibe added to statin therapy (EASY study)

An evaluation by Australian general practitioners

Leon A Simons

MD, FRACP, is Associate Professor of Medicine, University of New South Wales, and Director, Lipid Research Department, St Vincent's Hospital, Sydney, New South Wales. l.simons@notes.med.unsw.edu.au

Julie Symons

MSc, DipEd, is Acting Research Development Manager, External and Corporate Affairs, Merck Sharp & Dohme (Australia) Pty Limited, Sydney, New South Wales.

BACKGROUND

This study estimated changes in low density lipoprotein cholesterol (LDL-C) levels and proportion of patients attaining goal LDL-C <2.5 mmol/L when ezetimibe was added to existing statin monotherapy under Pharmaceutical Benefits Scheme (PBS) guidelines in a general practice setting.

METHODS

Target patients were those with coronary heart disease or diabetes mellitus eligible to receive ezetimibe under PBS guidelines. They were treated with ezetimibe 10 mg/day in addition to existing statin therapy for 6 weeks.

RESULTS

One hundred and thirty patients received treatment, but for effectiveness we derived a per protocol subpopulation of 95. Low density lipoprotein cholesterol was reduced by 29% (95% confidence limits, 25–34% reduction), and goal LDL-C <2.5 mmol/L was reached in 70% of patients (95% confidence limits, 59–79%). Six patients were withdrawn because of adverse events.

DISCUSSION

Changes in LDL-C and goal attainment in Australian general practice with the use of ezetimibe added to a statin were highly consistent with the findings from controlled clinical trials.

A large body of clinical trial data attests to the benefit of serum cholesterol reduction through statin therapy.[1] The National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand in 2001 suggested that goal low density lipoprotein cholesterol (LDL-C) should be <2.5 mmol/L.[2] Clinical trials published in 2004–2005 suggest that goal LDL-C should be lower still,[3,4] and by the end of 2005 these bodies had recommended a goal LDL-C <2.0 mmol/L for high risk patients.[5] An LDL-C <2.5 or <2.0 mmol/L will be difficult to achieve in some patients using diet plus statin therapy. The addition of ezetimibe, a novel inhibitor of cholesterol absorption, to ongoing statin therapy in controlled trials has achieved an additional 15–25% reduction in LDL-C and many more patients have achieved goal LDL-C levels.[6–8]

The present study sought to estimate the changes in LDL-C levels achieved and the actual rate of goal attainment when Australian general practitioners used ezetimibe in addition to a statin, in coronary heart disease (CHD) and diabetes patients eligible under the then current PBS guidelines.[9]

Methods

Study design

This was a phase IV, open label, single arm evaluation conducted in the general practice setting. Eighty-one GPs from around Australia enrolled to participate in the study; 43 of these GPs recruited at least one patient. Active general practice sites were distributed as follows: 13 sites in New South Wales, 12 in Queensland, seven in South Australia, seven in Western Australia and four in Victoria. Initially 300–500 patients were to be enrolled, but recruitment proved difficult and the required number of patients was later reduced to 120. Target patients were those with evidence of CHD or diabetes mellitus who had already used ≥40 mg/day of a statin for at least 3 months, and where current total cholesterol was >4.0 mmol/L for existing CHD or >6.5 for diabetes (or >5.5 for diabetes if high density lipoprotein (HDL) cholesterol is <1.0 mmol/L). These were the PBS subsidy guidelines at the time the study was conducted.[9]

Following consent procedures at an enrolment visit, patients were issued with ezetimibe 10 mg tablets to be taken once per day, in addition to their existing statin

therapy. Each patient was required to complete two documented study visits: the enrolment visit and a subsequent visit after 6 weeks therapy. The major reasons for study exclusion included triglycerides >4.0 mmol/L while using a statin and unstable or poorly controlled diabetes (HbA1c >9.0%). The study was conducted between February and November 2005. The protocol was approved by the National Research and Evaluation Ethics Committee of The Royal Australian College of General Practitioners (application NREEC 04-10) and patients gave informed, written consent.

Clinical and laboratory procedures

Standard clinical observations were performed at the enrolment and week 6 visits. Blood sampling was performed at enrolment or up to 4 weeks prior and repeated after approximately 6 weeks treatment with ezetimibe. Blood tests were recommended to be performed at the same local laboratory. Returned tablets were counted at week 6. Any adverse event was documented.

Sample size and statistical power considerations

No formal statistical tests were predefined in the protocol as the primary aims of the study were to estimate the percentage change in LDL-C and the proportion of patients achieving a goal LDL-C of <2.5 mmol/L, after 6 weeks treatment with ezetimibe. All effects estimated are presented as two sided 95% confidence limits. Based on 100/120 patients completing the program, the two sided 95% confidence interval for mean percentage change in LDL-C will have an interval extending no more than 3% from the observed mean, with 80% probability, assuming that the true standard deviation is 15%. For an anticipated mean change of 25%, the confidence limits would be no wider than 22–28%.

Table 1. Baseline characteristics of the intention to treat population (lipid values in mmol/L; mean and standard deviation for continuous variables)

Age (years)	65.6 ± 10.5
Males/females	77/53
Body mass index (kg/m^2)	29.7 ± 6.0
Statin use:	
• simvastatin	64 (49%)
• atorvastatin	49 (38%)
• pravastatin	16 (12%)
• fluvastatin	1 (1%)
Coronary heart disease	89 (68%)
Diabetes mellitus	53 (41%)
LDL cholesterol	3.1 ± 1.0
Total cholesterol	5.6 ± 1.2
HDL cholesterol	1.4 ± 0.4
Triglycerides	2.4 ± 1.9
HbA1c (%) (diabetics only)	7.5 ± 1.4

Results

One hundred and thirty patients consumed at least a single dose of ezetimibe. For drug safety purposes this group was analysed on an 'intention to treat' (ITT) basis. Entry characteristics of the ITT population are summarised in *Table 1*.

The ITT population was reduced by 35 patients (nine lost to follow up, 10 withdrawals [six because of adverse events], five with triglycerides >4.0 mmol/L, four with HbA1c >9.0% and seven with missing LDL-C data). As a result, the changes in LDL-C and other outcomes were analysed on a 'per protocol' (PP) basis in 95 patients (*Table 2*). Medicine containers were returned by 56 patients in the PP population. The average intake of test medication in these patients was 99%, range 60–130%.

Lipid levels at baseline in the PP population were broadly similar to those in the ITT population (*Tables 1* and *2*). Other features were also similar in the PP population (mean age 66.2, males 62%, mean body mass index 29.2, CHD 77%, diabetes 36%, simvastatin 47%). The changes in LDL-C levels after 6 weeks treatment are summarised in *Table 2*. LDL-C was reduced by 29%, with 95% confidence limits between 25 and 34% reduction. A goal LDL-C <2.5 mmol/L was reached in 70% of patients (95% confidence limits 59–79%). A goal LDL-C <2.0 mmol/L was reached in 50% of patients (39–60%). A multiple logistic model was used to evaluate prediction of achieving LDL-C goal <2.5 mmol/L. Entry LDL-C was the only significant predictor (odds ratio 0.19, 95% confidence limits, 0.08–0.45) in a model which included age, gender, CHD and diabetes status.

The changes in other lipid parameters are presented in *Table 2*. Total cholesterol was reduced by 19%, triglycerides were reduced by 11%, but there was no significant change in HDL cholesterol.

A summary of the nine adverse events reported during the study is presented in *Table 3*. Six patients required withdrawal of ezetimibe, which was followed by complete recovery. There were no significant changes in HbA1c, liver or muscle enzymes.

Table 2. Summary of changes in lipid levels in per protocol population (lipid values in mmol/L.; mean and standard deviation)

	Baseline (on a statin ≥40 mg for at least 3 months)	6 weeks (after treatment with ezetimibe 10 mg/day added to existing statin)	% change (95% confidence limits)
LDL cholesterol	3.0 ± 1.0	2.1 ± 0.9	–29 (–34, –25)
Total cholesterol	5.3 ± 0.9	4.3 ± 0.9	–19 (–21, –16)
HDL cholesterol	1.4 ± 0.4	1.4 ± 0.4	+3 (0, 6)
Triglycerides	2.0 ± 0.9	1.7 ± 0.8	–11 (–16, –5)

Discussion

Randomised, placebo controlled trials with statin drugs have clearly shown prevention of CHD and atherosclerotic stroke in subjects with or without prior cardiovascular disease.[1,3–5] Overall, the trials demonstrate a significant 12% reduction in all cause mortality for each 1 mmol/L reduction in LDL-C. This reflects a 19% reduction in coronary mortality, a 23% reduction in myocardial infarction or coronary death, or a 17% reduction in stroke over 5 years treatment.[1] The in trial reduction in CHD events is 25–30%, depending upon the patient group studied, and this is achieved with an acceptably low rate of adverse events.[5] These are reductions in relative risk. In the context of secondary prevention, the reductions in absolute risk are substantially greater.[1,2] While these are positive outcomes, it also appears that around 70% of patients destined to suffer an event in a 5 year trial will not benefit. This is the biggest challenge we face in the poststatin era.

Table 3. Summary of adverse events reported during the study

ID#*	Description	Action taken	Outcome	Relationship to study medication†
A	Dry skin rash	Rx§ interrupted	Continues	Probably not
B	Nausea and myalgia	Rx reduced	Continues	Probably
C	Nausea	Rx withdrawn	Recovered	Possibly
D	Palpitations, swollen lip	Rx withdrawn	Recovered	Probably
E	Leg pain	None	Continues	Probably not
F	Nausea/abdominal pain	Rx withdrawn	Recovered	Possibly
G	Oedema to lips, mouth	Rx withdrawn	Recovered	Possibly
H	Abdominal colic/gas	Rx withdrawn	Recovered	Definitely
I	Palpitations/dizziness	Rx withdrawn	Recovered	Probably

* Not actual study ID numbers
† Relationship of adverse event to study medication, ezetimibe, is the opinion of the GP
§ Rx = treatment

Although statins have effects beyond LDL-C reduction, these same trials also indicate that much of the benefit derived is related to LDL-C reduction. A philosophy has gradually emerged: 'LDL-C, the lower the better'.[4,10,11] Unfortunately, many patients do not reach goal LDL-C for reasons such as poor compliance, inadequate dose titration of statin or lack of efficacy of statin therapy.[12] The addition of ezetimibe to ongoing statin therapy in controlled trials has achieved an additional 15–25% reduction in LDL-C and many more patients have achieved goal LDL-C levels.[6–8]

It is recognised that patients enrolled in formal clinical trials may not always be representative of those seen in general practice. For example, those with multisystem disease, those on multiple medications and those with a past history of adverse events are often excluded. The present study was a short term examination of ezetimibe use under genuine field conditions, where Australian GPs could decide to prescribe ezetimibe in addition to existing statin therapy with few severe exclusions but with the need to satisfy PBS Authority requirements.

In such a setting we observed a 29% reduction in LDL-C, with 70% of patients reaching target LDL-C <2.5 mmol/L. While this finding is highly consistent with results from earlier controlled trials, care should be taken in making comparisons with other studies due to differences in entry cholesterol levels and selection of statin type and dose. In one multinational study however, with a broadly similar entry LDL-C level on statin (3.6 mmol/L), the reduction in LDL-C when ezetimibe 10 mg/day was added to a range of statins was 25% and the percentage of patients reaching target LDL-C <2.6 mmol/L was around 75%.[6]

In theory it would be easier for both doctor and patient to increase the dose of statin rather than add a second drug such as ezetimibe. In one study where the dose of atorvastatin was doubled from 10 to 20 mg/day, the additional LDL-C reduction achieved was only 9%. But the addition of ezetimibe to ongoing atorvastatin at 10 mg/day achieved a much greater LDL-C reduction of 24%.[13] Similar contrasts in LDL-C were noted when ezetimibe was added to a fixed dose of simvastatin compared with doubling of statin dose.[14]

The dose of statin most frequently observed at entry in the present study was 40 mg/day (65% of patients), but it should be noted that this study was neither designed nor powered to define any interaction between statin dose and use of ezetimibe. In terms of effect on triglycerides, ezetimibe added to statin resulted in a modest lowering, while changes in HDL cholesterol were minimal (*Table 2*), as reported in previous studies.[6–8]

We acknowledge some limitations with the present study: we could not recruit the larger number of patients envisaged, the study was uncontrolled, and the study duration was relatively short (but long enough to establish effectiveness). There were also some anticipated difficulties associated with conduct of a field evaluation in general practice, such as patients being lost to follow up, protocol violations at entry, and some documentation not provided. Despite these challenges, the value of assessing effectiveness of medications in a less controlled way is still important. Finally, the rate of adverse events noted was acceptably low and these events were entirely consistent with information already contained in the product information for ezetimibe.

Implications for general practice

- Statin therapy reduces CHD risk by 25–30%, but there remains a high residual risk.
- A proportion of patients on statin therapy do not achieve goal lipid levels.
- Low density lipoprotein cholesterol is reduced by a further 29% in this study when ezetimibe 10 mg/day is added to existing statin therapy of ≥40 mg.
- An LDL-C goal of <2.5 mmol/L is reached by 70% of patients with this treatment.
- Adding ezetimibe to statin therapy offers an alternative approach when patients with CHD or diabetes have not reached goal LDL-C on statin therapy alone.

Conflict of interest: this study was funded by Merck Sharp & Dohme (Australia) Pty Limited and Schering-Plough Pty Ltd, suppliers of Ezetrol® (ezetimibe). Protocol design was the responsibility of the authors and the sponsor, while data reduction and statistical analysis was conducted by an independent third party, Statistical Revelations Pty Ltd, Melbourne. Professor Simons received consultancy fees in relation to his role as principal investigator. Ms Symons is Acting Research Development Manager, External and Corporate Affairs, Merck Sharp & Dohme (Australia) Pty Limited, Sydney.

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afp **CORRESPONDENCE** email: afp@racgp.org.au