

Colesevelam: new alternative or adjunctive treatment to statins

Steve Chaplin MSc, MRPharmS and Paul Durrington BSc, MD, FRCPath, FRCP, FMedSci

KEY POINTS

- colesevelam (Cholestagel) is a bile acid sequestrant for the treatment of hypercholesterolaemia, licensed (in combination with diet) as monotherapy in patients for whom a statin is unsuitable or in combination with a statin when target lipid levels are not achieved by a statin alone
- available as 625mg tabs (180 = £92.66)
- compared with placebo, in patients with LDL-C about 4mmol per litre, monotherapy with colesevelam reduces LDL-C by 9-15 per cent
- compared with a statin alone, in patients with LDL-C greater than 4.14mmol per litre, the addition of colesevelam further reduces LDL-C by about 10 per cent (or approximately 0.5mmol per litre)
- the combination of colesevelam plus a statin has not been evaluated in patients for whom statin monotherapy fails to achieve target LDL-C
- the commonest adverse effects are increased triglyceride levels (only with monotherapy), constipation and dyspepsia



Colesevelam (Cholestagel) is a new bile acid sequestrant for treating hypercholesterolaemia either alone or in combination with a statin. Here, Steve Chaplin describes the clinical trial data relating to its efficacy and safety, and Professor Durrington comments on its place in reducing raised cholesterol levels.

Statins are the drugs of choice for lowering lipid levels in patients with hypercholesterolaemia when diet alone is unsuccessful. Alternatives for patients unable to tolerate a statin, for whom a statin is contraindicated or who need adjunctive therapy because target levels are not achieved with a statin alone include ezetimibe, a fibrate, nicotinic acid or a bile acid sequestering agent such as colestyramine or colestipol (Colestid).¹

The *BNF* recommends that combination treatment should be supervised by a specialist; in particular, combinations of a statin with a fibrate or nicotinic acid are associated with an increased risk of adverse effects.² The NICE clinical

guideline on secondary prevention of myocardial infarction³ makes no recommendations for the choice of a second-line agent.

The technology

Colesevelam hydrochloride is a bile acid sequestrant licensed as an adjunct to a statin plus diet to reduce LDL-cholesterol (LDL-C) levels in patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone, and as monotherapy as an adjunct to diet to reduce total and LDL-C in patients with isolated primary hypercholesterolaemia in whom a statin is considered inappropriate or is not well tolerated.

Colesevelam is not absorbed systemically. It binds bile in the

intestine, interrupting its enterohepatic recirculation. The resulting depletion of the bile pool increases hepatic demand for cholesterol and is associated with an increase in hepatic LDL-C receptors; clearance of LDL-C is increased, lowering serum levels. There is also an increase in very low-density lipoproteins, resulting in an increase in triglyceride levels.

The recommended dose of colesevelam as monotherapy is three 625mg tablets twice daily or six tablets once daily (3.75g per day); the maximum dose is seven tablets per day. As an adjunct to a statin, the recommended dose is four to six tablets daily (2.5-3.75g per day), either as a single or

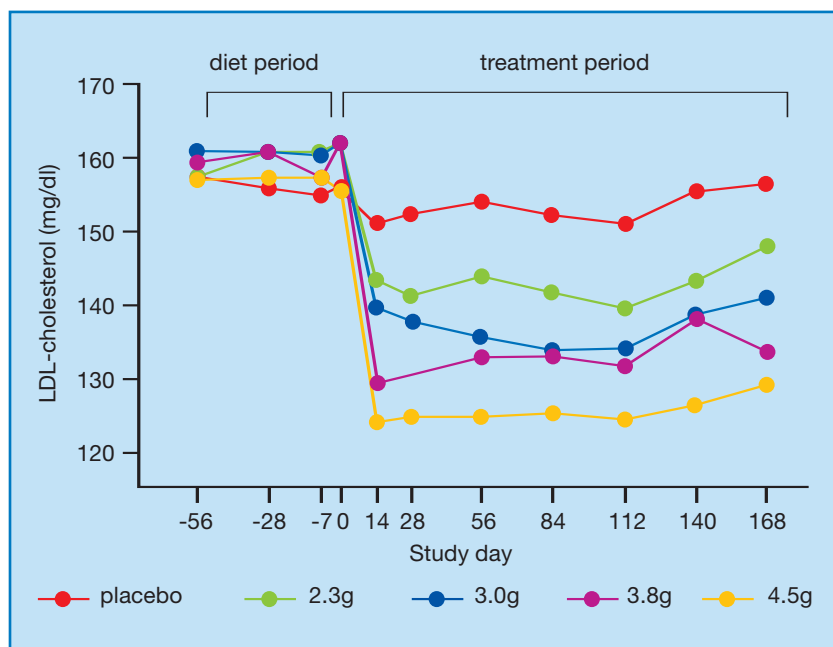


Figure 1. Dose-dependent reduction in LDL-cholesterol over 24 weeks' treatment with 2.3, 3.0, 3.8 and 4.5mg colesevelam daily⁵

divided doses; the maximum dose is six tablets per day. Colesevelam should be taken with a meal; no dose adjustment is necessary for older people.

Patients should be using a cholesterol-lowering diet; serum total cholesterol, LDL-C and triglyceride levels should be measured before treatment with colesevelam and periodically thereafter.

Colesevelam is contraindicated in patients with bowel or biliary obstruction. Caution is needed in patients with hypertriglyceridaemia >3.4mmol per litre (who were excluded from trials) and those with impaired gastrointestinal motility (dysphagia, swallowing disorders, severe gastrointestinal motility disorders, inflammatory bowel disease, liver failure or major gastrointestinal tract surgery) or constipation.

Anticoagulant therapy should be monitored closely in patients receiving warfarin or similar agents, since bile acid sequestrants have been shown both to reduce absorption of vitamin K and to

interfere with warfarin's anticoagulant effect.

Clinical trials

Key clinical evidence for colesevelam comprises one placebo-controlled trial and three studies of combined treatment with a statin.⁴⁻⁸ It has also been shown to have additive lowering effects on LDL-C levels in combination with ezetimibe^{9,10} and fenofibrate¹¹ but these combinations are not currently licensed. No comparative trials with colestyramine or colestipol have been published.

In the largest trial, 494 patients with LDL-C 3.3-5.6mmol per litre and a triglyceride level of 3.4mmol per litre or less after four weeks of a low-fat diet were randomised to placebo or colesevelam 2.3, 3.0, 3.8 or 4.5g per day; the primary endpoint was the mean change in LDL-C.⁵ Mean LDL-C at baseline was approximately 4.0mmol per litre.

A total of 382 patients completed 24 weeks of treatment, with similar proportions withdrawing from the trial in each group.

Colesevelam reduced LDL-C in a dose-dependent manner (see Figure 1). Mean final reductions in LDL-C were 0mmol per litre with placebo and 0.36mmol per litre (9 per cent of baseline), 0.49mmol per litre (12 per cent), 0.62mmol per litre (15 per cent) and 0.73mmol per litre (18 per cent) for increasing doses of colesevelam (all statistically significantly different from placebo).

Colesevelam also increased HDL-C (median 3-4 per cent *vs* -1 per cent with placebo) and triglyceride levels (median 5-10 per cent *vs* 5 per cent with placebo) with no clear relationship between dose and response.

In comparative trials in patients with mean baseline LDL-C greater than 4.14mmol per litre, the reduction in LDL-C achieved with colesevelam 2.3 or 3.8g per day was less than that observed with statin monotherapy.⁶⁻⁸ The combination of a statin plus colesevelam achieved a significantly greater reduction in LDL-C than a statin alone, equivalent to an additional reduction of 10-16 per cent (or approximately 0.5mmol per litre) compared with atorvastatin (Lipitor) 10mg per day or simvastatin 20mg per day.

Combination therapy reduced LDL-C below 3.0mmol per litre in all patients. By contrast with colesevelam monotherapy, the combination with a statin did not increase triglyceride levels.

These trials did not evaluate combined treatment in patients for whom statin monotherapy had been unsuccessful.

Adverse effects

The commonest adverse events reported in clinical trials were flatulence (11 *vs* 13 per cent with placebo), constipation (10 *vs* 6 per cent) and dyspepsia (6 *vs* 2 per cent). Triglyceride levels exceeded

7mmol per litre in 2 per cent of patients taking colesvelam and none taking placebo.

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By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

Colesvelam is a bile acid sequestering agent, a class of drugs already represented by colestyramine and colestipol. Unlike these, it is in tablet form and reportedly better tolerated. But why do we need any drugs other than statins to regulate LDL-C when the more potent statins can decrease LDL-C by more than 50 per cent? Some patients, of course, have such high pretreatment LDL levels that even with the maximum dose of the most potent statin they do not achieve a low enough target, so adjunctive therapy may be required.

Statin intolerance

There is, however, another group of patients in whom nonstatin drugs may be required: those who are considered intolerant of statins. Usually their statin treatment has been stopped because their GP has

found a rise in creatine kinase (CK) or abnormal serum liver function tests or because the patients have experienced aching in their limbs (as often as not involving joints or ligaments rather than muscles and local rather than generalised) and are convinced that they have statin-induced myalgia.

The explanation for these cases should be considered in the context of randomised, placebo-controlled statin trials. These show a high incidence of complaints of 'myalgia', both on placebo and active statin. One would expect this because aching in the muscles, joints and tendons is part of an active life, and the rate is only minutely greater in the actively treated patients.

The incidence of true myositis (CK >10 times upper limit of normal + symptoms) has been estimated to be <1 in 10 000 patient years. More minor elevations in CK unrelated to statin treatment are common because the upper limit

of normal set by laboratories is too low for physically active people. Often doctors, too, are unaware that CK levels may run at high levels in people of African origin, and those who exercise or have physically demanding occupations, regardless of whether they receive statin treatment.

The usual reason for the so-called rise in liver transaminases and gamma-glutamyl transpeptidase (GGT) – again only slightly more prevalent on active statin in placebo-controlled trials – is the higher frequency of nonalcoholic steatohepatitis in patients with dyslipidaemia. Once these enzyme activities are raised or close to the upper limit of normal as a consequence of fatty liver, they exhibit greater day-to-day variation and the impression can be gained that they are rising when they are not.

Given the great benefit of statins (a 21 per cent decrease in cardiovascular disease risk for each 1mmol per litre decrease in LDL-C)

clinicians should be wary of diagnosing statin intolerance, and in patients convinced they have statin-induced myalgia they should provide gentle encouragement and, if necessary, try the full gamut of different statins before giving up.

Alternatives

It is in this clinical context that alternative or adjunctive lipid-lowering drugs to statins must find their clinical role. Fibrates are under something of a cloud. With the exception of gemfibrozil, trial evidence has not convincingly shown that they decrease cardiovascular mortality, and gemfibrozil is the least suitable to combine with statin treatment.

It is in this environment that ezetimibe, a nonstatin cholesterol-lowering agent, has flourished. It has

recently been the subject of a NICE assessment and deemed cost-effective in high-risk patients intolerant of statins (although not approaching even the most expensive statin in this regard). The assessment was based not on any direct trial evidence for the clinical efficacy of ezetimibe, which is non-existent, but on a model of statin-induced LDL lowering.

Colesevelam, which will compete for the same niche market as ezetimibe, is also lacking direct evidence for clinical efficacy, but there is at least evidence for this class of drug from a primary prevention trial involving colestyramine, the Lipid Research Clinics (LRC) trial. In this a 19 per cent decrease in CHD risk compared to placebo was observed for a 12 per cent decrease in LDL-C.¹

Colesevelam thus represents a possible means of LDL reduction in genuinely statin-intolerant patients and those with particularly high cholesterol levels who require a greater reduction in LDL-C than can be achieved with the maximum tolerated or maximum licensed doses of statin drugs. Proof of its clinical efficacy and cost-effectiveness would strengthen such a view.

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By Paul Durrington, professor of medicine and leader of the Lipoprotein Research Group, Manchester University