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Title **Ezetimibe for the Treatment of Hypercholesterolemia: A Systematic Review and Economic Evaluation**

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Aim

To review the clinical and cost effectiveness of ezetimibe as a combination therapy or monotherapy in treating primary (heterozygous familial and nonfamilial) hypercholesterolemia in the UK.

Conclusions and results

Evidence from short-term, randomized controlled trials (RCT) demonstrates that ezetimibe is effective in reducing low-density lipoprotein cholesterol (LDL-c) when administered as monotherapy or in combination with a statin. However, when used as a monotherapy, ezetimibe's LDL-c lowering ability was less than that of statins alone. The cost effectiveness of ezetimibe is uncertain, but the economic model suggests that ezetimibe could be cost effective in treating individuals with high baseline LDL-c values, patients with diabetes, and individuals with heterozygous familial hypercholesterolemia. No published clinical outcome trials (>12 weeks) examining the cardiovascular benefit of ezetimibe were identified. In the absence of clinical endpoint data from trials, 13 (5 were multi-arm) phase III multicenter RCTs (of varying methodological quality) of short-term duration (12-48 weeks) with surrogate endpoint data (eg, LDL-c and total cholesterol [Total-c]) were included. For patients not adequately controlled with a statin alone, a meta-analysis of 6 studies showed that a fixed-dose combination of ezetimibe and statin treatment was associated with a statistically significant reduction in LDL-c and Total-c compared with statin alone (p<0.00001). Four studies that titrated the statin doses to LDL-c targets generally showed that the co-administration of ezetimibe and statin was significantly more effective in reducing plasma LDL-c concentrations than statin monotherapy (p<0.05 for all studies). For patients where a statin was considered inappropriate, a meta-analysis of 7 studies demonstrated that ezetimibe monotherapy significantly reduced LDL-c levels compared with placebo (p<0.00001). There were no statistically significant differences in LDL-c-lowering effects across subgroups. Ezetimibe therapy (either combined with a statin or monotherapy) appeared to be well tolerated compared to statin monotherapy or placebo, respectively. No ezetimibe studies reported data on health-related quality of life. Economic results varied widely depending on the treatment strategies evaluated. When comparing ezetimibe monotherapy with no treatment in individuals with baseline LDL-c values of 3.0-4.0 mmol/l, the results ranged from 21 000 pounds sterling (GBP) to GBP 50 000 per quality-adjusted life-year (QALY). Results for individuals with baseline LDL-c values over 5.0 mmol/l were below GBP 30 000 per QALY. When comparing the costs and benefits of adding ezetimibe to ongoing statin treatment compared with maintaining statin treatment at the current dose, most results were above values generally considered to be cost effective (GBP 19 000 to 48 000 per QALY). See Executive Summary link at www.hta.ac.uk/project/1529.asp.

Recommendations

See Executive Summary link at www.hta.ac.uk/project/1529.asp.

Methods

See Executive Summary link at www.hta.ac.uk/project/1529.asp.

Further research/reviews required

1) Long-term studies reporting clinical outcome data, direct comparisons with other lipid-lowering treatments, and data from patients who are truly intolerant of statins. 2) Lifetime adherence to combination therapies in relatively healthy younger and asymptomatic patients with no history of CVD. 3) Establish if reductions in lipids to predetermined targets provide additional reductions in cardiovascular events.

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