Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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Lipid modification: Evolocumab and clinical outcomes in patients with cardiovascular disease

Evolocumab (Repatha) belongs to a new class of lipid modification drugs that act as inhibitors of proprotein convertase subtilisin-kexin type 9 (PCSK9). The 'Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)' clinical trial of evolocumab is the first to evaluate the effects of this drug class on cardiovascular (CV) outcomes. In this study, which recruited people with a history of CV disease and who were receiving moderate-to-high intensity statins, evolocumab resulted in a 1.5% absolute risk reduction at 22 months in several composite CV outcomes. The risks for some individual non-fatal CV events were also reduced, but there was no observed effect on CV or overall mortality in this study.

Reference: Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. DOI: 10.1056/NEJMoa1615664

What do we know already?

- Evolocumab (Repatha) is a monoclonal antibody that inhibits the action of PCSK9, an enzyme involved in the degradation of low density lipoprotein (LDL) receptors on the surface of hepatocytes. Inhibition of PCSK9 leads to lower plasma LDL levels. Alirocumab (Praluent) is also a member of this drug class.
- Evolocumab has been licensed for the treatment of primary hypercholesterolaemia (heterozygous familial and non-familial), mixed dyslipidaemia and homozygous familial hypercholesterolaemia (see Summary of Product Characteristics [SPC] for full details). Administered by subcutaneous injection, the recommended dose of evolocumab for primary hypercholesterolaemia is 140 mg every 2 weeks or 420 mg once monthly (both doses being clinically equivalent). Higher doses may be used in homozygous familial hypercholesterolaemia. Annual treatment costs are £4,423 for 140 mg every 2 weeks and £6,124.60 for 420 mg monthly.
- In June 2016, NICE published guidance recommending evolocumab as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia only if:
    - the dosage is 140 mg every 2 weeks
    - LDL concentrations are persistently above the thresholds specified in the guidance, despite maximal tolerated lipid-lowering therapy
    - it is provided via the approved patient access scheme.
- With respect to disease oriented outcomes, evolocumab and alirocumab have been shown to reduce LDL concentrations by around 60% (see respective SPCs), and in the case of evolocumab induce regression of atherosclerosis in patients with coronary heart disease. However, the impact of PCSK9 inhibitors on patient-oriented CV outcomes and mortality was previously unknown.

What does this evidence add?

- FOURIER is a randomised, double-blind, placebo-controlled multinational trial investigating evolocumab when added to high- or moderate-intensity statin therapy in patients with clinically evident atherosclerotic CVD.
- Over the study's 2.2 year median follow-up period, relative to placebo, evolocumab produced a:
    - **15%** relative risk reduction in the primary endpoint (*a composite of CV death, myocardial infarction [MI], stroke, hospitalisation for unstable angina or coronary revascularisation*), and
    - a **20%** relative risk reduction in the secondary endpoint (*a composite of CV death, MI or stroke*).

  Absolute risk reductions were 1.5% for both outcomes. Overall, 74 patients needed to be treated over a period of 2 years to prevent one CV death, MI or stroke.
- Whilst evolocumab reduced the risk of CV events (although not mortality), the extent of the efficacy seen in this study of high risk patients with an average body weight of 85kg should be considered alongside treatment costs for PCSK9 inhibitors. Would better value for money be gained through promotion of lifestyle advice for such patients, including weight loss, increased exercise and smoking cessation (28% of participants in this study were smokers)? A recent review in The Lancet has warned that whereas statins are now generic and low cost, newer agents are costly and

there may be commercial pressure to create a market for PCSK9 inhibitors by highlighting claims of statin intolerance to justify the use of these newer agents – claims which are not supported by large-scale evidence from randomised trials.

- It has been suggested that prolonged exposure to extremely low LDL cholesterol levels may negatively affect neurocognitive function and may result in impaired delivery of fat-soluble vitamins. This study showed no signal of such adverse effects but ongoing surveillance of patients receiving longer term treatment will clearly be needed.

Study details

Participants:

- Between February 2013 and June 2015, 27,564 patients (24.6% women) at 1,242 sites in 49 countries were recruited for this study. Participants had to be aged between 40 and 85 years (mean age was 63 years) and have clinically evident atherosclerotic disease, defined as a history of MI (*in 81.1% of participants*), non-haemorrhagic stroke (*19.4%*) or symptomatic peripheral artery disease (*13.2%*) plus other characteristics that classed them as being at higher CV risk.
- Patients also had to have a fasting LDL cholesterol level of 70 mg per decilitre (1.8 mmol per litre) or higher, or a non-HDL cholesterol level of 100 mg per decilitre (2.6 mmol per litre) or higher while taking an optimised level of lipid-lowering therapy.
- At baseline, 69.3% of patients were taking high-intensity statin therapy (at least atorvastatin 20 mg daily or equivalent) and 30.4% moderate-intensity statin therapy. 5.2% were also taking ezetimibe.
- The use of other secondary prevention drugs was high, with 92.3% of patients taking anti-platelet therapy, 75.6% taking beta-blockers and 78.2% taking an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, an aldosterone antagonist, or both at trial entry.

Intervention:

- Participants were randomised (allocation concealed) in a 1:1 ratio to receive either subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month, according to patient preference) or matching placebo.

Outcomes and results:

- The primary efficacy endpoint was a composite of CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation. The key secondary efficacy endpoint was a composite of CV death, MI or stroke.
- All efficacy analyses were conducted on an intention-to-treat basis and no imputation was performed for missing data on clinical outcomes. Safety outcomes included all patients who underwent randomisation and received at least one dose of a study agent.
- The executive committee and Amgen, the trial sponsor, calculated that 1,630 end-point events were required to provide 90% power to detect a 15% relative risk reduction with evolocumab compared with placebo. Originally the study was planned to run for about 4 years, but this pre-specified number of events accrued more quickly than anticipated, and the study was terminated early, resulting in a median follow-up of 2.2 years.
- At 48 weeks, the mean percentage reduction in LDL cholesterol levels with evolocumab was 59% compared with placebo.
- Relative to placebo, evolocumab significantly reduced the risk of the primary endpoint by 15% (1,344 patients [9.8%] *vs.* 1,563 patients [11.3%]; hazard ratio, 0.85; 95% CI: 0.79 – 0.92; $p < 0.001$) and the key secondary endpoint by 20% (816 patients [5.9%] *vs.* 1,013 patients [7.4%]; hazard ratio, 0.80; 95% CI: 0.73 – 0.88; $p<0.001$). Absolute risk reductions were 1.5% for both these outcomes.
- The magnitude of the risk reduction for the primary endpoint increased over time, from 12% in the first year to 19% beyond the first year. Similarly, the risk reduction for the secondary endpoint increased from 16% in the first year to 25% beyond the first year.
- Evolocumab had no observed effect on CV mortality. There were reductions of 21% to 27% in the risk of MI, stroke and coronary revascularisation but no observed effect on the rates of hospitalisation for unstable angina, CV death or hospitalisation for worsening heart failure, or death from any cause.
- Benefits of evolocumab for both dosing regimens were consistent across major sub-groups, including age, sex and type of atherosclerotic disease, quartiles of baseline LDL cholesterol levels and intensity of statin therapy (irrespective of ezetimibe use).
- Overall, 74 patients would need to be treated over a period of 2 years to prevent a CV death, MI or stroke.
- 27,525 patients (99.9%) received at least one dose of a study agent and premature permanent discontinuation of the study regimen occurred in 12.5% of patients, with similar rates in the two groups.
- There were no significant differences between the study groups with regard to adverse events, with the exception of injection site reactions, which were rare but more frequent with evolocumab (2.1% *vs.* 1.6%). 90% of reactions were classified as mild. 0.1% of patients in each group stopped receiving the study agent because of an injection site reaction.

  The rates of new-onset diabetes and allergic reactions did not differ significantly between groups and the development of neutralising antibodies did not occur in any patient.

Level of evidence: Level 1 (good quality patient-oriented evidence) according to the SORT criteria.

Study funding: The study was supported by the manufacturer of evolocumab (Amgen).