Evolocumab and clinical outcomes in patients with cardiovascular disease

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Summary

Ischaemic heart disease remains the leading cause of death worldwide.[1] Decades of research have established that the accumulation of the cholesterol cargo carried by low density lipoprotein particles within the arterial wall is the initiating factor in atherogenesis and its clinical manifestation as coronary artery disease. Large scale epidemiological studies, mendelian randomisation genetic studies and trials of therapeutic interventions have established that low density lipoprotein cholesterol (LDL-C) is a causal factor in developing atherosclerotic heart disease.[2–5] The mainstay of therapy for reducing LDL-C has so far been with statin therapy initially followed by add-on therapy. Despite current lipid lowering therapies, a proportion of patients either fail to reach their target LDL-C with statins or are intolerant to statins thus limiting treatment options. While ezetimibe can be used as an add-on or alternative to statins, the modest 20% reduction in LDL-C precludes more widespread use. There is therefore, an unmet need for further LDL-C reduction with new treatments, among those with high atherosclerotic cardiovascular disease risk such as those with prevalent disease or with familial hypercholesterolaemia.

Since its discovery in 2003, the proprotein convertase subtilisin/kexin type 9 (PCSK9) pathway has rapidly come to the forefront of medicine from understanding its biology, its causal role in cardiovascular disease to now becoming the next therapeutic target in cardiovascular disease prevention.[6] A variety of approaches is being tested for PCSK9 inhibition; however, of those, the only drug therapy licensed for use both in the USA and the European Union is monoclonal antibody (mAb) therapy. Three mAbs have been in development to target PCSK9 but only two are currently licensed. Alirocumab, developed by Sanofi and Regeneron, and evolocumab developed by Amgen, are both fully human mAbs to PCSK9. The third was a humanised mAb called bococizumab produced by Pfizer. In November 2016, while recruiting for a Phase III trial, Pfizer announced it was withdrawing the development programme for bococizumab due to the presence of anti-drug neutralising antibodies which reduced its efficacy over time.

There are two clinical trial programmes established to study evolocumab and alirocumab (PROFICIO and ODYSSEY, respectively). From these, Phase III trial data with alirocumab and evolocumab have demonstrated significant reductions of over 50% in LDL-C beyond those achieved with statin therapy. Populations studied included those who were intolerant of statin therapy, at high risk of atherosclerotic cardiovascular disease or suffered with familial hypercholesterolaemia. From a safety perspective, reported adverse events were generally low and similar between treatment and control groups; no adverse neurocognitive effects were reported.

One of the outstanding questions has been whether reductions in LDL-C levels by monoclonal antibodies to PCSK9 would translate into improved cardiovascular outcomes in the long term. In the IMPROVE-IT trial, non-statin lipid lowering therapy in statin-treated individuals led to further reductions in LDL-C to a mean of 1.40 mmol/L and additional reductions in major adverse cardiovascular events.[7] Would a third drug class which reduces LDL-C levels to around 0.78 mmol/L also reduce cardiovascular disease risk?

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial was

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the first cardiovascular outcomes trial investigating PCKS9 inhibitors and specifically investigated evolocumab. In this placebo-controlled trial in 27,564 patients with previous myocardial infarction, ischaemic stroke or symptomatic peripheral vascular disease and an LDL ≥ 1.81 mmol/L or a non HDL-C ≥ 2.59 mmol/L on optimised statin therapy, were randomised to receive evolocumab 140 mg every 2 weeks or 420 mg every month or placebo. The levels of high and moderate intensity statin therapy were 69.5% and 30.2% in the treatment arm compared to 69.1% and 30.7% in the control arm. The primary efficacy endpoint was the time to major cardiovascular events defined as cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina or coronary revascularisation. The key secondary efficacy endpoint was the time to cardiovascular death, myocardial infarction or stroke. The study was event-driven and continued until at least 1,630 patients experienced a key secondary endpoint. Median duration of follow-up was 26 months. In March 2017, results from the FOURIER study were presented.[8]

The FOURIER trial demonstrated a 59% mean reduction in LDL-C in the evolocumab group compared to placebo to a median of 0.78 mmol/L. The reduction in LDL-C was maintained over time. The addition of evolocumab to statin therapy resulted in a significant reduction of 15% in the primary composite endpoint and 20% reduction in the secondary endpoint. There was a consistent benefit across all subgroups, including those on high-intensity statin and with a low LDL-C at baseline. These findings are consistent with findings from statin trials with reductions in major adverse cardiac events per mmol/L reduction in LDL-C.[9] The degree of risk reduction increased over time (from 12% in the first year to 19% beyond the first year with regards to the primary endpoint and from 16% to 25% beyond the first year for the secondary endpoint). There was no significant difference between study groups with regards to adverse events. There was additionally no observed difference in cardiovascular mortality when comparing between high intensity and moderate intensity statin therapy. This is consistent with other trial data.[9] Looking at individual outcomes, evolocumab had no effect on cardiovascular mortality but there were significant reductions of 21–27% in the risk of myocardial infarction, stroke and coronary revascularisation. There was also no effect on the rates of hospitalisation for unstable angina or worsening heart failure, cardiovascular death or death from any cause.

Opinion

Given the accrued benefits in risk reduction over time, one criticism of this trial is the short duration of follow-up. In FOURIER, median duration of follow-up was 26 months as opposed to the 4 year follow-up that was originally planned. The short follow-up was attributed to a 50% higher event rate than had been postulated and a rapid increase in sample size such that the last 10,000 patients recruited only had about 1 year of follow up. Of note, the definition of cardiovascular death included death due to heart failure, death due to cardiovascular haemorrhage (including stroke and aortic aneurysm) and death due to other cardiovascular causes (including pulmonary embolism or peripheral arterial disease), thus including events which may not be modifiable by lipid lowering therapy (which principally reduces atherosclerotic events).

Another criticism has been that cardiovascular risk reduction was less than expected when compared to the 2005 predictions by the Cholesterol Treatment Trialists.[5] The composite endpoint in FOURIER, however, included hospitalisation for unstable angina which was not included in the CTT trial and a much shorter duration of follow up.

This trial has many positives. In a population with stable vascular disease including coronary artery disease, cerebrovascular and peripheral arterial disease, it confirms that cardiovascular risk is further reduced by non-statin lipid lowering therapy. Additionally, LDL-C levels below 1.8 mmol/L down to 0.78 mmol/L are safe and well tolerated. It also provides further evidence that low LDL-C levels can reduce myocardial infarction and strokes in trials of relatively short duration but the effect on cardiovascular mortality may require longer follow up to observe significant benefit.

Since its discovery, PCKS9 inhibition has proven its efficacy in reducing LDL-C levels on top of standard lipid lowering therapy both as monotherapy and in those intolerant of statins. This is particularly relevant for patients at high risk of atherosclerotic cardiovascular disease or those with genetic conditions predisposing to premature atherosclerotic cardiovascular disease. Results from FOURIER confirm significant reductions in major adverse cardiovascular events with evolocumab and pave the way for further cardiovascular outcome trials within this field.

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