EXPERIMENTAL AND CLINICAL PHARMACOLOGY

PCSK9 inhibitors – clinical applications

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Keywords
alirocumab, bococizumab, evolocumab, ischaemic heart disease, LDL cholesterol, proprotein convertase subtilisin/kexin type 9

Aust Prescr 2016;39:168–70
http://dx.doi.org/10.18773/austprescr.2016.061

SUMMARY

The enzyme PCSK9 has an important role in regulating low-density lipoprotein (LDL) receptors and concentrations of LDL cholesterol. Inhibiting this enzyme could therefore reduce the incidence of ischaemic heart disease.

The monoclonal antibodies alirocumab, evolocumab and bococizumab are directed against PCSK9 and inhibit its activity. Phase II trials have shown alirocumab and evolocumab to be effective at lowering LDL cholesterol.

Preliminary results of these phase II trials show potential benefits in ischaemic heart disease. Reports of adverse effects, including muscular symptoms and neurocognitive changes, were low.

Large phase III cardiovascular outcome trials of these monoclonal antibodies will determine their safety and efficacy. These drugs may have a role in the management of patients at very high risk of cardiovascular events such as those with familial hypercholesterolaemia.

Introduction

The incidence of deaths from ischaemic heart disease in Australia has reduced since the 1960s. While about half of this reduction is due to interventions such as coronary revascularisation and secondary prevention, the remainder is due to addressing risk factors such as smoking, lipids and hypertension. However, ischaemic heart disease remains the leading cause of death in Australia, being responsible for over 20 000 deaths in 2011.[1]

There is ample evidence that statins (HMG-CoA reductase inhibitors) are effective and relatively safe drugs for the management of patients at high risk of cardiovascular events. However, there are limitations to their use. Drug intolerance is a major impediment, with muscular symptoms estimated to occur in around 10% of patients.[2] Although these symptoms are usually mild, they are a major cause of discontinuation and poor adherence to therapy. A large proportion of patients at high risk do not reach the recommended target concentration of low-density lipoprotein (LDL) cholesterol.[3]

Second-line treatments are less efficacious than statins. Ezetemibe was recently shown to reduce cardiovascular events, but the trial needed over 18 000 people at very high risk to be followed up for a median time of six years to show a significant advantage.[4] Fibrates such as fenofibrate have little effect on ischaemic heart disease, unless dyslipidaemia (increased triglycerides, decreased high-density lipoprotein (HDL)) and type 2 diabetes are present.[5] Torcetrapib, a drug that raises HDL, was associated with an increased rate of cardiovascular morbidity and mortality.

PCSK9 inhibitory antibodies

Studies of uncommon mutations, such as the LDL-receptor mutations in familial hypercholesterolaemia, have led to important therapeutic advances in the study of lipids and cardiovascular disease. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme involved in the regulation of LDL receptors and LDL cholesterol. By tagging LDL receptors for destruction in the liver, PCSK9 increases concentrations of LDL cholesterol.[6] Plasma PCSK9 concentrations are raised by statins and this could attenuate the effect of these drugs.

Research has focused on PCSK9 as a therapeutic target because blocking its action could reduce LDL cholesterol. The first candidates for therapies were humanised monoclonal antibodies. Currently alirocumab, evolocumab and bococizumab are in commercial development. These are all given by subcutaneous injection and reach a maximal effect 5–7 days after the dose, which lasts for about two weeks.

Phase I trials started in 2012, and showed large reductions in LDL cholesterol. The antibodies were well tolerated, including in patients intolerant of statins. In addition to the effect on LDL cholesterol, PCSK9 inhibition also reduces lipoprotein(a) and has favourable effects on other lipoproteins such as triglycerides, HDL and Apo B.[7] Lipoprotein(a) is a recognised risk factor for atherosclerotic disease and, to date, has not been shown to respond to any conventional therapies.

Clinical studies

One of the first studies of PCSK9 antibody therapies was the RUTHERFORD study. This involved 167 very high-risk patients with heterozygous familial hypercholesterolaemia, treated with evolocumab every four weeks for 12 weeks. These patients were on stable lipid-lowering treatment with a statin with or without ezetemibe. The highest dose of evolocumab resulted in a drop in LDL cholesterol from 3.8 to 1.7 mmol/L (55%, p<0.001 vs placebo).[8]

The phase II OSLER-1 and phase III OSLER-2 studies were two open-label trials of evolocumab in combination with standard therapy. They involved more than 4000 patients for a median of 11.1 months. In patients treated with evolocumab, there was a fall in median LDL-cholesterol concentration from 3.1 mmol/L to 1.24 mmol/L (61%) with little change seen in the control group. Although the study design only allowed cardiovascular events to be analysed as an exploratory analysis, the event rate was 0.95% in the study group, compared with 2.18% in the control group (relative risk reduction 56%, p=0.003).[9]

The ODYSSEY phase III double-blind trial of alirocumab versus placebo involved 2341 patients at very high risk. Following injections every two weeks there was lowering of LDL cholesterol after 24 weeks. Major cardiovascular events were lower in the alirocumab group compared with controls (1.7% vs 3.3%, p=0.02). Lipoprotein(a) was also observed to fall by 26%.[10]

Adverse effects

Arthralgia, headache, limb pain and fatigue were more frequent in the OSLER studies of evolocumab than in controls, but liver function and creatine kinase were unchanged. Injection site reactions led to six patients (0.2%) stopping treatment. Neurocognitive changes were more common with evolocumab, but were infrequent (0.9%, compared with 0.3% in the placebo group) and were not related to the concentration of LDL cholesterol.[9] A dedicated neurocognitive substudy of evolocumab is under way to give a more definitive assessment. The occurrence of adverse effects may have been confounded by the open-label method of the study, as patients treated with evolocumab were examined more frequently than controls. Evolocumab-binding antibodies were found in 0.3% of treatment and control patients, and were transient on repeat testing. No neutralising antibodies were observed.

In the ODYSSEY trial overall adverse event rates were similar in the alirocumab and placebo groups. Discontinuation due to adverse events was 7.2% in the alirocumab group and 5.8% in the control group. Myalgia was more frequent with alirocumab than with placebo (5.4% vs 2.9%, p=0.006). Other adverse events included injection site reactions, neurocognitive events related mainly to memory, ophthalmologic events, and changes in transaminase and creatine kinase concentrations. The rate of diabetes development was not significantly different between groups.[10]

Therapeutic use

To date, studies of anti-PCSK9 antibodies have examined the lowering of LDL cholesterol, with cardiovascular outcomes being analysed post hoc based on a relatively small number of events. Much larger trials are in progress, which should determine cardiovascular outcomes and less common adverse effects. The FOURIER study of evolocumab involves 27 500 high-risk patients with cardiovascular disease on background statin therapy. Similar trials of alirocumab and bococizumab are in progress.

Alirocumab was approved by the Food and Drug Administration in July 2015 for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolaemia or patients with clinical atherosclerotic cardiovascular disease. Alirocumab is available as a 75 mg/mL pre-filled pen or syringe and is given every two weeks by subcutaneous injection at a dose of 75–150 mg.[11] Shortly afterwards, evolocumab was approved for a similar group of patients. The recommended dose is 140 mg two-weekly or 420 mg once monthly.

Evolocumab is available in a 140 mg/mL single-use prefilled syringe or autoinjector.[12] The monthly dose of evolocumab is more than double the dose of two-weekly injections because the drug has non-linear pharmacokinetics. Its plasma concentrations do not increase in proportion to the administered dose.[13]

Evolocumab has been recently approved in Australia for use in combination with diet and exercise in adults with primary heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease in combination with a statin, or in combination with other lipid-lowering therapies in patients who are statin-intolerant. It is also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia, in combination with other lipid-lowering therapies.[14,15]

These new drugs for lowering LDL cholesterol may become a valuable addition to, or a substitute

for, current lipid-lowering therapies. Until the results from large phase III trials are able to clearly delineate harms and benefits, their role is likely to be restricted to patients with a high cardiovascular risk who do not reach targets for LDL cholesterol with oral therapy.

These trials may also uncover rare adverse effects. Hyperlipidaemia is an asymptomatic condition, and minor adverse effects may lead to discontinuation. The need for subcutaneous injection may also make patients reluctant to use the antibodies, and some patients may need to have their doses administered by health professionals. Biological drugs are expensive and cost is initially likely to be a barrier to their use.

Conclusion

PCSK9 inhibitory antibody therapies target a novel pathway in LDL-cholesterol metabolism, and early phase I and II trials show highly promising results. Results of large-scale and longer term phase III trials are awaited and these will yield better information about efficacy and adverse effects. Until the results of these trials are known, the use of antibodies is likely to be restricted to high-risk patients who have inadequate responses to, or are intolerant of, statins.

Conflicts of interest: none declared

Acknowledgement: I would like to thank Professor Chris Nolan for his thoughtful comments about the manuscript.

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