NEW DRUGS

New drugs

Evolocumab

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Approved indication: hypercholesterolaemia

Repatha (Amgen)
syringes or pre-filled pens containing 140 mg/mL
Australian Medicines Handbook section 6.5

The enzyme proprotein convertase subtilisin/kexin type 9 (PCSK9) reduces the number of receptors available to bind with low-density lipoprotein (LDL) cholesterol. Inhibitors of this enzyme therefore increase the number of receptors. This results in more LDL cholesterol being removed from the circulation.[1,2] Evolocumab is a PCSK9 inhibitor which has been approved for the treatment of hypercholesterolaemia including familial hypercholesterolaemia.

The drug is a monoclonal antibody that binds to PCSK9. It has to be given by subcutaneous injection and it can be injected every two weeks or once a month. The monthly regimen requires several injections to be given simultaneously.

After injection it takes 3–4 days to reach the peak serum concentration. A steady state is reached after about 12 weeks of treatment. The effective half-life is 11–17 days. As evolocumab is an antibody it is cleared like other proteins. Statins increase its clearance, but no dose adjustments are required. Although evolocumab has not been studied in patients with severe impairment, it can be used by patients with hepatic or renal impairment.

Homozygous familial hypercholesterolaemia

Patients with mutations in their LDL receptors have very high concentrations of LDL cholesterol and therefore an increased risk of cardiovascular disease. The TESLA Part B trial randomised 33 patients to add evolocumab and 17 patients to add placebo to their lipid-lowering therapy. At the start of the trial the mean LDL-cholesterol concentration was 9 mmol/L. After 12 weeks of injecting evolocumab 420 mg monthly this concentration fell by 23.1% while there was a 7.9% increase in the placebo group. There was also a significant reduction in apolipoprotein B.[3]

Heterozygous familial hypercholesterolaemia

The RUTHERFORD-2 trial randomised 331 patients who had heterozygous familial hypercholesterolaemia with LDL-cholesterol concentrations of at least 2.6 mmol/L despite lipid-lowering therapy. Two groups of 110 patients injected evolocumab 420 mg monthly or 140 mg every two weeks while 109 patients injected a placebo. After 12 weeks the concentration of LDL cholesterol had declined from a mean of 4.0 mmol/L to 1.8 mmol/L with monthly injections and from 4.2 mmol/L to 1.7 mmol/L with two-weekly injections. Concentrations were largely unchanged with placebo. Both regimens of evolocumab were also associated with significant reductions in apolipoprotein B and triglycerides.[4]

Primary hypercholesterolaemia

Most patients who require drug treatment for raised cholesterol will be prescribed a statin. In some cases this treatment will not achieve the target concentration for cholesterol. The patients may then be given an additional drug such as ezetimibe. The LAPLACE-2 trial looked at adding evolocumab or ezetimibe to treatment with a statin. This trial used evolocumab 140 mg every two weeks or 420 mg monthly. It also used three different statins at different doses so the 2067 patients were randomised to 24 different treatment groups. At the start of the study the patients had LDL-cholesterol concentration around 2.82 mmol/L. After 12 weeks this had reduced to approximately 1.28 mmol/L in patients taking evolocumab with atorvastatin 10 mg. The combination of evolocumab and atorvastatin 80 mg reduced the concentration to approximately 0.93 mmol/L. A primary outcome was the mean percentage change in LDL cholesterol from baseline for weeks 10 and 12 of the trial. For evolocumab these reductions were around 59–66% with moderate or high doses of statins. These changes were greater than those seen in the ezetimibe groups. Combined with atorvastatin, ezetimibe reduced LDL cholesterol by approximately 17–24%. Evolocumab also reduced concentrations of apolipoprotein B and triglycerides.[5]

The DESCARTES trial investigated treatment with evolocumab over a year. There were 905 patients who had an LDL-cholesterol concentration above 1.94 mmol/L despite lipid-lowering therapy. The patients were allocated to be treated with diet alone,

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

atorvastatin 10 mg, atorvastatin 80 mg or atorvastatin 80 mg plus ezetimibe. Within each of these groups the patients were given evolocumab 420 mg monthly or a placebo. After 52 weeks the mean LDL cholesterol fell from 2.69 mmol/L, across all groups, to 1.32 mmol/L with evolocumab, but was almost unchanged in the placebo groups. The largest percentage change (61.6%) was in the group treated with evolocumab and atorvastatin 10 mg in addition to diet. Treatment with evolocumab was also associated with reductions in apolipoprotein B and triglycerides.[6]

The MENDEL-2 trial assessed 615 patients who were not taking a statin. These patients had LDL-cholesterol concentrations averaging around 3.7 mmol/L. They were randomised to take evolocumab, ezetimibe or placebo. After 12 weeks patients injecting evolocumab every two weeks had reduced their LDL-cholesterol concentration by 57% compared with a 17.8% reduction with ezetimibe. The corresponding figures for monthly treatment were 56.1% and 18.6%. There was little change in the placebo groups.[7]

Evolocumab has also been investigated for patients with statin intolerance in the GAUSS placebo-controlled trials.[8] The GAUSS-2 trial enrolled 307 patients who had been unable to tolerate at least two statins. They were randomised to take daily ezetimibe, evolocumab 140 mg every two weeks, or evolocumab 420 mg monthly. At the start of the trial the average concentration of LDL cholesterol was approximately 5 mmol/L. After 12 weeks this had reduced by 53–56% with evolocumab and 15–18% with ezetimibe.

Safety

At the time of its approval in Australia evolocumab had been taken by 5710 patients in clinical trials. There were eight deaths from cardiovascular causes compared with three in the control group. In the one-year trial, two patients taking evolocumab died. Adverse events led to 2.2% stopping treatment compared with 1% of the control group. Common adverse effects that occurred more frequently with evolocumab included upper respiratory infections, influenza, back pain, myalgia, hypertension and erythema at the injection sites. Elevations of creatine kinase were also more frequent than in the control group.[6]

Injecting an antibody can cause allergic reactions. A small number (0.1%) of patients developed antibodies to evolocumab.

There have been no drug interaction studies. The effects of evolocumab in human pregnancy and lactation are unknown.

Discussion

There is no doubt that evolocumab lowers LDL cholesterol in a range of indications (see summary Table). However, this is a surrogate outcome and the drug's benefits on clinical outcomes are still being studied. There were few deaths in the clinical trials, but the proportion due to cardiovascular causes was greater with evolocumab than in the control groups (0.14% vs 0.10%). A meta-analysis of the PCSK9 inhibitors suggests that the cardiovascular mortality rate for the class is 0.19% compared with 0.33% without treatment. However, this reduction in cardiovascular mortality is not statistically significant.[9]

Patients who completed the clinical trials of evolocumab could participate in the OSLER extension studies. In these open-label studies 2976 patients took evolocumab and 1489 took standard therapy. After a median follow-up of 11.1 months, 29 patients taking evolocumab had a cardiovascular event compared with 31 in the control group. The difference in event rates (0.95% vs 2.18%) was statistically significant.[10]

The long-term safety of the class also needs further study. This will include monitoring for any effects on glucose metabolism and neurocognitive function. Over a one-year period neurocognitive events were reported in 0.6% of the patients taking evolocumab and 0.2% of the control group.

Table **Examples of trials of evolocumab efficacy**

Indication	Trial	Duration	Percentage reduction in LDL cholesterol at end of study	
			Evolocumab 420 mg monthly	Evolocumab 140 mg every two weeks
Homozygous familial hypercholesterolaemia	TESLA Part B[3]	12 weeks	23%	–
Heterozygous familial hypercholesterolaemia	RUTHERFORD-2[4]	12 weeks	56%	61%
Hypercholesterolaemia in patients using statins	LAPLACE-2[5]	12 weeks	52–59%	59–66%
Patients intolerant to at least two statins	GAUSS-2[9]	12 weeks	53%	56%

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When drug treatment is indicated for hypercholesterolaemia there is much more evidence to support treatment with statins. Injections of evolocumab will therefore be reserved for patients who cannot tolerate statins and when LDL-cholesterol concentrations remain significantly elevated despite treatment.[2]

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REFERENCES

1. Page MM, Watts GF. PCSK9 inhibitors – mechanisms of action. Aust Prescr 2016;39:164-7. http://dx.doi.org/10.18773/austprescr.2016.060
2. Schmidli R. PCSK9 inhibitors – clinical applications. Aust Prescr 2016;39:168-70. http://dx.doi.org/10.18773/austprescr.2016.061
3. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, et al.; TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet 2015;385:341-50. http://dx.doi.org/10.1016/S0140-6736(14)61374-X
4. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, et al.; RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 2015;385:331-40. http://dx.doi.org/10.1016/S0140-6736(14)61399-4
5. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, et al.; LAPLACE-2 Investigators. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA 2014;311:1870-82. http://dx.doi.org/10.1001/jama.2014.4030
6. Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L, et al.; DESCARTES Investigators. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014;370:1809-19. http://dx.doi.org/10.1056/NEJMoa1316222
7. Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J, et al.; MENDEL-2 Investigators. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2531-40. http://dx.doi.org/10.1016/j.jacc.2014.03.018
8. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, et al.; GAUSS-2 Investigators. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2541-8. http://dx.doi.org/10.1016/j.jacc.2014.03.019
9. Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y, et al. Effects of proprotein convertase subtilisin/kexin type 9 antibodies in adults with hypercholesterolemia: a systematic review and meta-analysis. Ann Intern Med 2015;163:40-51. http://dx.doi.org/10.7326/M14-2957
10. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al.; Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1500-9. http://dx.doi.org/10.1056/NEJMoa1500858

The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov), the European Medicines Agency (www.ema.europa.eu) and the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm).