New drugs

Alirocumab

Approved indication: hypercholesterolaemia

Praluent (Sanofi-Aventis)
pre-filled syringes containing 75 mg/mL and 150 mg/mL
Australian Medicines Handbook section 6.5, Drugs for dyslipidaemia

Following evolocumab, alirocumab is the second inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) to be approved in Australia.[1] Like evolocumab, alirocumab is a monoclonal antibody that binds to PCSK9. This leads to an increase in the number of low-density lipoprotein (LDL) receptors, enabling them to remove more LDL cholesterol from the circulation.[2,3] Alirocumab can therefore have a role in patients with hypercholesterolaemia that is not controlled by statins, or those who cannot tolerate statins.

Alirocumab is injected subcutaneously every two weeks or once a month. The maximum serum concentration is not reached until 3–7 days after injection. The median half-life of the antibody is 17–20 days, but this is reduced to 12 days if the patient is taking a statin. No data are available for patients with severe hepatic or renal disease, or in pregnancy and lactation.

Heterozygous familial hypercholesterolaemia

Patients with heterozygous familial hypercholesterolaemia have very high concentrations of LDL cholesterol. The placebo-controlled ODYSSEY FH I and II trials studied 735 patients whose LDL cholesterol was elevated despite treatment with high-dose statins. The 490 patients allocated to alirocumab injected 75 mg twice weekly, increasing to 150 mg if the LDL-cholesterol concentration remained elevated after eight weeks. In the FH I trial the mean cholesterol concentration after 24 weeks had fallen from 3.7 mmol/L to 1.8 mmol/L with alirocumab, but rose to 4 mmol/L with placebo. In FH II the reduction was from 3.5 mmol/L to 1.8 mmol/L with no change in the placebo group.[4]

Hypercholesterolaemia

Alirocumab has been studied in patients with a high risk of cardiovascular events who had hypercholesterolaemia despite statin therapy. It has been compared with placebo and ezetimibe.

Placebo-controlled trials

One trial, ODYSSEY COMBO I, recruited patients who were taking maximally tolerated doses of statins. It randomised 209 patients to inject alirocumab and 107 to inject placebo every two weeks. After 24 weeks the mean concentration of LDL cholesterol had fallen from 2.6 mmol/L to 1.3 mmol/L with alirocumab, but only from 2.7 mmol/L to 2.6 mmol/L in the placebo group.[5]

The ODYSSEY LONG TERM trial randomised 1553 patients taking high doses of statins to inject alirocumab and 788 to inject a placebo. After 24 weeks the LDL cholesterol fell from 3.17 mmol/L to 1.25 mmol/L compared with a fall from 3.15 mmol/L to 3.08 mmol/L with placebo. The trial continued for 78 weeks. At that time the mean LDL-cholesterol concentration was 1.5 mmol/L in the alirocumab group and 3.17 mmol/L in the placebo group.[6]

The feasibility of giving alirocumab every four weeks was studied in the ODYSSEY CHOICE 1 trial. This enrolled patients with hypercholesterolaemia who had a moderate to very high risk of cardiovascular disease. There were 458 patients randomised to inject alirocumab 300 mg every four weeks, 115 to inject 75 mg every two weeks and 230 patients had injections of placebo every two weeks. Most of these patients were already taking statins. By 24 weeks the four-weekly injections had reduced LDL cholesterol by 58.8% in patients taking statins and by 52.7% in patients not taking statins. The corresponding reductions with two-weekly injections were 51.6% and 50.2%, while there was almost no change in the placebo group.[7]

Trials with ezetimibe

The ODYSSEY MONO trial studied 103 patients with a 10-year risk of cardiovascular death of 1–5%. They were not taking statins. At the start of the trial the concentration of LDL cholesterol was approximately 3.6 mmol/L in both groups. After 24 weeks this was reduced by 47% with alirocumab and by 16% with ezetimibe.[8]

The ODYSSEY COMBO II trial enrolled patients with a high cardiovascular risk who had hypercholesterolaemia that was not controlled by maximally tolerated doses of statins. They continued this treatment, but 479 added alirocumab and 241 added ezetimibe. After 24 weeks the concentrations of LDL cholesterol had fallen from 2.8 mmol/L to 1.3 mmol/L with alirocumab and from 2.7 mmol/L

Aust Prescr 2019;42:29–31
https://doi.org/10.18773/austprescr.2018.071
First published 13 December 2018

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.

to 2.1 mmol/L with ezetimibe. At 52 weeks LDL cholesterol was 1.4 mmol/L in the alirocumab group and 2.2 mmol/L in the ezetimibe group.[9]

The ODYSSEY OPTIONS I trial compared alirocumab with ezetimibe and increased statin treatment. It involved 355 patients with a 10-year risk of cardiovascular death of at least 5%. These patients started a daily baseline regimen of atorvastatin 20 mg or 40 mg. They then added alirocumab or ezetimibe or doubled their statin dose. Patients taking atorvastatin 40 mg daily could also be randomised to switch to rosuvastatin 40 mg daily. After 24 weeks, the LDL-cholesterol concentration had fallen by 44.1% in patients taking alirocumab with atorvastatin 20 mg and by 54% in those taking it with atorvastatin 40 mg. The corresponding figures for added ezetimibe were 20.5% and 22.6%. Doubling the atorvastatin dose only reduced LDL cholesterol by about 5%, but it fell by 21.4% in patients switched to rosuvastatin 40 mg.[10]

To compare treatment options for patients with statin intolerance, the ODYSSEY ALTERNATIVE trial randomised 126 patients to take alirocumab, 125 to take ezetimibe and 63 to take atorvastatin 20 mg in a rechallenge group. Their mean baseline LDL cholesterol was approximately 5 mmol/L. After 24 weeks this had reduced by 45% with alirocumab and by 14.6% with ezetimibe.[11]

Safety

In the clinical trials 5–9% of patients stopped alirocumab because of a treatment-related adverse event. The most common adverse events with alirocumab were upper respiratory tract symptoms, pruritus and injection-site reactions. Although 6.1% of patients had injection-site reactions, only 0.2% stopped treatment because of them. Some patients will have hypersensitivity reactions and 4.8% will develop antibodies against alirocumab. Alirocumab had more musculoskeletal adverse effects than placebo. In the ODYSSEY ALTERNATIVE trial 15.9% of the patients taking alirocumab stopped treatment because of these effects. This was less than the 22.2% of the control group who stopped treatment when rechallenged with atorvastatin, but the difference was not statistically significant.[11] A small proportion of patients experienced confusion or memory impairment so there will be a need for neurocognitive adverse effects to be monitored after marketing. Similarly, alirocumab may have ophthalmological adverse effects in a small number of patients.

Discussion

The clinical trials show that alirocumab significantly reduces LDL cholesterol in a variety of patients. The percentage reductions are larger than with oral ezetimibe (see Table). However, patients who have high LDL-cholesterol despite taking a statin may prefer a daily tablet to an injection. If an injectable treatment is preferred then it is a choice between alirocumab and evolocumab. There is evidence that alirocumab 300 mg monthly has similar efficacy to 75 mg every two weeks. However, there were more injection-site reactions when alirocumab was given monthly.[7,12] For most patients in the trials LDL cholesterol was reduced by using 75 mg every two weeks, but the dose can be increased

Table **Examples of alirocumab efficacy**

Patient group	Trial	Percentage change in LDL cholesterol at 24 weeks (%)		
		Alirocumab	Ezetimibe	Placebo
Heterozygous familial hypercholesterolaemia (n=486)	ODYSSEY FH I[4]	−48.8	–	9.1
Heterozygous familial hypercholesterolaemia (n=249)	ODYSSEY FH II[4]	−48.7	–	2.8
Patients at increased cardiovascular risk not taking statins (n=103)	ODYSSEY MONO[8]	−47	−16	–
Patients at increased cardiovascular risk intolerant of statins (n=314 including atorvastatin control group)	ODYSSEY ALTERNATIVE[11]	−45	−14.6	–
Patients at increased cardiovascular risk on maximally tolerated statin dose (n=314)	ODYSSEY COMBO I[5]	−48.2	–	−2.3
Patients at increased cardiovascular risk on maximally tolerated statin dose (n=720)	ODYSSEY COMBO II[9]	−50.6	−20.7	–
Patients at increased cardiovascular risk on maximally tolerated statin dose (n=2341)	ODYSSEY LONG TERM[6]	−61.0	–	0.8

n number of randomised patients

to 150 mg if needed. At present there is not an option to increase the dose of evolocumab for primary hypercholesterolaemia. A systematic review concluded that for patients with a high cardiovascular risk who have high concentrations of LDL cholesterol despite statin therapy there is stronger evidence for alirocumab than for evolocumab.[13] However, cholesterol concentrations are a surrogate outcome and the effect of alirocumab on cardiovascular outcomes is not yet known. The long-term adverse effects of what could be a lifelong treatment are also unknown.

TT manufacturer provided additional useful information

REFERENCES

1. Evolocumab. Aust Prescr 2016;39:180-2. https://doi.org/10.18773/austprescr.2016.078
2. Page MM, Watts GF. PCSK9 inhibitors – mechanisms of action. Aust Prescr 2016;39:164-7. https://doi.org/10.18773/austprescr.2016.060
3. Schmidli R. PCSK9 inhibitors – clinical applications. Aust Prescr 2016:39;168-70. https://doi.org/10.18773/austprescr.2016.061
4. Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J 2015;36:2996-3003. https://doi.org/10.1093/eurheartj/ehv370
5. Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. Am Heart J 2015;169:906-15.e13. https://doi.org/10.1016/j.ahj.2015.03.004
6. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al; ODYSSEY LONG TERM investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1489-99. https://doi.org/10.1056/NEJMoa1501031
7. Roth EM, Moriarty PM, Bergeron J, Langslet G, Manvelian G, Zhao J, et al; ODYSSEY CHOICE I investigators. A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. Atherosclerosis 2016;254:254-62. https://doi.org/10.1016/j.atherosclerosis.2016.08.043.
8. Roth EM, Taskinen MR, Ginsberg HN, Kastelein JJ, Colhoun HM, Robinson JG, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. Int J Cardiol 2014;176:55-61. https://doi.org/10.1016/j.ijcard.2014.06.049
9. Cannon CP, Cariou B, Blom D, McKenney JM, Lorenzato C, Pordy R, et al; ODYSSEY COMBO II investigators. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J 2015;36:1186-94. https://doi.org/10.1093/eurheartj/ehv028
10. Bays H, Gaudet D, Weiss R, Ruiz JL, Watts GF, Gouni-Berthold I, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. J Clin Endocrinol Metab 2015;100:3140-8. https://doi.org/10.1210/jc.2015-1520
11. Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, et al; ODYSSEY ALTERNATIVE investigators. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. J Clin Lipidol 2015;9:758-69. https://doi.org/10.1016/j.jacl.2015.08.006
12. Stroes E, Guyton JR, Lepor N, Civeira F, Gaudet D, Watts GF, et al; ODYSSEY CHOICE II investigators. Efficacy and safety of alirocumab 150 mg every 4 weeks in patients with hypercholesterolemia not on statin therapy: the ODYSSEY CHOICE II Study. J Am Heart Assoc 2016;5:e003421. https://doi.org/10.1161/JAHA.116.003421
13. McDonagh M, Peterson K, Holzhammer B, Fazio S. A systematic review of PCSK9 inhibitors alirocumab and evolocumab. J Manag Care Spec Pharm 2016;22:641-53q. https://doi.org/10.18553/jmcp.2016.22.6.641

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the European Medicines Agency and the Therapeutic Goods Administration.