Alirocumab and evolocumab

A new era in cholesterol control

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Evolocumab and alirocumab are monoclonal antibodies to an enzyme (PCSK9) involved in regulating LDL cholesterol (LDL-C) levels. They have now been registered in Australia to treat raised LDL-C levels in specific patient groups and appear generally safe and well tolerated. At least 50% reduction in LDL-C level can be expected. Cost pressures may prevent their wider use.

Despite 'scare-mongering' in the lay and some medical media, statin therapy to reduce elevated LDL cholesterol (LDL-C) levels is effective in reducing future cardiovascular (CV) events, this being accompanied by an acceptable side effect profile. Regrettably, long-term statin therapy does not abolish CV risk, either because there is a residual elevation in LDL-C or because patients cannot tolerate statins (principally because of muscle problems) or other causal factors are at play. This important unmet need may be addressed in part by a new type of therapy: inhibitors of the enzyme proprotein convertase subtilisin-kexin type 9 (PCSK9).

What is the role of PCSK9 in regulating LDL-C?

PCSK9 has been shown to regulate LDL-C levels through binding to LDL receptors, limiting their recycling to the cell surface and hence reducing cellular uptake of LDL-C from the extracellular fluid (Figure). Loss-of-function mutations in the gene coding for PCSK9 have been found to be associated with low LDL-C and reduced coronary risk.[1] This discovery set the stage for development of drugs to inhibit PCSK9, to reduce LDL-C and potentially to achieve greater CV risk reduction.

No small molecule that is active after oral administration to inhibit PCSK9 safely has been identified, prompting the development of fully human monoclonal antibodies to PCSK9 through recombinant DNA technology. Thus far, two products have been registered in Australia for clinical use – evolocumab and alirocumab. These products are self-injected subcutaneously from a pre-filled, fixed-dose pen either once every 2 weeks (alirocumab or evolocumab) or once every 4 weeks (evolocumab only).

What have we learned from clinical trials with PCSK9 inhibitors?

Numerous studies have been conducted with alirocumab and evolocumab around the world, including centres in Australia. Reductions in LDL-C level greater than 45% have been recorded, with placebo injection or ezetimibe as the comparator.[2] These studies were conducted in the presence and also the absence of statin drugs (which actually increase native PCSK9 levels), and the proportionate reductions in LDL-C levels were similar. Serious side effects with PCSK9 inhibitors were little different from those observed with placebo.

It is not possible to cover the many individual studies with PCSK9 inhibitors, but it is informative to consider the data from two key reports (summarised in the Table).[3,4] Although the respective study groups differed in many important respects, evolocumab reduced LDL-C level by 61% at 48 weeks and alirocumab did so by 62% at 24 weeks and by 52% at 78 weeks. Lipoprotein(a), an LDL variant of importance in coronary disease, was reduced by 26% with evolocumab or alirocumab, but the clinical

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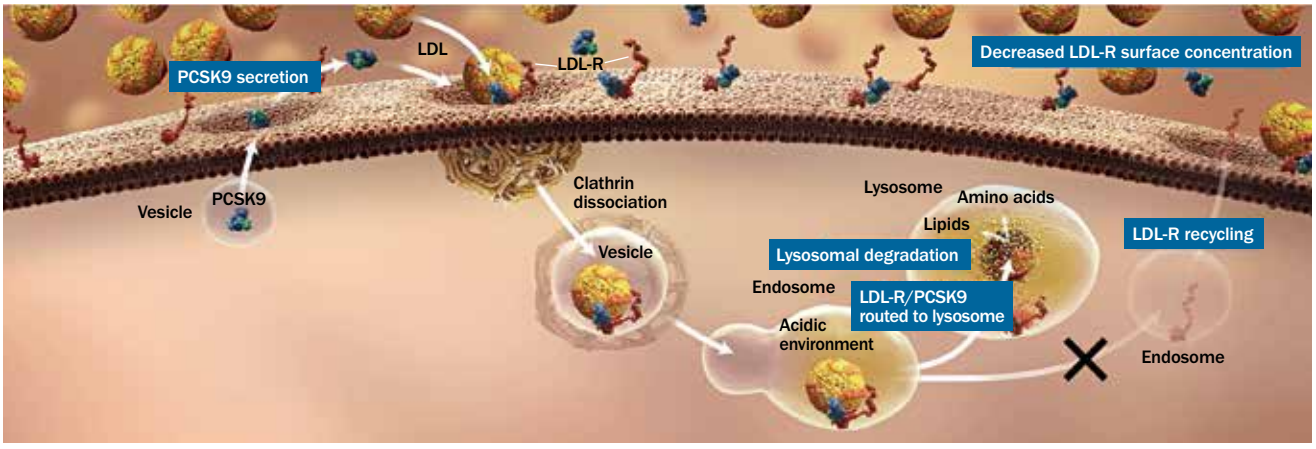

Figure. Role of PCSK9 in LDL-cholesterol receptor (LDL-R) recycling. PCSK9 is a protein secreted into the plasma, largely by the liver. PCSK9 binds to LDL-R, targeting it for degradation. With less recycling of LDL-R to the cell surface, clearance of LDL particles is reduced. Hence, inhibition of PCSK9 by a specific antibody results in more LDL-R recycling, increased clearance of LDL and ultimately reduced LDL-C levels.

Abbreviation: PCSK9 = proprotein convertase subtilisin-kexin type 9.

significance of this change is uncertain. There were minor changes in triglyceride or HDL levels with each drug.

Evolocumab reduced CV events by 53% (a prespecified exploratory outcome), and alirocumab did so by 48% (a post-hoc analysis). However, these are only preliminary findings, the number of CV events were small and confirmation is eagerly awaited in definitive studies of CV outcomes, which remain in progress (see below).

Side effects generally occurred with similar frequency in the PCSK9 and comparator arms with either PCSK9 inhibitor. There was a slight excess of neurocognitive events, albeit at a low rate, with evolocumab or alirocumab (e.g. memory changes, confusional state, mental impairments).

Who should be treated with a PCSK9 inhibitor?

The PCSK9 inhibitors are monoclonal antibodies, which are costly to develop and bring to market. Generic statins, in contrast, cost only around 20 cents per day. Hence, statins will remain the first choice in any patient requiring therapy to reduce LDL-C level, provided they are well tolerated.

The approved indications for alirocumab and evolocumab are broadly similar. They are indicated 'as an adjunct to diet and exercise in adults with heterozygous familial hypercholesterolaemia or clinical atherosclerotic CV disease when used (1) in combination with a statin, or statin with other lipid-lowering therapies or (2) in combination with other lipid-lowering therapies in patients who are statin intolerant.' Evolocumab is also indicated 'in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies'.

These indications potentially restrict the use of evolocumab or alirocumab to a narrow group of patients. Evolocumab may now be offered on private prescription for a cost to the patient of approximately $900 per 4-week period. PCSK9 inhibitors may not be available on the PBS until 2017 (perhaps with the exception of the very rare patients with homozygous familial hypercholesterolaemia). When ultimately subsidised on the PBS, the listing will likely be very restrictive, but the indications and PBS listing are likely to be broadened in later years.

A practical approach that is likely to be useful in the immediate future is to prescribe the PCSK9 inhibitors for the following patients.

1. Patients who have a markedly elevated LDL-C level (e.g. 5.0 mmol/L or higher) despite taking the maximum tolerated dose of a statin (and possibly ezetimibe), especially those at high risk of a future CV event (e.g. those with pre-existing CV disease). This would include many patients with heterozygous and all with homozygous familial hypercholesterolaemia.
2. Patients who are genuinely intolerant of statin drugs (usually because of muscle problems) or ezetimibe who are also described in item 1.

GPs may not become immediate prescribers of these drugs, but they will begin to see many patients who have been prescribed PCSK9 inhibitors by specialists.

How to use a PCSK9 inhibitor?

Practical experience suggests that the preferred frequency of administration of alirocumab or evolocumab is a single subcutaneous injection in the thigh, abdomen or arm once every 2 weeks. Alternatively, evolocumab may be administered once every 4 weeks but the equivalent dose is three injections (not two), and this approach is not preferred. Alirocumab is offered in two strengths in a 1 mL prefilled pen, 75 mg or 150 mg. Evolocumab is offered in a single strength of 140 mg in a similar 1 mL prefilled pen.

It only takes a few minutes to train

TABLE. SUMMARY OF FINDINGS IN TWO KEY REPORTS ON PCSK9 INHIBITORS[3,4]*

Study feature	Evolocumab study[3]	Alirocumab study[4]
Number in study	4465	2341
Comparator	Standard care	Placebo injection + standard care
Dose	140 mg every 2 weeks or 420 mg every 4 weeks	150 mg every 2 weeks
Duration	48 weeks	78 weeks
Males (%)	50	63
Coronary disease (%)	20	68
On statin drugs (%)	70	99.9
Diabetes (%)	13	35
LDL-C at entry (mmol/L)	3.1	3.2
LDL-C during study (mmol/L)	1.2 at 48 weeks	1.3 at 24 weeks, 1.5 at 78 weeks

Abbreviation: LDL-C = LDL cholesterol.
* Patients in both studies were randomised 2:1 to receive a PCSK9 inhibitor or comparator. The baseline data shown are those for the active treatment groups only.

patients with use of a 'dummy' pen containing no drug or needle. The product is stored at 4°C in a domestic refrigerator, but should be transferred to room temperature for 30 minutes before administration.

Alirocumab is started at the lower strength, and the dose may be uptitrated after 4 to 6 weeks if further reduction of LDL-C level is required. Evolocumab is used in a fixed dose without uptitration. Follow-up blood testing remains fairly standard: a check on lipid, creatinine, glucose and liver and muscle enzyme levels every 6 weeks during dose adjustment, thereafter at intervals of 3 to 6 months. Other background lipid therapy, if used, will likely continue unchanged. However, regular blood testing is essential to maintain patient motivation and compliance.

There have been no reports of drug–drug interactions with the PCSK9 inhibitors. No dose adjustment is required in older patients, patients with renal impairment with an estimated glomerular filtration rate over 30 mL/min/1.73m^2 or those with mild hepatic disease.

With respect to side effects, monitoring is needed for all the usual issues pertaining to statin therapy. In addition, there should be a check for any injection-site inflammatory reactions or neurocognitive events, as described above.

When will we see evidence on CV event reduction and long-term safety?

Two placebo-controlled megastudies evaluating CV event outcomes with evolocumab and alirocumab are now in progress. Both studies have broadly the same design, taking patients with prior coronary disease receiving standard care and randomised 1:1 to receive a PCSK9 inhibitor or matching placebo. The FOURIER Study with evolocumab includes more than 27,000 patients and is expected to report CV outcomes in 2017. The ODYSSEY Outcomes Study with alirocumab includes more than 18,000 patients and is expected to report CV outcomes in 2018.

Both these studies should yield definitive information on CV event reduction with the use of PCSK9 inhibitors, but only in the context of secondary prevention in patients stabilised on standard therapy including statins. But in patients already stabilised on statins, it can be difficult to show incremental benefit (e.g. unsuccessful studies with niacin, cholesterylester transfer protein [CETP] inhibitors, folate supplementation). It is difficult to conceive that an extra 50 to 60% reduction in LDL-C level would be futile, but we need to see the evidence.

We will need additional evidence in patients without prior CV disease. A study is in progress with a third unregistered PCSK9 inhibitor, bococizumab - the SPIRE-2 Outcomes Study. This study includes 10,600 patients, including an undefined proportion who do not have prior CV disease. Outcomes are expected to be reported in 2017.

All of these very large, placebo-controlled studies will yield further long-term safety experience.

Conclusion

The administration of fully human monoclonal antibodies to PCSK9 appears to be a generally safe and well-tolerated therapy to reduce elevated LDL-C levels. At least 50% reduction in LDL-C level can be expected. Information on CV event reduction and cost-effectiveness is eagerly awaited. Cost pressures may prevent more widespread use of drugs such as alirocumab and evolocumab. MT

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