CASE STUDY

New treatment for a patient who could not tolerate statins

LEON A. SIMONS MD, FRACP

A small proportion of patients with hypercholesterolaemia will be intolerant to statin drugs and they may be better managed in future years with a novel approach – regular subcutaneous injections of a human monoclonal antibody directed against PCSK9, a key regulatory enzyme.

Case scenario

Mr BB was referred for consultant opinion in January 2003, then aged 58 years, with a history of elevated cholesterol levels extending back more than 20 years (his background total cholesterol level was then about 8 mmol/L). His diet was favourable, and simvastatin and later atorvastatin had been used since 1991. He had used 10 mg/day without incident, but gradual uptitration to 40 mg/day became associated with severe, disabling myalgia and arthralgia in a generalised distribution. Atorvastatin was suspended and his symptoms completely resolved within seven days.

He had quit smoking in mid-2002 (previously 40 pack-years) and he had no symptoms of cardiovascular disease (CVD). He had a background of hypertension over some years now treated with an ACE inhibitor and a diuretic. He had no family history of premature CVD or cholesterol problems and had no children. Levels of electrolytes, creatinine, blood glucose, liver and muscle enzymes and thyroid stimulating hormones were within normal limits, as was his blood count.

Mr BB's GP started him on pravastatin 20 mg/day one week before my consultation.

Consultant's comment

On examination, Mr BB's body mass index was 23.5 kg/m^2 and his blood pressure was 120/80 mmHg. He had no corneal arcus or xanthomas, and no abnormal cardiovascular signs. His resting ECG was within normal limits and dipstick urinalysis showed no abnormality. A diagnosis of primary hypercholesterolaemia was made and he was judged to be at high risk of premature CVD by virtue of his age, cholesterol level, blood pressure history and smoking status. I endorsed ongoing therapy with pravastatin but postponed blood testing for one visit.

Case scenario continued

Pravastatin 20 mg/day seemed to be well tolerated and the dose was eventually uptitrated to 40 mg/day, yet Mr BB's lipid profile remained unsatisfactory:

- *total cholesterol 6.2 mmol/L (reference range <4.0 mmol/L)*
- *triglycerides 0.8 mmol/L (reference range <2.0 mmol/L)*
- *HDL-cholesterol 1.2 mmol/L (reference range >1.0 mmol/L)*
- *LDL-cholesterol 4.6 mmol/L (reference range <2.0 mmol/L).*

Key points

- **A novel approach to treat the small proportion of patients with hypercholesterolaemia who are intolerant to statins is being developed. These patients may be better managed in future years with regular subcutaneous injections of a human monoclonal antibody directed against PCSK9.**
- **This treatment may reduce LDL-cholesterol levels by about 50% and so far appears to be safe and well tolerated.**
- **Inhibition of PCSK9 is similarly effective in the presence or absence of a statin, but we await proof that such treatment will reduce future coronary risk.**

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Professor Simons is Associate Professor of Medicine and Director, University of NSW Lipid Research Department, St Vincent's Hospital, Sydney, NSW.

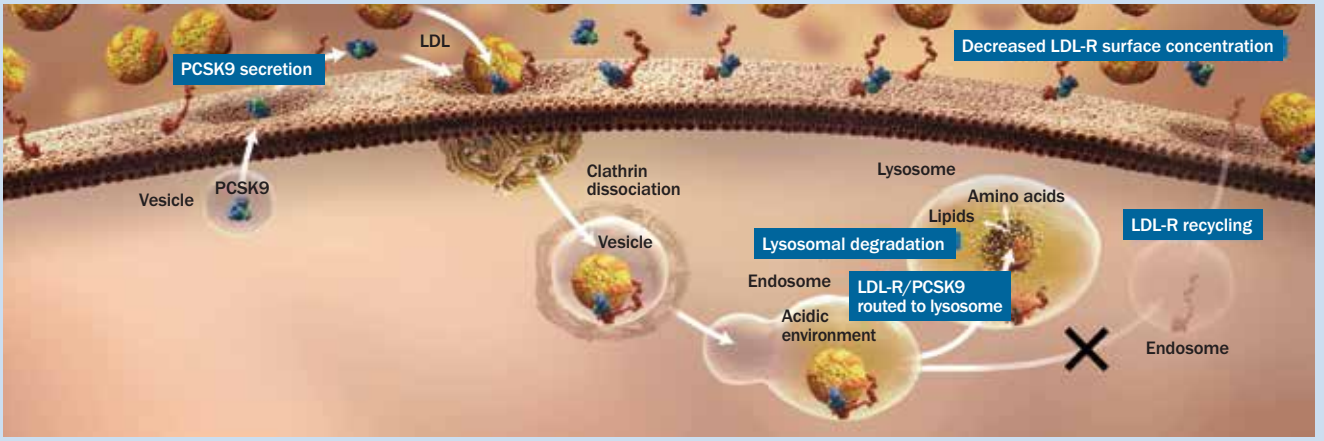

Figure. Role of PCSK9 in LDL-cholesterol receptor regulation.

Abbreviations: LDL-R = LDL-cholesterol receptor; PCSK9 = proprotein convertase subtilisin/kexin type 9.

His levels of creatinine, blood glucose, liver and muscle enzymes were within normal limits. He returned in September 2003 complaining of fatigue and generalised myalgia, similar to his previous presentation. There was no material change in his blood tests and his creatine kinase level was 195 U/L (reference range <200 U/L).

The use of cholestyramine or niacin seemed too risky in this patient and a fibrate did not seem appropriate. After a washout period of one month he was started on ezetimibe 10 mg/day, which was well tolerated. By December 2003 his lipids had improved marginally and were as follows:

- *total cholesterol 5.5 mmol/L*
- *triglycerides 0.9 mmol/L*
- *HDL-cholesterol 1.2 mmol/L*
- *LDL-cholesterol 3.9 mmol/L.*

A compromise was declared and he was referred back to his GP for follow up.

Mr BB was referred back to me for further review many years later in January 2010 with no new historical features. He had unilaterally suspended ezetimibe in September 2009 (no side effects) and his lipid profile now showed the following:

- *total cholesterol 7.7 mmol/L*
- *triglycerides 2.1 mmol/L*
- *HDL-cholesterol 1.0 mmol/L*
- *LDL-cholesterol 5.7 mmol/L.*

Consultant management

Mr BB was restarted on ezetimibe but now in combination with a very small dose of rosuvastatin, half of a 5 mg tablet on two mornings each week. Myalgia began to reappear after two months and he was returned to ezetimibe solo therapy without side effects.

In November 2011 he was invited to participate in a randomised, double-blind, placebo-controlled trial of a totally new concept in cholesterol management – a monthly subcutaneous injection of a human monoclonal antibody to a key regulatory enzyme known as proprotein convertase subtilisin/kexin type 9 (PCSK9). The product used in this study is known as evolocumab (or AMG-145) and the concept underlying this treatment is described below.

Case scenario continued

Mr BB was allocated at random to receive active drug in a mid-range dose for 12 weeks, followed by long-term open-label treatment in the full dose every four weeks. The treatment has been well tolerated and a battery of safety tests, including checking the patient's blood count, coagulation, glycaemic control, and his levels of electrolytes, creatinine, liver and muscle enzymes and thyroid stimulating hormone etc, have remained favourable. His LDL-cholesterol level has ultimately been reduced by 55% through a combination of evolocumab and ezetimibe. His progress lipid levels are summarised in the Table.

PCSK9 as a treatment target

PCSK9 is a protease proprotein produced in the liver and secreted into the plasma as functional PCSK9. Extracellular PCSK9 binds to the LDL-cholesterol receptors on the surface of the liver and other cells and is internalised within the endosome. The LDL-cholesterol receptor/PCSK9 complex is then routed to the lysosome for degradation, thereby preventing the recycling of LDL-cholesterol receptors back to the cell surface. By preventing LDL-cholesterol receptors from recycling back to the surface, PCSK9 reduces the concentration of LDL-cholesterol receptors on the surface of cells, resulting in a lower LDL-cholesterol clearance and elevated levels of plasma LDL-cholesterol and total cholesterol.[1,2] This is illustrated in the Figure.[1]

This regulatory pathway assumed clinical relevance with the discovery of gain-of-function mutations in the *PCSK9* gene, resulting in elevations in LDL-cholesterol levels, yet another form of genetic hypercholesterolaemia. Similarly, loss-of-function mutations in the human *PCSK9* gene, found in 1 to 3% of the population, have been associated with lower levels of circulating PCSK9, lower plasma LDL-cholesterol levels and a lower incidence of coronary heart disease.

Therefore, inhibition of PCSK9 became a treatment target. Although we await the discovery of small orally active inhibitor molecules, several pharmaceutical companies have developed human monoclonal antibodies

Table. Summary of lipid results at key time points during treatment with evolocumab in Mr BB

Period	Total cholesterol (mmol/L)	Triglycerides (mmol/L)	HDL-cholesterol (mmol/L)	LDL-cholesterol (mmol/L)
Study entry, no lipid drugs	8.8	3.8	0.9	6.2
After 12 weeks evolocumab (mid-range dose)	6.7	1.9	1.2	4.7
After 48 weeks evolocumab (full dose) + ezetimibe	3.9	1.9	1.0	2.1
After 100 weeks evolocumab (full dose) + ezetimibe	4.6	1.8	0.9	2.8

directed against PCSK9. Subcutaneous injections given every two or four weeks have been shown to reduce LDL-cholesterol by 40 to 60%, in a wide spectrum of patients, whether they are concurrently using statins or not. Reductions in lipoprotein(a) have also been noted with this treatment. In general, the treatment has been well tolerated and the emergent safety profile has not identified any specific areas of concern.

Given these very large reductions in LDL-cholesterol levels, can one assume that coronary events will be reduced? Epidemiological data suggest they should be. However, several controlled intervention studies involving many thousands of patients have now commenced with the use of inhibitors to PCSK9 and we await the results with great interest.

There are important drug regulatory hurdles to be overcome before we will see routine availability in Australia of any of these antibody products. Perhaps we will see availability within two to three years. It is beyond the scope of this article to cover detailed aspects of PCSK9 physiology and clinical data. Interested readers will find relevant source material in two recent papers.[1,2] **CT**

References

1. Stein EA, Wasserman SM, Dias C, Scott R, Raal F. AMG-145. Anti-PCSK9 monoclonal antibody, treatment of lipoprotein disorders. Drugs Fut 2013; 38: 451-459.
2. Urban D, Pöss J, Böhm M, Laufs U. Targeting the proprotein convertase subtilisin/kexin type 9 for the treatment of dyslipidemia and atherosclerosis. J Am Coll Cardiol 2013; 62: 1401-1408.

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