A patient with familial hypercholesterolaemia unable to achieve target LDL-cholesterol levels

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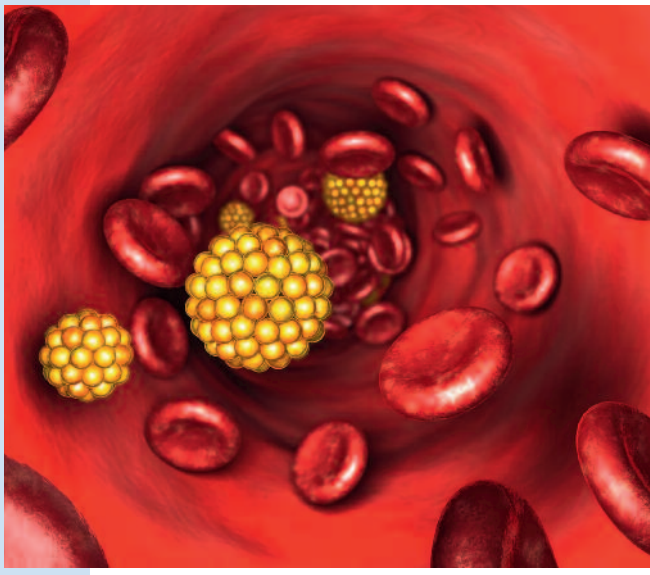

Without treatment, a man with heterozygous familial hypercholesterolaemia has a 51% chance of presenting with coronary disease by age 50 years and a woman has a 58% chance by age 60 years.

Case scenario

Mr BB is a 45-year-old man who was treated for an acute coronary syndrome three years ago. He underwent coronary angiography; a culprit lesion was stented and he made a good clinical recovery. He remained free of any cardiac symptoms and follow-up cardiac testing (with a stress echocardiogram) was favourable. In regard to background risk factors, he was a nonsmoker, normotensive and nondiabetic, but was 3 kg over the reference range of weight for his height with a body mass index of 27.0 kg/m^2. He did not show any evidence of corneal arcus or tendon xanthomas.

Mr BB's lipid levels were tested on presentation with the acute coronary syndrome and were found to be adverse, with the following results:

- *cholesterol 10.6 mmol/L*
- *triglycerides 1.7 mmol/L (desirable <2.0 mmol/L)*
- *HDL-cholesterol 1.0 mmol/L (desirable >1.0 mmol/L)*
- *LDL-cholesterol 8.8 mmol/L (desirable <1.8 mmol/L).*

Full blood count, fasting plasma glucose, electrolytes, creatinine, liver and muscle enzymes and thyroid function were all within normal limits. Dipstick urinalysis showed no evidence of proteinuria.

His family history was informative. Mr BB migrated to Australia from Lebanon at the age of 22 years leaving all his close family behind. His father, who died suddenly at the age of 41 years, was a heavy smoker, but no further information was available. His father had one sibling who died from a heart attack at the age of 47 years. His mother was alive and well, aged 61 years. Mr BB has two siblings but he could not provide any information about them. A diagnosis of heterozygous familial hypercholesterolaemia (FH) seemed very likely, caused by the Lebanese FH allele.

Mr BB was visited during his hospital admission by his 12-year-old son and 10-year-old daughter and the opportunity was taken to assess their respective lipid profiles. Total cholesterol in his son was 4.0 mmol/L (with all other parameters being within normal limits), but it was elevated in his daughter at 8.8 mmol/L (triglycerides 0.8 mmol/L, HDL-cholesterol 1.2 mmol/L and LDL-cholesterol 7.2 mmol/L [desirable <2.5 mmol/L]).

Mr BB was discharged from hospital on a low-fat diet, and prescribed antiplatelet therapy, an ACE inhibitor, a β-blocker and atorvastatin 80 mg/day. He remained clinically well over the intervening years and has been largely supervised by his GP.

Key points

- **Patients with heterozygous familial hypercholesterolaemia (FH) have a high risk of manifesting with premature coronary disease.**
- **Treatment with statins (and other standard cardiovascular medications) is likely to be beneficial.**
- **Multiple lipid-regulating drugs may not achieve target LDL-cholesterol readings in patients with FH, but a 50% reduction in LDL-cholesterol levels is acknowledged as an acceptable secondary goal.**

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Consultant comments

As hypothyroidism and nephrosis had been excluded, Mr BB's Lebanese extraction, the highly elevated LDL-cholesterol levels in patient and daughter and the adverse family history of premature coronary disease in his father and family place the diagnosis of heterozygous FH beyond any reasonable doubt. His Lebanese extraction has been stressed because the gene frequency of this Mendelian dominant gene is far higher in the Lebanese population, one in 200 compared with one in 500; however, it does occur in all populations. Recent research suggests that the gene frequencies may indeed be greater than those quoted. Some, but not all, patients with FH may have a premature corneal arcus or tendon xanthomas, but this is not common and is not a prerequisite for the diagnosis.

We need to look back to the pre-statin era to appreciate the natural history of this diagnosis. In 1969 it was estimated that in men with FH the chance of a first presentation with coronary heart disease was 51.4% by age 50 years, with a 23.5% chance of coronary death. The respective risks in women were 57.5% and 15.4% by age 60 years.[1] Hence, although some patients with FH will not experience premature coronary heart disease, this is a condition with a bad prognosis and one where treatment with statins (plus other standard medications) is likely to be highly beneficial.[2]

Mr BB was correctly diagnosed and discharged on appropriate treatment. His 10-year-old daughter also appeared to be manifesting signs of FH. Specific gene testing for the Lebanese FH allele is available in some centres, but was not necessary in this instance. She needed dietary and lifestyle advice, specifically about future tobacco avoidance, and prescription of statin therapy at a later point in time. There are differing opinions as to how early she should be started on statins.

Case scenario continued

Mr BB followed the dietary advice and took his prescribed drugs faithfully over the intervening three years. However, he never achieved the new Heart Foundation goal of an LDL-cholesterol level under 1.8 mmol/L. His GP monitored potential risk factors and checked his lipid profile at half-yearly intervals. The most recent results, which were representative of earlier ones, were as follows:

- *total cholesterol 5.5 mmol/L*
- *triglycerides 1.4 mmol/L*
- *HDL-cholesterol 1.1 mmol/L*
- *LDL-cholesterol 3.8 mmol/L.*

His GP was frustrated at the patient's failure to achieve the goal LDL-cholesterol level. He phoned this consultant to ask about additional treatment options, in particular whether the dose of atorvastatin should be increased or perhaps be switched to rosuvastatin.

Consultant comments

Although the Heart Foundation guideline does advocate an LDL-cholesterol level below 1.8 mmol/L in this clinical setting, Canadian and European guidelines also acknowledge that a 50% reduction in the level of LDL-cholesterol is an acceptable secondary goal.[3,4] Mr BB had achieved a 57% reduction in LDL-cholesterol level and this needed to be communicated to the patient in optimistic terms.

I advised against an increase in dose of atorvastatin because he was already using the maximum approved dose, something well supported by clinical evidence of coronary heart disease prevention. A switch to rosuvastatin was a possibility, but Mr BB might not achieve much further reduction in LDL-cholesterol level.

Employing the principle for LDL-cholesterol of 'lower the better', I recommended that the existing dose of atorvastatin be supplemented with ezetimibe 10 mg/day. Although firm evidence of coronary heart disease prevention with ezetimibe is still awaited, Mr BB should achieve a much lower LDL-cholesterol level with this combined therapy.

Case scenario continued

Mr BB was somewhat reassured by this feedback through his GP and he commenced ezetimibe. Blood tests were taken eight weeks later and showed an improving trend, yet his LDL-cholesterol level remained higher than desirable, with results as follows:

- *total cholesterol 4.2 mmol/L*
- *triglycerides 1.3 mmol/L*
- *HDL-cholesterol 1.0 mmol/L*
- *LDL-cholesterol 2.6 mmol/L.*

Electrolytes, glucose, liver and muscle enzymes remained within normal limits. His GP then requested that I see the patient in person.

Consultant comments

Having already achieved a 70% reduction in LDL-cholesterol level since the coronary event, it seemed unlikely that further conventional treatment would lower his LDL-cholesterol level much further, desirable though this might be. The use of cholestyramine or high-dose niacin appeared problematic. LDL-cholesterol apheresis is popular in some centres overseas but is not widely available in Australia, and is also expensive and burdensome. Ultimately, I recommended a switch from atorvastatin 80 mg/day to rosuvastatin 40 mg/day, with ezetimibe to continue unchanged. Mr BB was asked to return for review in eight weeks.

Eight weeks later, his LDL-cholesterol level was 2.4 mmol/L, not significantly changed from previously. I informed Mr BB that this was probably the best he could achieve with conventional therapy, that he was progressing quite nicely and should continue with his treatment unchanged.

Conclusion

A new type of therapy is currently under evaluation and might become available for general use in Australia in the next three to four years. This therapy is regular subcutaneous injections of a human monoclonal antibody directed against PCSK9, a key enzyme regulating LDL-cholesterol receptor activity. This treatment has been shown to reduce LDL-cholesterol levels by 50% or more against a background of statin therapy and may represent the next major advance in cardiovascular medicine.[5] **CT**

References

A list of references is available on request to the editorial office.

COMPETING INTERESTS: None. The views expressed are purely those of the author.

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