Editorial Comment

PCSK9 inhibitors for homozygous familial hypercholesterolemia: useful but seldom sufficient

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Homozygous familial hypercholesterolemia (FH) is an extremely rare disorder that has had an extraordinarily large influence on our understanding of cholesterol metabolism and disorders thereof that promote atherosclerosis. Robert Frost once said "Nature keeps hinting at us" and in the 1970s Goldstein and Brown took one of Nature's hints. By investigating the cause of the extreme increase in serum cholesterol in a patient with homozygous FH they discovered the low density lipoprotein (LDL) receptor and its absence in their patient (1,2), a discovery that earned them the Nobel Prize. Now as then, homozygous FH with its predilection to lethal aortic root atheroma (3,4) remains the ultimate therapeutic challenge for lipidologists, cardiologists, cardiac surgeons and the pharmaceutical industry and the yardstick against which numerous lipid-lowering measures have been tested. The near complete absence of LDL receptors in FH homozygotes renders these patients relatively unresponsive to drugs that work by upregulating LDL receptors such as statins although the latter are highly effective in FH heterozygotes, who have only a partial lack of receptors. Hence, first line therapy for homozygotes has for many years relied upon treatment modalities that do not depend upon the presence of LDL receptors, such as plasma exchange and lipoprotein apheresis (5). Recently, another LDL receptor-independent form of treatment, the microsomal triglyceride transfer protein (MTP) inhibitor lomitapide, has been shown to be highly effective as an adjunct or substitute for apheresis in FH homozygotes (6), albeit with a side effect profile that necessitates considerable caution in its use.

Although statins have proved highly effective in most patients with heterozygous FH, a minority is insufficiently responsive to or intolerant of these drugs. Such patients benefit greatly from the most recent addition to the category of LDL receptor-dependent lipid-lowering compounds, the propertin convertase subtilisin kexin 9 (PCSK9) inhibitors, which block the LDL receptor-degrading action of PCSK9 and thereby promote receptor-mediated LDL catabolism. For example, two open-label trials of the anti-PCSK9 monoclonal antibody evolocumab showed that doses of 140 mg injected every 2 weeks or 420 mg monthly reduced LDL cholesterol by 61% and halved the hazard ratio for cardiovascular events (7). However, as with statins, these compounds are much less effective in FH homozygotes. The open-label TAUSSIG trial assessed the safety and lipid-lowering efficacy of evolocumab 420 mg given once or twice monthly in 106 patients with homozygous FH, most of whom were on a statin and ezetimibe and a third of them were also on lipoprotein apheresis (8). Reductions in LDL cholesterol after 48 weeks of evolocumab averaged 23% and were similar between patients on or not on apheresis, with an overall mean LDL cholesterol concentration on treatment of 260 mg/dl (6.7 mmol/L). Notably, these reductions in LDL cholesterol are far less than those observed in heterozygous FH (9), as too was the meagre 12% decrease in lipoprotein(a).

Against this background, Blom and colleagues report in this issue of the *Journal of the American College of Cardiology* the results of the ODYSSEY HoFH Randomised Trial, a double-blind, placebo-controlled trial of the anti-PCSK9 monoclonal antibody alirocumab in 69 FH homozygotes drawn from various parts of the world (10). All were receiving conventional forms of stable lipid-lowering therapy at entry to the 12 weeks double blind phase of the study and during the subsequent 12 weeks of open label treatment, including statins (97%), ezetimibe (86%), apheresis (15%) and lomitapide (15%). Mean baseline LDL

cholesterol was 295 mg/dl (7.6 mmol/l) in the alirocumab group and 260 mg/dl (6.7 mmol/l) in those on placebo, levels being lowest in patients undergoing apheresis or on lomitapide. LDL cholesterol levels decreased by 26.9% after 12 weeks on alirocumab and increased by 8.6% in those on placebo, a net difference of 35.6% (P< 0.0001). At week 24, when all patients were on alirocumab, the overall decreases in LDL cholesterol and Lp(a) were 27.3% and 11.6% respectively and there was a 10% increase in HDL cholesterol. Pharmacokinetic and pharmacodynamic data showed an incremental increase in serum alirocumab in the alirocumab group that plateaued after 10 weeks and a reciprocal decrease in serum PCSK9 that reached its nadir at 4 weeks. The frequency of treatment emergent adverse events did not differ between the two treatment groups and none was serious.

What do the results of ODYSSEY mean for clinicians? The open label TAUSSIG study showed that the anti-PCSK9 monoclonal antibody evolocumab reduced LDL cholesterol levels in homozygotes from baseline by 20 - 30% and the ODYSSEY trial corroborates this finding using a different monoclonal antibody, alirocumab, under double blind, placebo-controlled conditions. The spectrum of LDL receptor mutations was similar in the two trials, as was the wide variability of individual responses of LDL to treatment. Percentage reductions in LDL cholesterol in patients in the alirocumab group who were on apheresis were less than in those not on apheresis but there was no evidence that apheresis lowered alirocumab levels and LDL cholesterol concentrations at 12 weeks were similar in both groups, in keeping with the results of TAUSSIG. However, in neither trial were LDL cholesterol levels reduced to anywhere near the target levels stipulated by the European Atherosclerosis Society for adult homozygotes with or without cardiovascular disease, < 70 mg/dl (<1.8 mmol/) and < 100 mg/dl (<2.5 mmol/l) respectively (11).

A novel feature of the ODYSSEY study is the inclusion of patients on lomitapide. Their number was small but analysis of Supplementary table 1 shows that LDL levels at 12 weeks were substantially lower in patients receiving both lomitapide and alirocumab than in those on alirocumab alone. The take home message is that PCSK9 inhibition with monoclonal antibodies provides a useful adjunct to, but not a substitute for, more radical forms of therapy for homozygous FH, such as lipoprotein apheresis and lomitapide. However, homozygotes with a significant degree of residual LDL receptor activity sometimes show a remarkable response to evolocumab or alirocumab, so it is worth giving one of them a trial before resorting to those more drastic measures.

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Figure: The author.