

Novel options for homozygous familial hypercholesterolaemia?

Homozygous familial hypercholesterolaemia (FH), is a rare condition characterized by markedly elevated levels of low-density lipoprotein (LDL) cholesterol, accelerate atherosclerosis and an extremely high risk of coronary events from a young age. Affected individuals may be true homozygotes, with mutations in both alleles of the same gene, or more commonly, compound heterozygotes with different mutations in each allele of the same gene, or double heterozygotes with mutations in two different genes affecting LDL receptor function.¹

Statin and lipoprotein apheresis represent the mainstay of treatment.¹ Yet even with additional treatments, including evolocumab, lomitapide and (US only) mipomersen, patients rarely attain LDL cholesterol goal, with impact on patient life expectancy and quality of life. There is clearly the need for additional therapeutic options; novel agents discussed at the **Clinical Latebreaker Session** on Tuesday provided preliminary evidence with emerging treatments.

In a proof-of-concept study, evinacumab (REGN1500), a human monoclonal antibody to angiopoietin-like protein 3 (ANGPTL3), produced substantial lowering of LDL-C levels in four patients with homozygous FH. According to lead author, **Professor Daniel Gaudet (University of Montreal, Canada)**: *'We are in a very exciting era for homozygous FH research with novel therapies emerging from genetic insights. As is the case for PCSK9, the rationale for the development of a novel monoclonal antibody targeting ANGPTL3 has been driven by family pedigrees which showed that individuals with loss of function ANGPTL3 mutations had lower LDL cholesterol levels.'*

ANGPTL3, a protein expressed almost exclusively in liver, plays a key role in lipoprotein metabolism. The precise mechanism for ANGPTL3 is not elucidated, although it is known to act as an inhibitor of lipoprotein lipase and endothelial lipase, and promote uptake of circulating very low density lipoprotein-triglycerides into white adipose tissue.² Genetic studies have shown that people with one mutation resulting in the loss-of-function of ANGPTL3 have lower LDL cholesterol levels; those with two loss-of-function mutations not only have >50% lower LDL cholesterol levels, but also >75% lower plasma levels of triglycerides compared with unaffected individuals.^{3,4} Additionally, studies in LDLR deficient animal models showed that inhibition of ANGPTL3 with the monoclonal antibody evinacumab reduced plasma lipids,⁵ suggesting that patients with homozygous FH may benefit.

Professor Gaudet presented initial results from 4 patients genotyped for homozygous FH included in an ongoing open-label phase II study with evinacumab.⁶ At baseline, all patients received evinacumab 250 mg subcutaneous (1 dose), a 15 mg/kg intravenous dose at week 2, and two patients received single doses of 450 mg subcutaneously at weeks 12, 13, 14 and 15. At the end of the 16-week study, patients completed a further 10-week follow-up period. Patients who were on apheresis in the 4 weeks before screening for the study were excluded. All patients were on maximal statin plus ezetimibe, and one patient also received lomitapide 20 mg once daily. Baseline LDL cholesterol ranged between 4.0 and 13.4 mmol/L (mean 8.6 mmol/L); lipoprotein(a) ranged between 121 and 395 nmol/l (mean 222.5 nmol/L).

The mean reduction in LDL cholesterol at week 4 was 54.8% (range 25-90%), representing an absolute reduction of 4.5 mmol/l (0.4 to 10.1 mmol/L). Half of the patients attained an LDL cholesterol <2.5 mmol/L). One patient on statin, ezetimibe plus lomitapide (baseline LDL cholesterol 21.3 mmol/L) had a 90% reduction, and 6 months after intravenous injection his LDL cholesterol was 1.8 mmol/L. Although

there was only a small number of patients, treatment was generally well tolerated. In his conclusions, Professor Gaudet indicated that evinacumab may have potential in these very high risk patients.

Results from another study were perhaps less promising.⁷ This study tested MBX-8025, a peroxisome proliferator-activated receptor delta agonist, which had been shown to decrease LDL cholesterol in subjects with mixed dyslipidaemia, as well as in an animal model of homozygous FH. In this 12-week, open label study, dose escalation was performed monthly (MBX-8025: 50, 100, and 200 mg orally daily) in 13 adults with genetically confirmed homozygous FH (baseline LDL cholesterol 9.5 mmol/L, range 7.1-13.5 mmol/L). All patients were on maximal statin and ezetimibe, and eight were also receiving lipoprotein apheresis (either weekly or every 2 weeks).

In most patients (n=9), the LDL cholesterol lowering response was <30%, i.e. generally less than that observed with the PCSK9 inhibitor evolocumab.⁸ Additionally, there was an unexpected increase in circulating PCSK9 levels, although this did not appear to be dose-dependent. The investigators proposed that testing MBX-8025 in combination with evolocumab in a subsequent trial to dampen the PCSK9 response.

In the poster sessions, there were further data with evolocumab in 106 homozygous FH patients (14 aged <18 years) in the Trial Assessing Long-Term Use of PCSK9 Inhibition in Subjects with Genetic LDL Disorders (TAUSSIG) study.^{9,10} The LDL cholesterol lowering response with evolocumab was sustained in the long-term, with mean reduction in LDL cholesterol by 23% (1.8 mmol/L) at weeks 24 and 48. Of the 34 patients on apheresis, 18% were able to stop or reduce the frequency of treatments. Additionally, there was evidence to suggest cardiovascular event rates were lower than in earlier studies in homozygous FH patients on standard lipid lowering therapy, with an annual event rate of 2.1%/year (1.7 years' follow-up), albeit in small absolute numbers (n=4).¹¹⁰ None of the patients died over the follow-up period.

Professor Eric Bruckert (Endocrinology Department and Apheresis Center, Hôpital Pitié Salpêtrière, Paris France) discusses these findings in a video on the EAS website.

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