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GENE THERAPY

## TARGETING apoC-III TO LOWER TRIGLYCERIDES

Familial chylomicronaemia syndrome (FCS) is a rare genetic disorder caused by mutations in the gene encoding lipoprotein lipase (LPL), and is characterized by severe hypertriglyceridaemia, chylomicronaemia, and an increased risk of recurrent pancreatitis. Except for LPL gene replacement therapy, which is now conditionally available in Europe, current triglyceride-lowering agents are not effective in controlling chylomicronaemia, and patients are required to restrict their consumption of dietary fats. Gaudet *et al.* now show that inhibiting apolipoprotein C-III (apoC-III), an inhibitor of LPL, in patients with FCS can reduce triglyceride levels in patients with less than 5% of LPL activity.

Three patients with FCS who were homozygous or compound heterozygous for null *LPL* mutations were recruited for this study. Each patient received a 300 mg dose of ISIS 304801, an antisense inhibitor of apoC-III mRNA synthesis, once per week for 13 weeks by subcutaneous injection. All three patients were followed up for 91 days after administration of the last dose of ISIS 304801.

Baseline apoC-III levels were elevated in all three patients (18.9, 35.1, and 19.8 mg/dl), compared with a normal range of 10–15 mg/dl in healthy individuals. By the end of the treatment period, apoC-III levels were reduced to 5.5, 3.4, and 3.5 mg/dl, respectively. Triglyceride levels in the three patients were also decreased in parallel with the reductions in apoC-III; by the end of the treatment period, triglyceride levels were 56–86% lower than at baseline in the three patients. Furthermore, ISIS 304801 administration also reduced triglyceride and cholesterol levels in chylomicrons.

The finding that apoC-III inhibition lowered triglyceride levels in FCS was unexpected, given the recognized role of apoC-III in modulating triglyceride levels by inhibiting the LPL-dependent clearance pathway. However, these results suggest that apoC-III can also regulate lipoprotein metabolism via LPL-independent pathways. The investigators conclude that apoC-III is "a central and pleiotropic regulator of the metabolism of triglyceride-rich lipoproteins, and our data provide improved contextual understanding with respect to studies of association among plasma apoC-III levels, triglyceride levels, and overall health".

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**Original article** Gaudet, D. *et al.* Targeting APOC3 in the familial chylomicronemia syndrome. *N. Eng. J. Med.* **371**, 2200–2206 (2014)