

## GENE THERAPY

## Inhibiting apoC-III synthesis in patients with hypertriglyceridaemia

Apolipoprotein C-III (apoC-III) has a critical role in the regulation of plasma triglyceride levels. In a randomized, placebo-controlled, phase II study, Gaudet and colleagues assessed the effect of ISIS 304801, an antisense inhibitor of apoC-III synthesis, on fasting apoC-III levels in patients with severe or uncontrolled hypertriglyceridaemia.

Patients with a fasting triglyceride level of 350–2,000 mg/dl who were not receiving triglyceride-lowering therapy were recruited into the ISIS 304801 monotherapy cohort, whereas patients with a fasting triglyceride level of 225–2,000 mg/dl who were receiving a stable dose of fibrate were recruited into the ISIS 304801–fibrate treatment cohort. Eligible patients were randomly assigned to receive either ISIS 304801 (dose range 100–300 mg) or placebo, once weekly for 13 weeks.

In total, 57 patients were treated in the ISIS 304801 monotherapy cohort and 28

were treated in the ISIS 304801–fibrate cohort. Administration of ISIS 304801 resulted in a dose-dependent and prolonged reduction in plasma apoC-III levels in both treatment cohorts. In the ISIS 304801 monotherapy group, plasma apoC-III levels were reduced by  $40.0 \pm 32.0\%$ ,  $63.8 \pm 22.3\%$ , and  $79.6 \pm 9.3\%$  in the 100 mg, 200 mg, and 300 mg groups, respectively, compared with an increase of  $4.2 \pm 41.7\%$  in the placebo group. In the ISIS 304801–fibrate cohort, apoC-III levels decreased by  $60.2 \pm 12.5\%$  and  $70.9 \pm 13.0\%$  in the 200 mg and 300 mg groups, respectively, versus a reduction of  $2.2 \pm 25.2\%$  in the placebo group. Concomitant with these reductions in apoC-III levels, a decrease of 31.3–70.9% was observed in triglyceride levels.

According to the study investigators, this “reduction in [apoC-III] levels resulting from short-term treatment with ISIS 304801 is a finding that could have clinical relevance”. Given that elevated

levels of apoC-III have been associated with coronary heart disease and atherogenesis, reducing apoC-III might be cardioprotective. In addition, the results further support the relationship between apoC-III and triglyceride levels, given the direct effect of ISIS 304801 on circulating triglycerides. To conclude, the investigators reiterate that these results “support the continued development of ISIS 304801 for the treatment of patients who remain at risk for cardiovascular events and pancreatitis because of very high triglyceride levels”.

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