Nature Reviews Cardiology **10**, 682 (2013); published online 22 October 2013; doi:10.1038/nrcardio.2013.163

DYSLIPIDAEMIA

RNAi targeting *PCSK9* decreases lipid levels in a human trial

PCSK9 binds to LDL receptors and targets them for degradation, thereby increasing levels of LDL cholesterol. Kevin Fitzgerald and colleagues have now used an RNAi molecule called ALN-PCS to target PCSK9 in a phase I trial. This trial is "the first human proof of concept for an RNAi therapeutic impacting a clinically validated endpoint", says Fitzgerald.

In this single-blind, dose-escalation study, 32 participants with LDL-cholesterol levels ≥3.00 mmol/l were randomly assigned to receive placebo ($n = 8$) or a single dose of ALN-PCS (0.015–0.400 mg/kg). No drug-related serious adverse events were observed during the 6 month follow-up, although a mild rash that resolved spontaneously was seen in the majority of patients, including in the controls. The authors attributed this rash to the premedication given to both groups—dexamethasone, paracetamol, and histamine receptor blockers. Evan Stein, who was not involved in this research but has consulted for companies developing antibodies against PCSK9, thinks the rash is more likely caused by the lipid vesicle or ALN-PCS itself. "There were 4/6 and 6/6 patients in the 2 highest doses who had the rash compared to 4/8 placebo patients overall, and very few at the lower doses," he says. Steroids in the premedication should prevent or reduce such reactions, he says, and he fears these reactions will be more severe when premedications aren't used.

In patients receiving the highest dose of ALN-PCS (0.400 mg/kg, $n = 3$), circulating PCSK9 and LDL-cholesterol levels were reduced by a mean of 70% and 40% respectively ($P < 0.0001$ for both). These reductions lasted for 2–3 weeks.

"We are very encouraged by the ALN-PCS Phase I safety and efficacy data," says Fitzgerald. He plans "larger multidose studies, without the use of premedication, to address long-term safety and tolerability of ALN-PCS". His company, Alnylam, has also injected the drug subcutaneously into nonhuman primates, and plans to try this delivery method in human trials soon.

Megan Cully

Original article Fitzgerald, K. *et al.* Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled, phase 1 trial. *Lancet* doi:10.1016/S0140-6736(13)61914-5