

## LIPIDS

# Monoclonal antibody therapy lowers LDL-cholesterol levels

The monoclonal antibody REGN727 significantly reduced LDL-cholesterol levels in patients with hypercholesterolemia and in healthy controls, according to data from three phase I clinical trials published in the *New England Journal of Medicine* and a phase II trial published in the *Journal of the American College of Cardiology* and presented at the 2012 ACC Scientific Sessions in Chicago, IL, USA.

REGN727 binds proprotein convertase subtilisin/kexin 9 (PCSK9) and blocks the

interaction of the enzyme with hepatic LDL receptors, which remove LDL cholesterol from the blood. This blockade prevents PCSK9-mediated LDL receptor degradation and thus reduces levels of circulating LDL cholesterol.

By contrast, statins inhibit cholesterol production and increase the expression of both LDL receptors and PCSK9. Increased levels of circulating PCSK9 might limit the effectiveness of statin therapies.

PCSK9 is “intimately involved in regulating LDL cholesterol in the blood stream,” says researcher Dr Evan A. Stein from the Metabolic and Atherosclerosis Research Center, Cincinnati, OH, USA. “Blocking its action is an extremely effective potential treatment for ... high cholesterol”.

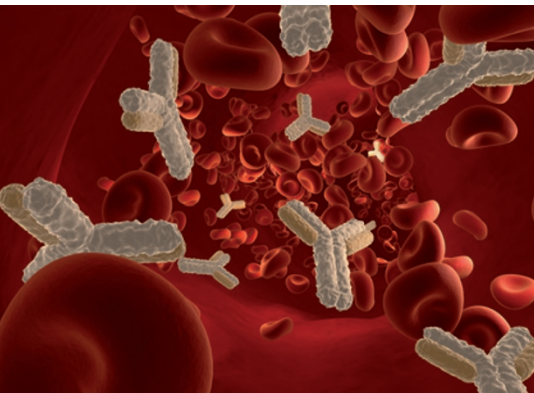
Data from the phase I trials showed that, in a dose-dependent manner, REGN727 significantly reduced levels of LDL cholesterol in healthy adults ( $P < 0.001$ ), atorvastatin-treated adults with familial ( $P < 0.001$ ) or nonfamilial ( $P < 0.001$ ) hypercholesterolemia, and adults with nonfamilial hypercholesterolemia who

were managing their symptoms by diet alone ( $P = 0.002$ ). In the phase II trial, 150 mg REGN727 reduced levels of circulating LDL cholesterol by 72% from baseline when administered subcutaneously every 2 weeks for 12 weeks in atorvastatin-treated patients with LDL-cholesterol levels  $> 100$  mg/dl.

“The effects [of REGN727] on LDL are robust and may increase slightly ... over time,” concludes Dr Stein, who believes that these data are potentially very exciting for patients who do not tolerate or do not respond to statins. Further development of REGN727 therapy is underway and phase III trials have been announced.

Ellen F. Carney

**Original articles** Stein, E. A. *et al.* Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. *N. Engl. J. Med.* **366**, 1108–1118 (2012) | McKenney, J. M. *et al.* Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J. Am. Coll. Cardiol.* doi:10.1016/j.jacc.2012.03.007



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