TRIAL WATCH

PCSK9 antibody reduces LDL cholesterol

Preliminary Phase II trial results for REGN727 — a human proprotein convertase subtilisin/kexin type 9 (PCSK9)-specific monoclonal antibody co-developed by Regeneron and Sanofi — indicate that it effectively and safely reduces levels of low-density lipoprotein-cholesterol (LDL-C) in patients with hypercholesterolaemia undergoing statin therapy.

Statins are widely used to lower levels of LDL-C in patients with hypercholesterolaemia, which is a major risk factor for cardiovascular events. However, "while statins have revolutionized preventive cardiology and routine management of dyslipidaemia, there are two major categories of unmet needs", notes Professor Robert Hegele, Robarts Research Institute, University of Western Ontario, Canada. "First, despite maximal doses and combinations of currently approved drugs, some patients fail to attain their recommended LDL-C target levels, and still suffer heart attacks and strokes. Second, a substantial proportion of patients cannot tolerate existing agents owing to various side effects," he explains.

PCSK9 has recently emerged as a novel target to lower LDL-C levels. Professor Nabil G. Seidah of the Clinical Research Institute of Montreal, Canada, explains: "PCSK9 was first implicated in cholesterol homeostasis following the demonstration that gain-of-function mutations in the *PCSK9* coding region result in a large increase in circulating LDL-C. Subsequent studies revealed that PCSK9 enhances the degradation of the LDL receptor (LDLR)." As a reduction in LDLR levels would decrease LDL metabolism, it was therefore proposed that PCSK9 inhibition might lower LDL levels, and several PCSK9-targeted therapies are now in development (Supplementary information S1 (table)). Furthermore, "studies in mice and humans have shown that statins upregulate *PCSK9* and *LDLR* mRNA, suggesting that an inhibitor of PCSK9 might enhance the LDL-C-lowering effect of statins", says Seidah.

Indeed, the recent REGN727 Phase II trial data support this hypothesis. In one multidose 12-week trial involving 75 patients with heterozygous familial hypercholesterolaemia exhibiting elevated LDL-C levels despite receiving statin therapy, the addition of REGN727 achieved mean LDL-C reductions from baseline ranging from 30% to more than 65%, depending on the dose. And in another 8-week single-dose trial, which studied 90 patients with primary hypercholesterolaemia on a stable low dose of atorvastatin, REGN727 reduced mean LDL-C levels by more than 65%; switching patients to a high dose of atorvastatin with or without REGN727 reduced mean LDL-C levels by 17% and 65%, respectively. A third multidose, 180-patient Phase II trial investigating REGN727 in combination with atorvastatin in patients with primary hypercholesterolaemia is ongoing, and a Phase III trial is expected to commence in the second quarter of 2012.

Importantly, REGN727 was found to be well tolerated in both trials. "Inhibiting PCSK9 function is expected to be specific and to have fewer side effects than statins, which have a more extended repertoire of consequences aside from only reducing LDL production and increasing its uptake by the liver. Combination therapy consisting of a statin and a PCSK9 inhibitor may be beneficial, as it would reduce the effective dose of the former," explains Seidah. "Assuming that the early indications of good tolerability and no unforeseen side effects are borne over the long term, PCSK9 inhibition provides a new treatment option for patients who cannot tolerate existing treatments. The Phase II study results suggest the PCSK9-specific antibodies will work synergistically with statins and provide additional significant reductions in LDL-C levels," adds Hegele.

However, there may be some limitations to this approach. "In mice, loss of PCSK9 results in inefficient liver regeneration following partial hepatectomy, suggesting that reducing PCSK9 levels may have limitations in patients with hepatic diseases or patients who need to undergo liver transplants. Furthermore, LDLR and CD81, which are receptors of the hepatitis C virus, could be upregulated in the absence of PCSK9. Finally, the injection of monoclonal antibodies may not be that safe for long-term use," cautions Seidah. "The difficult but possible identification of an orally active PCSK9 inhibitor may be the next future statin-equivalent drug," he concludes.

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