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TRIAL WATCH

Antisense agent reduces LDL–cholesterol levels in high-risk patients

A Phase III trial of the antisense agent mipomersen in patients with homozygous familial hypercholesterolaemia has demonstrated a 25% reduction (versus 3% for placebo) in levels of low-density lipoprotein (LDL)–cholesterol after 26 weeks of treatment.

Mipomersen — which is being developed by Genzyme and Isis Pharmaceuticals — is a synthetic antisense oligonucleotide that targets messenger RNA encoding apolipoprotein B100 (APOB100). As John Burnett, Consultant Medical Biochemist, Clinical Lipidologist and Clinical Professor at the University of Western Australia, explains: "APOB100 is the structural backbone of LDL that is essential for the assembly and secretion of triglyceride-rich lipoproteins. Because each LDL particle contains a single molecule of APOB100, which cannot be exchanged or lost to other lipoproteins, plasma APOB100 concentrations reflect the number of circulating atherogenic lipoprotein particles. Like LDL–cholesterol, plasma levels of APOB100 are directly related to the incidence of coronary events and cardiovascular deaths."

Homozygous familial hypercholesterolaemia is a rare genetic disorder characterized by extremely high LDL–cholesterol levels. In the trial, the average LDL–cholesterol level of patients at baseline was greater than 400 mg per dl (10.3 mmol per l). Addition of mipomersen (given once a week by injection) to the lipid-lowering therapy currently used by the patients (such as statins and ezetimibe) resulted in an average reduction in LDL–cholesterol levels of more than 100 mg per dl (2.6 mmol per l).

This benefit of mipomersen is based on a novel mechanism of action that can work independently of, or synergistically with, standard medications that reduce LDL–cholesterol levels. "Most treatments to lower plasma LDL particle concentration — for example, statins — do so by inducing clearance of LDL through upregulation of cell surface LDL receptors," says Robert Hegele, Director of the Blackburn Cardiovascular Genetics Laboratory and Professor of Medicine and Biochemistry at the University of Western Ontario, Canada. "However, patients with homozygous familial hypercholesterolaemia completely lack functional LDL receptors, so they are unresponsive to the usual treatments. Targeting APOB100 overcomes this deficiency."

In the trial, the ratio of LDL to high-density lipoprotein levels in patients receiving mipomersen decreased by 34%. Treatment also reduced levels of other atherogenic lipids, including lipoprotein A, very low-density lipoprotein–cholesterol and triglycerides. However, in four patients, levels of liver transaminases were more than three times the upper limit of normal.

As Burnett notes, "Longer-term and more detailed safety evaluations of mipomersen on human hepatic function are needed. In addition, the ability of mipomersen to reduce atherosclerosis and beneficially affect the morbidity and mortality of coronary heart disease has yet to be shown in clinical trials."

Mipomersen might also provide a new option to reduce LDL–cholesterol levels in patients with other inherited disorders of lipoprotein metabolism, such as severe refractory heterozygous familial hypercholesterolaemia and familial combined hyperlipidaemia. "In addition, mipomersen could benefit hyperlipidaemic patients with no obvious genetic disease aetiology who are intolerant of statins or who fail to reach their target LDL level for reduction of cardiovascular risk even with the highest tolerated doses of statins," says Hegele.

Indeed, Genzyme and Isis have completed enrolment for a Phase III trial of mipomersen in patients with heterozygous familial hypercholesterolaemia (which is more common than the homozygous form of the disease) and for a Phase III trial of individuals with hypercholesterolaemia who are at risk of coronary heart disease, with results from both studies expected later this year.