モノクローナル抗体阻害とスタチンの組み合わせのLDL-Cに関する評価

LAPLACE-2：Evolocumabはスタチン単独療法時よりもさらにLDL-Cを良好に低下させ、この結果から2剤併用療法の有効性が示唆される

LAPLACE-2: Evolocumab safely drops LDL cholesterol well below statin-only baseline suggesting efficacy of 2-drug approach

モノクローナル抗体evolocumabはスタチンに追加することにより低密度リポ蛋白（LDL）コレステロールを極めて有意に低下させたとの第III相LAPLACE-2試験の結果が、第63回American College of Cardiology学会で発表された。Evolocumabは、PCSK9を阻害することにより肝臓による血液からのLDL除去能を上昇させる。1,899人の患者が、evolocumabまたはプラセボ、evolocumabとプラセボ、プラセボおよびエゼチミブ、またはプラセボのみの異なる用量およびスケジュールに割り付けられた。Evolocumab治療を受けた全グループにおいてプラセボと比較し極めて有意なLDLコレステロール低下を示した：evolocumab注射を2週間毎に施行する群で66～75%、4週毎の群で63～75%。LDLコレステロール<70mg/dLを達成したのは中等度強化スタチン群で86～94%であり、高度強化群で93～95%であった。エゼチミブは、中等度強化スタチン群でLDLコレステロールを17～20%低下させ、高度強化群で51～62%低下させた。Evolocumabを追加することにより、LDLコレステロールレベルが中等度強化スタチン群で39～49mg/dLに低下し、高度強化群で33～39mg/dLに低下した。

Full Text

The monoclonal antibody evolocumab produced highly significant reductions in low-density lipoprotein (LDL) cholesterol as an add-on to statins in all treatment groups, according to data from the LAPLACE-2 study presented at the American College of Cardiology's 63rd Annual Scientific Session.

"High-risk patients – such as those with clinical cardiovascular disease, high LDL cholesterol levels or diabetes – are ideally treated with high-intensity statins that lower LDL cholesterol by at least 50 percent, but that isn't always possible," said Jennifer G. Robinson, M.D., M.P.H., director of the Prevention Intervention Center at the University of Iowa College of Public Health.

"Many patients can't tolerate high-intensity statins and cannot achieve desired LDL reductions with moderate- or low-intensity statins, and those with high cholesterol levels often need more than high-intensity statins to lower LDL levels adequately." Robinson said evolocumab may be useful for these patients. Unlike statins, which are taken in pill form, evolocumab is administered as an injection.

LAPLACE-2 is a large phase III study of evolocumab in patients randomly assigned to a high- or moderate-intensity statin to reduce LDL cholesterol. Evolocumab works by inhibiting PCSK9, which leads to an increase in the liver's ability to clear LDL cholesterol from the blood. High-intensity statins such as 80-mg atorvastatin and 40-mg rosuvastatin lower LDL by 50 percent or more; moderate-intensity statins such as 40-mg simvastatin, 10-mg atorvastatin and 5-mg rosuvastatin drop LDL levels by 30 to nearly 50 percent. Evolocumab was also compared with ezetimibe, another drug commonly used to lower LDL cholesterol. After a four-week period to stabilize lipids with one of these five statin regimens, 1,899 patients were randomly assigned to different doses and schedules of evolocumab or placebo, evolocumab and placebo, placebo and ezetimibe, or placebo only.

All evolocumab-treated groups showed highly significant reductions in LDL cholesterol versus placebo: 66 percent to 75 percent on a schedule of evolocumab injections every two weeks, or 63 percent to 75 percent on a four-week schedule. Patients achieved an LDL cholesterol level of less than 70 mg/dL in 86 percent to 94 percent in the moderate-intensity statin groups and 93 percent to 95 percent in the high-intensity groups. Ezetimibe reduced LDL cholesterol by 17 percent to 20 percent in moderate-intensity statin groups and 51 percent to 62 percent in high-intensity groups. Adding evolocumab reduced LDL cholesterol levels to 39 mg/dL to 49 mg/dL with moderate-intensity statin regimens and 33 mg/dL to 39 mg/dL with high-intensity regimens. Evolocumab also significantly reduced non-HDL cholesterol, apolipoprotein B and lipoprotein (a) levels.

Efficacy and safety endpoints were met. Evolocumab was well tolerated, with adverse event rates similar to those in placebo and ezetimibe-treated groups and no sign of liver damage or muscle problems.

"Heart attack and stroke remain the leading cause of death in the United States and around the world," Robinson said. "People are excited about PCSK9 inhibitors because they'll let us test whether a whole lot more LDL lowering will result in large additional reductions in cardiovascular events in statin-treated patients."

The ongoing FOURIER trial will assess whether additional lowering of LDL cholesterol with evolocumab, on top of high- and moderate-intensity statin therapy, reduces the number of cardiovascular events over a period of years.

Robinson was an investigator for LAPLACE-2 and consults for Amgen, which funded the study.

ACC2014特集