PCSK9阻害薬の長期的有効性 (Abstract 402-08)

新たなクラスのコレステロール低下薬は1年間の心血管イベントを劇的に減少させた

New class of cholesterol-lowering medications dramatically reduces cardiovascular events at one year

Evolocumab—LDLコレステロールを劇的に低下させることがこれまでに示された治験薬—を内服した患者は、標準治療を受けた患者に比べ、死亡、心筋梗塞または脳卒中発症、入院または血管形成術を必要とする確率が半分に減少したとの研究結果が、第64回American College of Cardiology年次集会で発表され同時に*New England Journal of Medicine*オンライン版に掲載された。Evolocumabは、血中からLDLコレステロールを除去する肝臓の機能を低下させる蛋白である、前駆蛋白質転換酵素サブチリシン／ケキシン9型（PCSK9）を阻害することにより作用するヒトモノクローナル抗体である。研究者らは、この薬剤のLDL低下能を評価したトライアル終了にあたり、さらに今回の1年延長トライアルに参加した患者4,465人を調査した。このオープンラベルスタディにおいて、そのほとんどが中・高程度の強化スタチン療法を施行された標準治療群における心血管イベントは2.18%であった。一方、evolocumabで治療された患者における1年間のイベント率は0.95%であった。Evolocumab群における心血管イベントの53%低下は、複合エンドポイントに含まれた各主要心血管イベントにおいて、また患者サブグループに関係なく一貫していた。

Full Text

Patients taking evolocumab—an investigational therapy previously shown to dramatically lower LDL cholesterol—were half as likely to die, suffer a myocardial infarction or stroke, be hospitalized or need angioplasty compared with those who received standard care, according to research presented at the American College of Cardiology's 64th Annual Scientific Session and simultaneously published online in the *New England Journal of Medicine* in San Diego.

In this open-label study, the rate of cardiovascular events was 2.18 percent after one year in the standard of care group, most of whom were on moderate or high intensity statin therapy. In contrast, patients treated with evolocumab had approximately half the risk or a 0.95 percent event rate after one year.

Evolocumab reduced LDL cholesterol by 61 percent in previous trials. Evolocumab is a human monoclonal antibody that works by blocking proprotein convertase subtilisin-kexin 9 (PCSK9), a protein that reduces the liver's ability to remove LDL cholesterol from the blood.

"The reduction in LDL was profound and that may be why we saw a marked reduction in cardiovascular events so quickly," said Marc Sabatine, M.D., chairman of the TIMI Study Group and a senior physician in the Division of Cardiovascular Medicine at Brigham and Women's Hospital in Boston, and the study's lead author. "It suggests that if we can drive a patient's LDL cholesterol down a large amount to a very low level, we may start to see a benefit sooner than would be expected with a more modest intervention."

At the start of the study, the average LDL cholesterol measure was 120 milligrams per deciliter. Patients receiving evolocumab were able to achieve an absolute reduction of more than 70 milligrams per deciliter reaching 48 milligrams per deciliter on average. Sabatine said this achieved level of LDL cholesterol is much lower than that achieved in the treatment arm of most other trials.

Researchers studied a total of 4,465 patients who, upon completing one of 12 phase II or III trials that evaluated the drug's ability to lower LDL cholesterol, subsequently enrolled in this one-year extension study to investigate the therapy's effect on long-term safety, LDL-lowering and cardiovascular outcomes. Researchers re-randomized patients 2:1 to receive evolocumab injected under the skin either every two or four weeks plus standard care, or standard care alone, which consisted of the lipid-lowering therapy recommended by their treating physician, usually moderate or high-intensity statin therapy. A central committee that was blinded to the treatment groups then reviewed the data and reported the number of deaths, major coronary events, myocardial infarction, stroke, unstable angina requiring hospitalization and coronary revascularization.

The 53 percent reduction in cardiovascular events in the evolocumab group was consistent across each of the major cardiovascular events included in the composite endpoint—death, heart attack, stroke, hospitalization and angioplasty—and among patient subgroups; no differences were found based on age, baseline LDL levels, statin use, primary or secondary prevention or whether they had valve disease.

Adverse events were largely balanced between the two-week and four-week treatment arms and evolocumab was well tolerated.

Still, the results are limited by the nature of the trial, in which there were relatively few cardiovascular outcomes (only 60). An ongoing, highly anticipated trial of 27,500 patients to investigate evolocumab's effect on cardiovascular outcomes is underway; however, data are not expected until 2017.

"We won't have any definitive answers until this larger trial we are doing is complete, but these data now give us a sense for the potential clinical benefit of these drugs," Sabatine said. "We know from previous research that evolocumab lowers LDL cholesterol, but these data offer support for their potential to reduce major adverse cardiovascular events in our patients."

The drug makes sense biologically too, he said. "Patients who genetically have lower levels of PCSK9 activity also have a lower rate of adverse cardiovascular outcomes. Now in our analyses, we see this PCSK9 inhibitor appears to reduce adverse cardiovascular outcomes."

He said the findings are especially good news for patients who, despite taking a statin, are not able to lower LDL cholesterol enough or who cannot tolerate statins for a variety of reasons. Evolocumab is one of three PCSK9 inhibitors being studied in large clinical trials.

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