モノクローナル抗体はスタチン療法の有効性に上乗せできる

新たなモノクローナル抗体を注射することによりスタチンのLDL低下の有効性が上乗せされる

Injection of novel monoclonal antibody adds to effectiveness of LDL lowering with statins

新たなモノクローナル抗体は循環LDLコレステロールを40～72%低下させ、現在の標準治療に抵抗性の患者の新たな治療選択となる可能性をもつとの研究結果が第61回American College of Cardiology学会で発表され、Journal of the American College of Cardiologyオンライン版に掲載された。近年の発見により、スタチン療法がLDL受容体の破壊に繋がる酵素であるPCSK9の産生を刺激することが示された。今回のスタディでは、PCSK9に結合しその作用を遮断しLDL受容体の変性を防ぐモノクローナル抗体SAR236553/REGN727の効果を試した。この多施設無作為化トライアルではLDLコレステロール値が100mg/dL以上の患者183人を観察した。循環LDLコレステロールは、50、100、または150mgを2週毎に投与する群に割り付けられた患者において、それぞれ40%、64%、および72%低下した。LDLコレステロールは200または300mgを4週毎に注射された患者において、43%および48%低下した。プラセボ群では循環LDLコレステロールが5%減少した。

Full Text

A novel monoclonal antibody identified in a new study dramatically lowered circulating LDL cholesterol by 40 percent to 72 percent, a development with potential to provide a new option for patients who are resistant to cholesterol-lowering drugs such as statins or to the current standard of care, according to research presented at the American College of Cardiology's 61st Annual Scientific Session.

The traditional statin therapy lowers LDL cholesterol by inhibiting the production of cholesterol in liver cells, causing an increase in the number of LDL receptors on the cell surface. These receptors grab LDL circulating in the blood and deliver it into the liver, where it is subsequently processed and flushed out of the body. About one in five people with high low-density lipoprotein (LDL) are resistant to cholesterol-lowering drugs such as statins, and for many others the current standard of care does not lower cholesterol enough.

A recent discovery showed that statin therapy stimulates the production of PCSK9, an enzyme that leads to the destruction of LDL receptors. The present study tested SAR236553/REGN727, a monoclonal antibody that binds to PCSK9, blocking its effects and preventing the degradation of LDL receptors.. More LDL receptors mean more LDL is brought out of the blood into the liver, and circulating levels of LDL cholesterol decrease.

"We've known for 30 years that lowering LDL cholesterol with statins lowers the risk of heart disease and that the more you can lower LDL cholesterol, the greater reduction in that risk," said James McKenney, PharmD, chief executive officer of National Clinical Research, and the study's lead investigator. "However, we know in some cases that even the best statin can't get LDL cholesterol as low as it should be."

This multi-center, randomized trial looked at 183 patients who had an LDL cholesterol reading of 100 mg/dL or higher. The patients had already been treated with atorvastatin for more than six weeks at stable doses of 10, 20 or 40 mg. The participants were divided into six groups: a placebo control; three groups who received a subcutaneous injection of SAR236553/REGN727 every two weeks (Q2W) at doses of either 50, 100, or 150 mg; and two groups who received an injection of SAR236553/REGN727 at 200 or 300 mg every 4 weeks (Q4W), alternating with placebo shots at two weeks. The study's primary endpoint was the percentage LDL cholesterol reduction from baseline to after 12 weeks.

Dr. McKenney reported a remarkable dose-response to SAR236553/REGN727 injections. Circulating LDL cholesterol was lowered by 40 percent, 64 percent, and 72 percent in patients assigned to 50, 100, or 150 mg Q2W doses, respectively. LDL cholesterol was reduced by 43 percent and 48 percent for patients who received 200 or 300 mg Q4W injections. The placebo group reported a 5 percent reduction of circulating LDL cholesterol.

"Our LDL cholesterol treatment goals were less than 100 or 70 mg/dL," Dr. McKenney said. "All of the participants receiving one of our doses met those goals."

Dr. McKenney said the results surprised him, "Statins are good medicines and getting a 70 percent reduction on top of them is remarkable."

The SAR236553/REGN727 antibody was discovered two years ago, and these are the first Phase II results for an anti-PCSK9 antibody to be presented. Dr. McKenney said a longer study is needed to establish the long-term safety of the antibody, but the results from this trial were promising, with only one adverse reaction reported.

"This is a very hopeful step in the treatment of heart disease in this country," said Dr. McKenney.

This study was funded by Sanofi US, Bridgewater, N.J., and Regeneron Pharmaceuticals, Tarrytown, N.Y. Dr. McKenney reports that he is an employee of a research company that has received research funding from Regeneron and Sanofi.

The study was published online in the Journal of the American College of Cardiology at the time of presentation.

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