

PCSK9 INHIBITORS: IMPACT ON HIGH-RISK PATIENTS AND APPROPRIATE CLINICAL USE

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Abstract

•PCSK9 gene was identified as the third gene of familial hypercholesterolemia (FH) in 2003. Gain-of-function (GOF) mutations in PCSK9 gene cause autosomal-dominant hypercholesterolemia, and we have reported PCSK9 GOF mutation account for 5% of FH heterozygotes in Japan. Simultaneously, loss-of-function (LOF) mutations in PCSK9 gene were found to be common in the Western countries, and the lower LDL-C levels of PCSK9 LOF carriers were protective against cardiovascular disease in many cohorts.

•PCSK9 has become a promising target of cardiovascular disease, and monoclonal PCSK9 antibodies, evolocumab and alirocumab, have proved their cardiovascular risk reduction in addition to maximum tolerated dose of statins. Now PCSK9 siRNA drug, inclisiran, has been in clinical trial stage.

•Cardiovascular disease has been a great burden in many countries. Even though statins have saved many lives, big residual risk still exists. PCSK9 inhibitors propose one answer for this. “Further big reduction in LDL-C.”

•PCSK9 antibodies reduce LDL-C levels further 60% over maximum tolerated lipid-lowering drugs, and show less serious adverse events probably than statins. However, expensive cost of these drugs requires us appropriate use from the viewpoint of medical economics.

•Japan Atherosclerosis Society (JAS) Working Group reported statement for appropriate use of PCSK9 inhibitors. One of the best indications should be secondary prevention of heterozygous FH patients with particularly high risk and difficulties to achieve LDL-C less than 70mg/dL with maximum tolerated statin with ezetimibe. In secondary prevention of non-FH, if LDL-C levels cannot be achieved less than 70mg/dL with maximum drugs, the patient may be a FH. Also, PCSK9 inhibitors are useful for high-risk patients with statin intolerance. If PCSK9 inhibitor shows poor efficacy, this strongly suggests a possibility of homozygous FH, because PCSK9 inhibitor with statins is the best clinical test of LDL-receptor function.

•PCSK9 inhibitors should be used among patients still in very high-risk with maximum lipid-lowering drugs. These patients will be benefitted greatly from their use.

Keywords

PCSK9 inhibitor, familial hypercholesterolemia, statin intolerance, acute coronary syndrome