Cardiovascular Risk Management Targeting Inflammation in Addition to Lipid-lowering Therapy

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Myocardial infarction is often caused by the rupture of unstable plaque in atherosclerosis with mild-to-moderate stenosis. Research has revealed that local tissue inflammation is closely involved in the rupture of atherosclerotic plaque.¹ Stabilization of atherosclerotic plaque by strictly managing the risk factors for coronary artery disease is a crucial strategy to prevent the recurrence of myocardial infarction. Among the risk factors for coronary artery disease, high LDL cholesterol (LDL-C) level contributes most to the development of atherosclerosis. The incidence of cardiovascular events decreases in conjunction with decreasing LDL-C levels by statins (the incidence decreases by 28 % for every 38.7 mg/dL drop in LDL-C level).² Lipid-lowering drugs besides statins include ezetimibe, which is a cholesterol absorption inhibitor, and monoclonal antibodies against PCSK9 (i.e., PCSK9 inhibitors; PCSK9 is an enzyme that clears the LDL-C receptor from the liver). Research has revealed that administering ezetimibe or a PCSK9 inhibitor along with a statin more potently lowers LDL-C level than administering statin alone, thereby further reducing the incidence of cardiovascular events.^{3,4} If an individual is at a risk of developing cardiovascular disease, the predominant theory on LDL-C is “the lower the better,” i.e., the LDL-C level should be lowered to its fetal level (approximately 40 mg/dL). At present, no studies have indicated that mortality increases at LDL-C level <40 mg/dL. Potent lowering of LDL-C level reduces the risk of cardiovascular events by approximately 40 %. In other words, the risk of such events remains at approximately 60 % despite potent lowering of LDL-C level. Therefore, what is this residual risk?

The results of the CANTOS trial were announced at a recent European Society of Cardiology Congress (ESC2017, Barcelona, Spain).⁵ Remarkably, it was found that a drug with only anti-inflammatory action and no lipid-lowering action inhibited the development of

cardiovascular disease. Subjects in the trial were patients with a history of myocardial infarction and a high-sensitivity CRP level of ≥ 2 mg/L. In the trial, the efficacy of canakinumab, a selective IL-1 β inhibitor, was examined. Canakinumab provides an anti-inflammatory action by blocking the IL-1 β –CRP pathway and is used to treat rheumatic arthritis-related diseases. In patients with persistently elevated CRP level after non-fatal myocardial infarction, inhibiting IL-1 β caused CRP level to decrease in a dose-dependent manner. Because IL-1 β is an inflammatory regulator, inhibiting IL-1 β caused CRP level to decrease, which is not surprising, but the key point is that CRP level decreased even though LDL-C level remained unchanged. Patients who were administered canakinumab at a dose of 150 mg every 3 months had a reduced risk of myocardial infarction, stroke, and cardiovascular mortality after 4 years. IL-1 β is a cytokine that plays an essential role in regulating inflammation; therefore, inhibiting its action can lead to complications such as exacerbating infection. Nonetheless, no differences in the incidence of serious infections between groups were noted in the trial.

In the JUPITER trial, patients with high-sensitivity CRP levels above 2 mg/L but with LDL-C levels below 130 mg/dl were administered a statin for primary prevention.⁶ It was found that decreased LDL-C and CRP levels reduced the risk of cardiovascular events. Accordingly, observers stated that statins might reduce the risk of cardiovascular events through lipid-lowering action “coupled with” anti-inflammatory action. Unlike the results of the JUPITER trial, the results of the CANTOS trial were unaffected by lipids, and anti-inflammatory action alone reduced the recurrence of atherosclerosis. Inflammation is a key component of residual cardiovascular risk despite potent lipid-lowering therapy, and drugs such as canakinumab could be used to potentially target that inflammation. ■

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