Targeting Inflammation and Immune System in Acute Myocardial Infarction

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Over more than two decades, the concept of atherosclerosis has developed and lead to inflammatory hypothesis. Inflammation plays an important role on pathogenesis of atherothrombosis and coronary heart disease (CHD), including acute coronary syndrome (ACS).[1,2]

One of inflammatory markers, C-reactive protein (CRP), is a biomarker for the acute-phase of inflammatory response, which is produced by hepatocytes through stimulation of pro-inflammatory cytokines, particularly interleukin-6 (IL-6). It is associated with an increased cardiovascular risk in patients with previous history of atherosclerosis. Some studies have reported that the increase of CRP level is an independent prognostic marker for recurrent and non-fatal myocardial infarct (MI) or death due to cardiac diseases.[3,4]

Gal-3 is a marker involved in fibrosis, inflammation and reconstruction of cardiac tissue. Some studies have demonstrated that there is an elevated level of systemic Gal-3 in the events of acute myocardium infarct (AMI).[5]

Meanwhile, myeloperoxidase (MPO) is a proteolytic enzyme released by activated neutrophils and is considered as a systemic marker of neutrophils activation.[6] In ST-elevation myocardium infarct (STEMI), the plasma level of MPO shows a biphasic response with a peak at the early stage immediately before primary coronary intervention (PCI) takes place and the second peak occurs at 24 hours after reperfusion.[7] MPO is also independently associated with hospital mortality in a population of patients with STEMI.[8]

Although the management of ACS has been demonstrated to be beneficial for secondary prevention of coronary heart disease (such as using statin and aspirin) and also seemed to have positive effect on inflammation, the identification of effective management, specifically targeting inflammation, has been not been comprehensively understood.[9]

The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) supported targeting inflammation as a potential effective treatment for chronic coronary heart disease. In the CANTOS study, canakinumab, a monoclonal antibody that inhibits interleukin-1β, reduced the level of hsCRP and caused lower risk of composite endpoint of death due to cardiovascular diseases, myocardial infarct or stroke compared to placebo.[10]

However, non-specific anti-inflammatory treatment using methotrexate in the Cardiovascular Inflammation Reduction Trial (CIRT) study did not show any reduced hsCRP and demonstrated that there is no benefit associated with cardiovascular outcomes,[11] which left us with a question whether direct intervention on inflammation could improve cardiovascular outcomes.

Acetylcysteine, a thiol-containing

antioxidant, is often used to treat various pulmonary diseases and acute acetaminophen intoxication.[12] Some studies have reported that administration of NAC, in combination with NTG and streptokinase, was associated with significantly less oxidative stress, a trend toward more rapid reperfusion, and better preservation of left ventricular function in patients with evolving acute myocardial infarction.[13] Sochman et al[14] reported that patients treated with streptokinase and NAC (100 mg/kg) had significantly more favourable values of the monitored parameters than those treated with streptokinase alone.

Trisulo et al.[15] reported the effect of 600 mg N-acetylcysteine (NAC) supplementation 3 times daily for 3 days on immune system of patients with AMI. The investigators randomly included 32 AMI patients with ST segment elevation (STEMI) who received fibrinolytic treatment: 17 patients received standard therapy and 600 mg of oral NAC every 8 hours for 3 days and 15 patients received standard therapy as the control. The levels of high sensitivity C-reactive protein (HsCRP), MPO, and Galectin-3 of both groups were evaluated at admission and after 72 hours of care. Data regarding those receiving PCI and statin treatment in both groups were not being reported.

At admission, there was no significant difference regarding HsCRP, MPO, and Gal-3 levels between NAC and control group; while after 72 hours receiving NAC treatment, the levels of HsCRP, MPO, and Gal-3 were significantly lower in the treatment group compared to the control group. In the NAC group, after 72 hours compared to at admission, there were significant differences of HsCRP, MPO, and Gal-3 levels; while in the control group, such differences were not found. There were significant differences on HsCRP, MPO and Gal-3 levels between the NAC and control groups; therefore, it is concluded that oral 600 mg NAC supplementation every 8 hours for 72 hours can lower HsCRP, MPO and Gal-3 levels in AMI patients receiving fibrinolytic therapy. Data about side effects had not been reported in the study.

Results of the study has provided additional evidence that inflammatory and immune system targeting drugs can lower the levels of some inflammatory and fibrosis markers. It opens greater opportunity for further studies to provide evidences whether those drugs are also beneficial in reducing cardiovascular outcome in ACS patients without causing side effects. Whether NAC can be used as additional therapy to provide better management of AMI or not, still needs further studies with bigger sample size of patients to evaluate the effect of NAC on cardiovascular morbidity and mortality.

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