Acute decompensated heart failure (ADHF) is a major, growing health problem throughout the world. In contrast to advances in the therapy of chronic HF, meaningful improvements in treatment and outcomes are scant in patients with ADHF. Despite several attempts, no medical therapy has been shown to improve the natural history of ADHF. Activation of systemic inflammation and worsening of renal function are common and strongly associated with the pathogenesis of ADHF and poor outcomes.1,2 Previous studies have shown that the early use of high-dose statin loading has anti-inflammatory and renoprotective effects in patients with acute coronary syndrome (ACS).3,4 These findings suggest that early high-dose statin loading may be an effective adjunctive therapy for ADHF, but this remains to be confirmed.

Is High-Dose Statin Loading Effective for Acute Decompensated Heart Failure?
– Insight of Inflammation and Acute Kidney Injury –

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In this issue of the Journal, Oh et al5 investigate the acute effects of high-dose statin loading (atorvastatin 80 mg/day for 3 days) on surrogate biomarkers in hospitalized patients with ADHF in a prospective, single-center, randomized controlled, open-label pilot study. They show that oral high-dose atorvastatin loading was safe, but did not effectively reduce surrogate biomarkers of ADHF from admission to hospital day 4. This study is interesting and important because it is the first to investigate the safety and acute efficacy of high-dose statin loading in patients with ADHF. However, several points require further clarification, and these results must be confirmed by prospective studies in larger numbers of patients.

Why Was High-Dose Atorvastatin Loading Ineffective for Reducing Surrogate Biomarkers of ADHF?
The inability of high-dose atorvastatin to reduce surrogate biomarkers of ADHF might be attributed to several factors. First, the study by Oh et al5 was underpowered because of the small sample size. In addition, before hospitalization, statins had been received in 39% of the statin-loading group and 24% of the control group. Most previous studies assessing the effects of statin loading excluded patients who had received statins, because the effects of statin loading should be examined in only statin-naïve patients. Furthermore, the clinical characteristics and pathophysiology of ADHF are complex and multifactorial. Patient selection may therefore play an important role in determining the effects of a given therapy. The efficacy of pharmacological therapy may be related to left ventricular function, ischemic vs. nonischemic etiology, underlying disease, comorbidities, and concomitant medications. To evaluate the effects of adjunctive pharmacological therapy, considerably larger numbers of patients are needed.

Second, the dose and duration of atorvastatin used in the study by Oh et al5 might have been inadequate to produce discernible effects in patients with ADHF. The MIRACL study6 demonstrated that high-dose atorvastatin (atorvastatin 80 mg/day started within 24–96 h after admission and continued for 16 weeks) enhanced the decline in inflammatory markers such as high-sensitivity C-reactive protein (hsCRP) in patients with non-ST-segment elevation ACS. Both the dose and duration of atorvastatin was adequate to decrease inflammatory markers in the MIRACL study.6 However, the conditions and pathophysiology of HF differ from those of ACS. The efficacy and safety of statins in patients with HF remain controversial. Neurohumoral activation involving proinflammatory cytokines plays an important role in the pathogenesis of HF, and inflammatory markers such as hsCRP are useful prognostic factors in patients with chronic HF. Sola et al demonstrated that atorvastatin attenuates adverse left ventricular remodeling and reduces several inflammatory markers in patients with nonischemic HF.7 Recently, however, 2 large, well-conducted, randomized, placebo-controlled studies, the CORONA8 and GISSI-HF9 trials, showed no benefit of statin treatment in terms of improving clinical outcomes in patients with chronic systolic HF. The retrospective analysis of the CORONA study10 showed that rosuvastatin treatment was associated with better outcomes in patients with high baseline hsCRP levels. Although the efficacy of statins in patients with chronic HF has not been established by large randomized trials, hsCRP-guided statin treatment might be beneficial in this population. However, as compared with chronic HF, ADHF is a dynamic process differing substantially from the more stable phase of chronic HF. In ADHF, excessive inflammatory and neurohumoral overactivation and worsening of renal function can occur, further contributing to the development and progression of ADHF. Therefore, a higher loading dose or a longer duration of statin treatment than those used in the study by Oh et al5 might be needed to attenuate these conditions. The effects of pharmacological intervention most likely depend on the dosage and/or duration of treatment.
Another limitation is that the effects of statin loading cannot be adequately evaluated on the basis of the changes in surrogate biomarkers from admission to hospital day 4. After hospital day 4, activation of systemic inflammation and worsening of renal function may persist, even if a patient’s condition has stabilized.

Furthermore, in the study by Oh et al.,

worsening renal function (WRF) was defined as an increase in serum creatinine by >0.3 mg/dl. The PRATO-ACS study showed that high-dose rosuvastatin given on admission to patients with ACS who were scheduled to undergo an early invasive procedure prevents contrast-induced acute kidney injury. However, in the PRATO-ACS study, contrast-induced acute kidney injury was defined as an increase in serum creatinine concentration by ≥0.5 mg/dl or to ≥25% above the baseline level within 72 h after contrast administration. A standard definition of “WRF” is unavailable, and the incidence of WRF has varied widely according to the definition used in previous studies. In the study by Oh et al.,
high-dose statin loading did not significantly improve renal function as compared with the control group. However, renal function as assessed by estimated glomerular filtration rate (eGFR) significantly improved from admission to hospital day 4 in the statin group, but not in the control group. Moreover, high-dose statin loading substantially and significantly decreased urinary albumin excretion (UAE). These improvements were also seen in the control group, but tended to be better in the statin group. UAE is a powerful prognostic marker independent of renal function in patients with chronic HF. A recent meta-analysis of randomized, placebo-controlled trials demonstrated that statins are associated with significant reductions in UAE. A recent meta-analysis of randomized studies showed that high-dose statin loading substantially and significantly decreased urinary albumin excretion (UAE). These improvements were also seen in the control group, but tended to be better in the statin group. UAE is a powerful prognostic marker independent of renal function in patients with chronic HF. A recent meta-analysis of randomized, placebo-controlled trials demonstrated that statins are associated with significant reductions in UAE.

Future Treatment of ADHF

ADHF is the most common cause of cardiovascular hospitalization and is now a worldwide clinical problem because of its high rates of mortality, morbidity, and readmission. However, the basic treatment of ADHF has not changed, and therapeutic strategies remain challenging. Although high-dose statin loading was not shown to be effective in the study by Oh et al., further investigations of this pharmacological therapy are needed.

Disclosures

None.

References