COMMENT

Statins for heart failure: still caught in no man’s land?

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ABSTRACT

Statins are well-known for their ability to lower serum cholesterol levels, but have properties beyond mere cholesterol reduction, including an improvement in endothelial dysfunction, release of endothelial progenitor cells, anti-inflammatory properties and a number of antitumour activities. In the present issue of Clinical Science, Stumpf et al. show that a 4-week treatment course with the lipophilic statin atorvastatin ameliorates left ventricular remodelling and function, reduces serum levels of TNF-α (tumour necrosis factor-α), IL (interleukin)-6 and MCP-1 (monocyte chemoattractant protein-1), and increases both serum and myocardial levels of IL-10. The authors hypothesize that this shift from a pro- to an anti-inflammatory response might be beneficial in the clinical setting, because patients with low levels of IL-10 may fare worse than those with higher levels. In light of the recent setbacks with rosuvastatin in large-scale clinical trials, this notion requires further investigation, but highlights the need to identify those patients with heart failure who are likely to benefit from statin therapy.

Statins can lower serum cholesterol levels. That fact is beyond doubt. Patients with or at high risk of atherosclerosis benefit from statin treatment: another fact that is well supported by a large number of studies in both primary and secondary prevention. However, whether or not cholesterol reduction with statins is an aim worth pursuing in certain chronic conditions is an entirely different matter, and particularly the concept of cholesterol reduction in patients with HF (heart failure) has recently been called into question [1].

The good news about statins is that they possess properties beyond mere cholesterol reduction. These pleiotropic effects include an improvement in endothelial dysfunction [2], release of endothelial progenitor cells, anti-inflammatory properties and a number of antitumour activities [3,4]. The improvement in endothelial function mediated by atorvastatin, for example, which has been demonstrated in an elegant animal model of HF post-myocardial infarction, is probably due to an increase in NO production and a reduction in its inactivation [5]. Atorvastatin at a dose of 10 mg once a day for 4 weeks also achieved an improvement in forearm vasodilatory responses to reactive hyperaemia in patients with HF [6].

A large number of studies have shown the beneficial effects of statins with regards to markers of inflammation including CRP (C-reactive protein), TNF-α (tumour necrosis factor-α), and IL (interleukin)-1 and IL-6 [7–10]. Overactivity of the immune system has been a matter of ongoing concern in patients with HF for almost two decades now [11], and, in particular, TNF-α and its soluble receptors have been demonstrated to be markers of an adverse prognosis in patients with this disease [12,13]. However, large-scale studies to directly antagonize this cytokine with specific antibodies involving more than 2000 patients ended in disappointment [14,15]. It therefore appears the right time to choose novel weapons

Key words: atorvastatin, heart failure, inflammation, interleukin-10, myocardial infarction.

Abbreviations: CI, confidence interval; CORONA, Controlled Rosuvastatin Multinational Trial in Heart Failure; CRP, C-reactive protein; HF, heart failure; HR, hazard ratio; IL, interleukin; LVEF, left ventricular ejection fraction; TNF-α, tumour necrosis factor-α.

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in the battle against HF, and the overactivity of the immune system is still an interesting target [16].

As statins possess anti-inflammatory properties, the results of prospective large-scale studies of these drugs in patients with HF were eagerly awaited. The results of two such trials are currently available. The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) study was a double-blind study that enrolled 5011 patients with ischaemic disease and an impaired LVEF (left ventricular ejection fraction), who were randomized to placebo or rosuvastatin at a dose of 10 mg once a day [17]. Patients were treated for a median follow-up of 32.8 months. Unfortunately, no significant difference in the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke, was observed between the rosuvastatin and the placebo groups (HR [hazard ratio], 0.92 [95% CI [confidence interval], 0.83–1.02]; P = 0.12). The prospective multicentre randomized double-blind GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca) trial was published in late August 2008 [18]. For this study, 4574 patients were randomized to the same regimen with rosuvastatin (10 mg once a day) or placebo. As with the CORONA study, there was no difference in the primary end points of time to death (HR, 1.00 [95% CI, 0.90–1.12]; P = 0.94) and time to death or hospitalization for cardiovascular reasons (HR, 1.01 [95% CI, 0.91–1.11]; P = 0.90) between the two study arms.

The publication of these two studies was a serious blow to the ‘statins in HF’ story. An earlier, yet less heeded, setback was the publication of a prospective study that was initially named the UNIVERSE (rosUvastatin Impact on VEntricular Remodeling, cytokineS and neurohormonEs) trial, in which 86 patients were randomized to placebo or rosvastatin at an increasing dose (target: 40 mg once a day) in a double-blind fashion [19]. Treatment for 6 months did not yield any improvement in the plasma levels of CRP, TNF-α, IL-6 or BNP (B-type natriuretic peptide). Additionally, there was no significant improvement in LVEF.

One may wonder whether these studies should set an end to studying statins in HF. However, as Sir Arthur Conan Doyle pointed out “it is a capital mistake to theorize before you have all the evidence. It biases the judgement” [20]. Thus one may alternatively wonder whether rosuvastatin was simply the wrong statin or used at a wrong dose. Indeed, rosuvastatin is one of the very few hydrophilic statins [21], and it has been suggested that lipophilic statins might be able to enter biological membranes more easily, which yields more pleiotropic effects [22]. On the other hand, it is intriguing to note that higher cholesterol levels are associated with better (not worse) survival in patients with HF in several retrospective analyses [23,24]. A potential explanation is that cholesterol-containing lipoproteins can detoxify the bacterial cell-wall component endotoxin [25,26], which appears to play a significant role in patients with HF during oedematous decompensation [27], but it may also be responsible for immune activation in these patients under stable conditions [11]. The results available should therefore set the stage to undertake studies in HF that fulfill two criteria: (i) to investigate statins at doses that do not lower cholesterol values (but confer pleiotropic effects), and (ii) to use statins other than rosvastatin and potentially pravastatin, the second hydrophilic substance.

The study by Stumpf et al. [28] in the present issue of Clinical Science comes therefore at the right time. Although the authors [28] do not provide data on cholesterol, they show that a 4-week treatment course with the lipophilic statin atorvastatin ameliorates left ventricular remodelling and function, reduces serum levels of TNF-α, IL-6 and MCP-1 (monocyte chemoattractant protein-1), and increases both serum and myocardial levels of IL-10. The authors hypothesize that this shift from a pro- to an anti-inflammatory response might be beneficial in the clinical setting, because patients with low levels of IL-10 may fare worse than those with higher levels, as suggested by several studies [29]. This notion highlights another important fact: we need to identify those patients who are likely to benefit from statin therapy. This was not even an inclusion criterion in the studies of antibody therapy against TNF-α [30]. It could well be that the levels of pro- or anti-inflammatory markers could help in that sense. It also appears that it is a very long way until we have ‘all the evidence’ for a clear statement about statins in HF.

REFERENCES
Comment

8 Solheim, S., Seljeflot, I., Arnesen, H., Eritsland, J. and Eikvar, L. (2001) Reduced levels of TNF-α in hypercholesterolemic individuals after treatment with pravastatin for 8 weeks. Atherosclerosis 157, 411–415


30 Anker, S. D. and Coats, A. J. (2002) How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. Int. J. Cardiol. 86, 123–130