Review

Immunological Aspects of the Statins' Function in Patients with Heart Failure: A Report from the Annual Conference of ESC – Heart Failure 2005

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The annual meeting of the Heart Failure Association of ESC in Lisbon, in June 2005, was exceptionally successful. There were many very interesting presentations and workshops with the unique title: *Statins in heart failure- Cholesterol-lowering is not the only goal.* Heart failure (HF) is a progressive disease with coronary artery disease (CAD) as the most often underlying etiology. Treatment to prevent progression of heart failure has been targeted to reverse the consequences of HF and to a less extent the cause – the atherosclerotic plaque itself. On the average 50% of patients with heart failure are treated with lipid intervention. Lipid-lowering treatment with statins clearly reduces morbidity and mortality of patients with documented CAD. Since the prevalent etiology of heart failure is CAD, its prevention may reduce heart failure progression. However, recent studies suggest that pleiotropic effects of statins are more important than the influence related to their cholesterol lowering mechanism. Furthermore it is suggested that low levels of circulating lipoproteins and cholesterol may be independent predictors of impaired outcome in patients with heart failure. There are some possible explanations for this finding. High levels of cholesterol can be beneficial to heart failure patients; cholesterol-rich serum lipoproteins are able to modulate inflammatory immune function because they bind and detoxify bacterial lipopolysaccharide, a very strong stimulator of the release of proinflammatory cytokines that promote heart failure progression and death. So current recommendations strongly emphasize that the aim of treatment of HF is not to lower cholesterol. *Cellular & Molecular Immunology*. 2005;2(6):433-437.

Key Words: heart failure, hypothesis, statins, pleiotropic effect

Introduction

The annual meeting of the Heart Failure Association of European Society of Cardiology (HFA of the ESC) "HEART FAILURE 2005" in Lisbon, Portugal, June 11-14, 2005, was exceptionally successful. At the Opening Ceremony, the HFA celebrated the 10th Anniversary of Heart Failure within the ESC. Over 4,000 participants took part in this event, 1,195 abstracts were submitted for the review process, out of which 554 have been accepted.

It was a very successful meeting which took place in great scene. Lisbon is a beautiful town with special atmosphere and with great moist climate from Tag River and Atlantic Ocean. During the conference the weather – sunny with the temperature till 24 degrees, was suitable to the important debates which took place in modern Lisbon Congress Centre on the Praça das Indùstrias (1).

There were many very interesting oral presentations and posters. In our opinion two workshops were uniquely interesting. The first - *Clinical research methodology in heart failure* (Chairmen: Prof. Mcmurray from Glasgow and Prof. Abreu E Lima from Porto) was dedicated to two essential subjects - the suitable preparing of a manuscript to be published in the best medical journal and the preparation and management of clinical trial. Among the second, I think the most interesting one was *Statins in heart failure - Cholesterol - lowering is not the only goal* (Chairmen: Prof. Kjekshus from Oslo and Prof. Charron from Paris), whose authors presented the mechanisms, influence and the role of statins in patients with heart failure (1).

Dr. M Boehm from Homburg/Saar described the basic

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mechanisms of inflammatory hypothesis of heart failure and the potential role of statins in this condition.

Heart failure (HF) is a progressive disease with coronary artery disease (CAD) as the most often underlying etiology. Treatment to prevent progression of heart failure has been targeted to reverse the consequences of HF and to a less extent the cause - the atherosclerotic plaque itself. On the average, 50% of patients with heart failure are treated with lipid intervention. Heart failure is associated with an increase in low-density lipoproteins (LDL) and triglycerides while high-density lipoproteins (HDL) are lower. In NYHA (New York Heart Association) class IV, cholesterol is reduced due to depressed production in the liver (2).

Lipid-lowering treatment with statins clearly reduces morbidity and mortality of patients with documented CAD (both in primary - WOSCOPS [*West of Scotland Coronary Prevention Study*], AFCAPS/TexCAPS [*Air Force/Texas Coronary Atherosclerosis Prevention Study*] and HPS (*Heart Protection Study*) studies, and in secondary prevention- 4S [*Scandinavian Simvastatin Survival Study*], CARE [*Cholesterol and Recurrent Events*] and LIPID [*Long term Intervention with Pravastatin in Ischemic Disease*]). Since the prevalent etiology of heart failure is CAD, its prevention may reduce heart failure progression. Consistent with this hypothesis, a subanalysis of the 4S trial showed that simvastatin treatment (20-40 mg) could prevent the occurrence of overt heart failure in patients with coronary artery disease - reduced overall mortality from 12% to 8% (a 30% reduction), and the decrease in mortality was almost exclusively the result of a 42% reduction in coronary death (3, 4).

According to the outcomes obtained in 4S study, the essential conclusion that heart failure may be a target condition for treatment with statins in patients with CAD arose. The above hypothesis was further supported by a retrospective analysis in chronic heart failure patients in the *Losartan Heart Failure Survival Study* (ELITE II), where the overall mortality was reduced from 17.6% in patients treated without statins, to 10.6% among patients treated with statin ($p < 0.003$). Additionally, the use of statins was associated with a 36% reduction in relative hazard for death. Next two studies supported the above observations. The first one reported on statin therapy being an independent predictor of improved survival without the necessity of urgent transplantation in patients with advanced (mean EF - 25%), both ischemic and non-ischemic HF. The second one was a retrospective analysis of the OPTIMAAL Trial (*Losartan versus captopril following acute myocardial infarction*). The effect of initiating statin or β-blocker treatment on patients with heart failure following acute myocardial infarction was compared with that of neither or both treatments. Early initiation of statins alone was associated with a 26.1% decrease of all-cause mortality. The effect of statins appeared to be additive to that of β-blockers, and the combination of statins and β-blockers was associated with a 48.3% risk reduction (5, 6).

Furthermore, the studies of last few years suggest that pleiotropic effects of statins are even more important than the influence related to their cholesterol lowering mechanism. It has been hypothesized that the inhibition of hydroxymethyl glutaryl coenzyme A reductase can interfere with the synthesis of anti-inflammatory components, thus down-regulating cytokine and chemokine production, which is activated in patients with heart failure.

Based on this encouraging evidence, there is suggestion that low levels of circulating lipoproteins and cholesterol may be independent predictors of impaired outcome in patients with heart failure. There are some possible explanations for this supposal. High levels of cholesterol can be beneficial to heart failure patients; cholesterol-rich serum lipoproteins are able to modulate inflammatory immune function because they bind and detoxify bacterial lipopolysaccharide, a very strong stimulator of the release of proinflammatory cytokines that promote heart failure progression and death (*endotoxin-lipoprotein hypothesis*) (4, 7).

Dr. Ulf Landmesser (Hanover, Germany) discussed how low cholesterol levels are associated with poor outcomes in patients with congestive heart failure. An elevated serum cholesterol level was a risk factor for the development of HF in the Framingham study. However, the presence of heart failure was an exclusion criterion in nearly all former trials of statins. Only two large lipid trials (CARE, HPS) allowed including patients with mild to moderate HF. Consequently, in recent heart failure randomized controlled trials the use of statins is increasing, e.g., in the COMET (*Carvedilol Or Metoprolol European Trial*) and BEST (*Beta-blocker Evaluation of Survival Trial*) trials the proportion of patients on statins was 21 and 23% respectively, while in the EPHESUS (*Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study*), CHARM trial (*Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity*), and in conventionally-treated arm of the MADIT II (*Multicenter Automatic Defibrillator Implantation Trial-II*) trial this proportion was 47, 53 and 65% respectively (8).

Statins were shown to reduce inflammation and restore endothelial function, and their actions that may be beneficial to the patients with heart failure. In available studies statins appeared to improve the autonomic cardiac control - heart rate variability, baroreflex sensitivity, to prevent post-infarction ventricular remodeling and reduce LV mass, as well as to improve renal function. Other important benefits included promotion of bone-marrow endothelial progenitor cells mobilization and re-endothelisation of injured arteries. Clinically proven antiarrhythmic effects of statins in the AVID study (*Antiarrhythmics Versus Implantable Defibrillator*) and in patients with atrial fibrillation may provide additional gains. In addition, antithrombotic action lengthens the list of beneficial effects of statins that may prove promising in HF patients (8, 9).

According to the facts presented above, Dr. Ulf Landmesser proved that statins have an essential role in the management of congestive HF, what is most of all connected with their pleiotropic effects. His team examined the beneficial effects of statins in animal models of post-

myocardial infarction HF. They have also evaluated the influence of simvastatin on endothelial function. In their study, patients with congestive HF were randomized to 4 weeks of treatment with either simvastatin (10 mg, once daily) or ezetimibe (10 mg, once daily). They observed that both simvastatin and ezetimibe reduced low-density lipid cholesterol by approximately 15%; however, the flow dependent dilation (FDD) was markedly improved after simvastatin compared to baseline, whereas there was no significant change after ezetimibe administration. They also obtained that simvastatin significantly increased the activity of extracellular superoxide dismutase, an important anti-oxidant, and increased the number of functionally active endothelial progenitor cells, while ezetimibe had no effect to either of these areas (10).

Dr. Stephen Anker (London, UK) presented the lecture titled *The purpose of statin therapy in CHF*. He agreed with his predecessors that statin therapy has a different function in the management of chronic heart failure (CHF). He emphasized that the aim of treatment is not to lower cholesterol.

As it was mentioned above the lipoproteins especially LDL and high-density lipoprotein (HDL) cholesterol bind to endotoxin and neutralize their effect, it was suggested that it is important to maintain elevated cholesterol levels in end-stage heart failure. However, it is not known yet if this relationship is causal or just an epiphenomenon and it is not clearly defined which lipoprotein is the important one in this context (2, 5). Mehra et al. had studied 132 patients listed for heart transplantation, and it was suggested that the important lipoprotein is HDL, because low HDL was the strongest predictor of worsening heart failure. The increase in HDL may therefore be a therapeutic goal in end-stage heart failure. Further, in severe heart failure the combination of reduced liver flow and depressed cholesterol synthesis may result in low levels of circulating cholesterol. Cytokines and endotoxins have been found to stimulate triglycerides and cholesterol synthesis. Conversely, statins have been found to suppress the release of inflammatory cytokines which therefore may be additive to the direct and beneficial lipomodulation by inhibition of HMG CoA reductase (11).

As the last lecturer appeared, one of the most experienced statin scientists Prof. Kjekshus from Oslo added that, despite the established understanding that low cholesterol is associated with a poor prognosis in CHF, such patients significantly benefit from statin therapy. Statins target HMG CoA reductase, therefore they may also inhibit multiple metabolic effects of this enzyme. He noted that some of this drug class benefits could be the reduction of cholesterol plaques and inhibition of the pro-inflammatory effects produced by HMG CoA reductase. He presented several trials which showed the role of statins in patients in CHF. He mentioned the beneficial role of statins in inhibition of co-enzyme Q10 (CoQ10), which further promotes the production of high density-lipid (HDL) cholesterol. At the end of his presentation he showed the outcomes of his own research, where over 4,400 CAD patients with no history of CHF simvastatin were administered. He observed that patients who received statin were less likely to develop CHF (12, 13).

Statins block the rate limiting step in cholesterol biosynthesis in the liver and other tissues. They have been shown to improve endothelial function by inducing *constitutive nitric oxide synthase* (*cNOS*) gene transcription. Some statins might be able to reduce vascular production of reactive oxygen species (ROS). They have been found to reduce C reactive protein (CRP) values after myocardial infarction and in hypercholesterolaemia. Moreover, statins might decrease the production of TNF-α, IL-1, and IL-6 from macrophages, the cytokines which play the most important role in heart failure occurrence (2, 4).

The results of the recent studies suggested that heart failure should be treated as chronic inflammatory process, where the most important role was played by the pro-inflammatory cytokines. Among many cytokines - interleukin-1, -2, -3, -4, -6, TNF-α and interferon-γ (IFN-γ), the most essential effect seems to be the production of TNF-α, IL-1 and IL-6. In SOLVD study (*Studies of Left Ventricular Dysfunction*) the concentration of TNF-α correlated with the exacerbation of heart failure symptoms, and the high concentration volume was the independent risk factor of death (14).

TNF-α exerts its effects through TNF-α receptors (TNFR), which are expressed by almost all nucleated cells. TNFR-1 appears to be the main signaling receptor, and the most of deleterious effects caused by TNF-α seem to be mediated *via* this receptor. TNFR-2 appears to have a more protective role in the heart. Many previous studies have identified both types of receptors in non-failing and failing human myocardium. After translation, both receptors are inserted into the cell membrane of the respective cell. Proteolytic cleavage by TNF-α converting enzyme (TACE) yields the soluble forms. It is suggested that soluble TNFRs stabilize the TNF-α molecule, thus potentiating its detrimental long term actions. However, higher concentrations of TNFRs appear to inhibit TNF-α activity. It is suggested that high plasma concentrations of soluble TNFRs primarily indicate a history of raised TNF-α values and what is important the reproducibility of plasma concentrations of soluble TNFRs is higher than TNF-α concentration. This may be the reason why soluble TNFRs predict short and long term prognosis better than TNF-α in patients with HF (15, 16).

Some unfavorable effects seem to be associated with raised TNF-α production in failing heart. TNF-α has been implicated in the development of left ventricular dysfunction and its remodelling, increased cardiac myocyte apoptosis, the development of anorexia and cachexia, reduced skeletal muscle blood flow and endothelial dysfunction, severity of insulin resistance, activation of the inducible form of nitric oxide synthase (iNOS), β-receptor uncoupling from adenylate cyclase, and some other effects.

TNF-α is not the only cytokine which worsens heart failure. According to the cytokine hypothesis, HF progresses because cytokines exacerbate haemodynamic abnormalities or exert direct toxic effects on the heart. Increased concentrations of IL-6 have been shown in the circulation of patients with HF. IL-6 can induce myocyte hypertrophy,

myocardial dysfunction and muscle wasting. While increased concentrations of IL-6 were found to be associated with a poorer prognosis in HF patients, those of the soluble IL-6 receptor (IL-6R) were not. Interestingly, it is a small transmembrane glycoprotein termed gp130, but not IL-6R itself, which renders cells susceptible to IL-6. Indeed, IL-6 can act on cells lacking the expression of IL-6R after complex formation with soluble IL-6R. Both gp130 and IL-6R are always required for signalling. Their concentrations and the overall level of bioactivity of IL-6 are increased in the failing heart (15, 17).

As an example, in one of the recent studies Tousoulis et al. evaluated the effect of atorvastatin alone or in combination with vitamin E on endothelial function and serum levels of IL-6, TNF-α and vascular cells adhesion molecule (sVCAM-1) in patients with ischemic heart failure. Male patients with ischemic cardiomyopathy were randomly divided into three groups and received either atorvastatin 10 mg/day, a combination of atorvastatin 10 mg/day plus vitamin E 400 IU/day, or no statin or antioxidant treatment (controls) for 4 weeks. They observed that forearm vasodilatory response to reactive hyperemia (RH%) was significantly improved in both the atorvastatin-treated ($p < 0.01$) and atorvastatin plus vitamin E ($p < 0.05$) groups, but the increase was significantly higher in the atorvastatin-treated group ($p < 0.05$). Serum levels of IL-6, TNF-α and sVCAM-1 were decreased in the atorvastatin-treated group ($p < 0.05$ for all), but remained unaffected in the other two groups. Authors concluded that low dose atorvastatin treatment improves endothelial function and reduces the expression of pro-inflammatory cytokines and adhesion molecules in patients with ischemic heart failure, an effect partly depressed by vitamin E (18).

Another important cytokine in the setting of HF is IL-1. IL-1 has been demonstrated in the myocardium of patients with idiopathic dilated cardiomyopathy, and it depresses myocardial contractility in a dose-dependent manner. This effect is synergistic with that of TNF-α, and the stimulation of iNOS seems to be involved. Additional findings have shown IL-1 being involved in myocardial apoptosis, hypertrophy and arrhythmogenesis (19).

Gullestad et al. emphasized the influence of the inflammatory mediators in the pathogenesis of CHF, for contributing to cardiac remodelling and peripheral vascular disturbances in their recent article. They presented the recent studies, where there were shown the raised levels of inflammatory cytokines such as TNF-α, IL-1β and IL-6 in HF patients in plasma, circulating leukocytes, atherosclerotic lesions, and in the failing myocardium itself. They took note that the rise in inflammatory mediators wasn't accompanied by a corresponding increase in anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β), thus resulting in an inflammatory imbalance in the cytokine network. Authors emphasized that traditional cardiovascular drugs have little influence on the cytokine network in HF patients and results from randomised, placebo-controlled anti-TNF studies suggest lack of effect of such therapy. More general immunmodulating treatments, such as pentoxyfylline, intravenous immunoglobulin, thalidomide and statins, have shown promising results in smaller studies, which need to be confirmed in larger studies with hospitalisations and death as the end points. In addition, further research in this area will have to be more precise in identifying the most important factors in the immunopathogenesis of CHF (20).

All participants of the workshop emphasized that application of statins in patients with HF still arouses many controversies, and there is still much work to show the real role of statins in heart failure, however one is unquestionable - the role of statins in CHF patients is significantly beneficial. In order to deliver the unquestionable evidence of significant beneficial influence of statins therapy in heart failure, it is necessary to perform large prospective and randomized clinical studies. Maybe such information will be provided from still continuing trials: CORONA (*COntrolled ROsuvastatin multiNAtional trial in heart failure*), where the effect of rosuvastatin has been evaluated in patients above 60 years old and symptomatic systolic heart failure (EF ≤ 35% for NYHA [New York Heart Association] class II, or 40% for NYHA III/IV), GISSI-HF (*Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico - Heart Failure*), where the effect of rosuvastatin and whale-oil on morbidity and mortality of patients with heart failure is compared, and finally from Australian UNIVERSE Study (*rosUastatiN Impact on VEntricular Remodelling lipidS and cytokinEs*), where authors evaluated the rosuvastatin influence on inhibiting of heart remodeling in group of patients with heart failure (21, 22).

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