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ORIGINAL ARTICLE

Atorvastatin improves cardiac function and remodeling in chronic non-ischemic heart failure: A clinical and pre-clinical study

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Abstract *Aims:* The aim was to evaluate the cardio-protective effect of atorvastatin in combination with standard chronic heart failure (CHF) therapy that might improve cardiac function, remodeling, and further delay the progression of CHF in patients and rats.
Methods and results: CHF patients (n = 20 per group) with left ventricular ejection fraction (LV-EF) <45% were randomized into: standard anti-failure treatment alone (controls) and standard anti-failure treatment plus atorvastatin (40 mg/day) for 6 weeks. After 6 weeks, the patients were assessed using echocardiography. Laboratory evaluation for lipid profiles, high sensitive C-reactive protein (hs-CRP), cardiac troponin-T (cTnT) and malondialdehyde (MDA) were performed in all patients. In parallel, rats (n = 10 per group) received treatment for 4 weeks and were divided as follows: saline treated (control, 1 ml intraperitoneal, IP), doxorubicin treated (2.5 mg/kg, IP), atorvastatin–doxorubicin treated (10 mg/kg, orally), and digoxin–doxorubicin treated (0.02 mg/kg, orally). The same laboratory analysis including histopathology of heart tissues was performed on the rats.
In patients, atorvastatin improved heart function (increased LV-EF%, LV-fraction shorting (LV-FS%), and E/A velocity ratio; decreased LV-end diastolic diameter (LV-EDD) and LV-end systolic diameter (LV-ESD)) and significantly reduced serum lipid profiles, cTnT, hs-CRP and MDA versus patient controls. In rats, atorvastatin improved signs of CHF, systolic blood pressure, reduced

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serum lipid profiles, cTnT, hs-CRP and tissue MDA; less cardiac necrosis and fibrosis with enhancement of neo-vascularization versus other doxorubicin-treated rats.

Conclusions: Atorvastatin with standard CHF therapy improved cardiac function and remodeling. Cardio-protective "pleiotropic" actions of atorvastatin are anti-inflammatory, anti-fibrotic and anti-oxidative. Thus, atorvastatin has a potential therapeutic value in the management of CHF patients.

1. Introduction

Although 3-hydroxy-3-methylglutaryl (HMG) coenzyme-A reductase inhibitors (statins) prevent important causative factors for chronic heart failure (CHF), myocardial damage and ischemia, the benefits of statins and lowering low-density lipoprotein (LDL-c) in CHF patients have been questioned.[1] Statins, in addition to standard medications for heart failure, are associated with an improvement in morbidity and mortality and significantly reduced subsequent hospitalizations among patients taking them as compared to the placebo group.[2,3] Statin therapy was associated with improved survival in both; patients with ischemic heart failure and patients with non-ischemic heart failure.[4] A previous meta-analysis[2,3,5] of 10 randomized placebo-controlled trials (6 for atorvastatin, 3 for rosuvastatin, and 1 for simvastatin) suggest that statins may be safe and improve left ventricular (LV) ejection fraction (LV-EF), decrease brain natriuretic peptide (BNP) levels and decrease hospitalizations for worsening CHF.[4,6]

Despite recent therapeutic advances, the appropriate role of drug-specific statin therapy in the CHF population, however, remains unclear.[2] There exists an increasing need to find new therapeutic strategies to reduce high mortality and morbidity in this population. Statins, a class of agents for lowering blood lipids, have been shown to reduce adverse cardiovascular events in atherosclerosis related diseases in patients with documented coronary artery disease (CAD).[7] Consequently, the current guidelines for the management of CHF target the causal pathological disease, control of heart rate, and reduction of fluid retention. Thus, combined therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, β-adrenergic or aldosterone blockers, and diuretics seems to be the current (standard) optimal therapeutic strategy.[4,7] Most of these effects can target important components of the complex physiopathology of heart failure.[8] Thus, concern has been raised about the potential benefits of statins in patients with CHF of multiple etiologies.[4,6]

Several studies in rat models and patients have suggested that statins may directly improve LV relaxation and function by reducing LV hypertrophy and fibrosis, and increasing arterial compliance.[9,10] Some of the effects of statins improve endothelial function.[11,12] However, the best-characterized pleiotropic effects of statins are their anti-inflammatory[13] and antioxidant actions[14,15] and their protective effect against endothelial and LV dysfunction.[12,16] We chose a rat model with doxorubicin induced heart failure because of the commonly known cumulative cardiotoxic effect in cancer patients.[17–20] To date, no such studies have been performed on the cardio-protective potential of atorvastatin in doxorubicin-induced cardiomyopathy.

In this study, we investigated whether the early use of atorvastatin in combination with standard CHF therapy might improve cardiac function and remodeling in CHF patients and also further delay the progression of CHF in doxorubicin-induced heart failure in rat models.

2. Methods

2.1. Clinical study

2.1.1. Subjects

The present study included 40 patients recruited from the Cardiology Department outpatient clinic at Menoufiya University Hospital between January 2010 and March 2012. Eligible patients were men and women of 35–75 years of age with a clinical diagnosis of CHF. Written informed consent was obtained from each participant before inclusion in the study. Ethical approval for this investigation was obtained from the Research Ethics Committee, Faculty of Medicine, Menoufiya University.

CHF diagnosis was determined by echocardiography evaluation. These patients were chosen according to the following inclusion and exclusion criteria: *Inclusion Criteria:* (1) patients who had symptoms according to New York Heart Association (NYHA) functional class II or III, assessed by a detailed history and clinical examination; (2) patients with non-ischemic heart failure with no history of myocardial infarction and cardiac catheterization without significant CAD; (3) patients with findings of a dilated LV end diastolic diameter (LV-EDD) (>60 mm), affected LV fraction shortening (LV-FS) ($<25\%$) and LV-EF ($<45\%$); and (4) patients who used standard anti-heart failure drugs in the form of loop diuretics and spironolactone, β-blockers, ACE inhibitors or angiotensin II receptor blockers with or without digoxin, regularly, for at least 1 month prior to the study. *Exclusion criteria:* (1) patients with CHF caused by ischemic heart diseases; (2) valvular heart diseases; (3) rhythmic dysfunction; (4) renal, hepatic, or pulmonary dysfunction; (5) patients with uncontrolled diabetes; and (6) patients with uncontrolled hypertension (HTN).

All patients with non-ischemic CHF were randomized and divided into two groups (20 patients in each group): (a) Control group: received standard anti-failure treatment in unchanged dose for at least one month before the study and for 6 weeks during the study without any statin therapy. (b) Statin-treated group: received standard anti-failure treatment in unchanged dose for at least one month before the study