A Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Simvastatin in Non-Ischemic Heart Failure: The Simvastatin in Non-Ischemic Heart Failure (SNIHF) Study Group

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A. Study Purpose and Rationale

HMG Co-A reductase inhibitors, statins, are a potent class of drugs with the ability to significantly lower total and LDL cholesterol. The efficacy of statins as treatment for hypercholesterolemia, and in the primary and secondary prevention of coronary artery disease, has been demonstrated by several large, randomized, placebo-controlled clinical trials. (1-5)

However, statins may have more global cardiovascular effects independent of their effects on LDL cholesterol. These pleiotropic effects have been suggested by a variety of studies that show statins may improve vascular endothelial function, stabilize atherosclerotic plaques, and reduce inflammation and oxidative damage. (6-9) Thus the use of statins for novel indications other than the lowering of cholesterol and the primary and secondary prevention of coronary artery disease are currently being investigated.

One potential novel application for statin therapy is in the treatment of congestive heart failure. Heart failure is now recognized as complex neuro-hormonal state with the chronic elevation of circulating catecholamines, the activation of the renin-angiotensin pathway, the synthesis of pro-inflammatory cytokines, all of which ultimately lead to the progression of cardiac dysfunction. (10) Current first line therapeutic modalities for heart failure focus on suppression of these maladaptive neuro-hormonal mechanisms with beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and aldosterone blockade.

The role of statins in the treatment of congestive heart failure has not been studied in a large, long-term prospective trial, and the benefits of statin therapy in heart failure remain unclear. Statins have several potential mechanisms through which they may benefit patients with congestive heart failure. Statins increase the bioavailablity of nitric oxide in the vascular endothelium, and increase the expression of the endothelial nitric oxide synthase (eNOS) gene, while at the same time decreasing levels of endothelin-1 expression, thus helping to restore vascular endothelial reactivity and reducing the chronic vasoconstriction associated with heart failure. (11-13) Statins have postulated anti-inflammatory effects and reduce levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-a), possibly through effects on the signaling molecule NF-kappa-beta. (14-17) Chronic inflammation plays a role in the progression of heart failure and accelerates cardiac myocyte apoptosis, such that attenuating this inflammatory state may aid in the treatment of heart failure. In a similar vein, some evidence suggests that statins reduce oxidative stress by suppressing free radical formation in the vascular endothelium, and thus by decreasing oxidative damage to the myocardium, statins may indirectly improve cardiac performance. (8,18,19)

However, there are also some theoretical concerns about the safety of statins in heart failure patients. In chronic heart failure, low cholesterol levels correlate with higher heart failure mortality, raising questions about the safety and suitability of drugs that further lower cholesterol levels in these patients. (20,21) In addition, statins have been shown to decrease levels of ubiquinone (coenzyme q10), an essential coenzyme required by mitochondria for ATP production. Ubiquinone has itself been used as a potential therapy for heart failure, with mixed results, but nevertheless, decreasing ubquinone levels with statins may theoretically worsen aerobic metabolism and reduce ventricular function and exercise tolerance in heart failure. (22,23)

The current evidence for the safety and efficacy of statins in heart failure patients is largely from retrospective analyses. Most of the large prospective clinical trials of statins for the secondary prevention of coronary artery disease excluded patients who had moderate to severe heart failure. However, retrospective review of the 4S and CARE studies showed a roughly 20% lower incidence of new-onset heart failure in the study groups treated with simvastatin. (4,5,24)

Recent retrospective studies have suggested a potential mortality benefit among heart failure patients treated with statins. Retrospective review of the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial, a prospective, randomized clinical trial of amlodipine versus placebo in severe heart failure, demonstrated a 62% relative risk reductive in mortality for statin therapy in severe class IIIB or class IV heart failure of any etiology, with benefit not significantly affected by adjustment for serum cholesterol levels. (25)

A similar retrospective analysis of 551 patients with both ischemic and non-ischemic heart failure, an ejection fraction <40%, and NYHA class III or IV symptoms, who were treated at a single heart failure center and evaluated for heart transplant also demonstrated improved survival without the need for urgent transplantation in both non-ischemic and ischemic heart failure patients, with a relative risk reduction of death of approximately 18-19% in both groups. (26)

Lastly, a non-randomized, retrospective review of the OPTIMAAL study, which compared losartan and captopril post-acute myocardial infarction complicated by heart failure, suggested that early initiation of beta-blocker and statins post-MI reduced one year mortality, and also suggested that the effects of statins and beta-blocker therapy were additive. (27)

At present, only one small, short-term, randomized, placebo-controlled clinical trial of a statin in heart failure patients has been conducted. This trial studied 51 patients with non-ischemic idiopathic dilated cardiomyopathy, randomized to low dose simvastatin or placebo. The patient in the simvastatin group showed improvement in ejection fraction, NYHA functional class, inflammatory markers, brain-type natriuretic peptide and endothelial function after 14 weeks of therapy. (16) However, promising as this study may be, there has not been a large, prospective randomized, placebo-controlled clinical trial of statins in heart failure, which has examined their effect on hospitalization or overall mortality.

Given that patients who have ischemia as the underlying etiology for their heart failure already have an indication for therapy with statins, it would be challenging from an ethical perspective to study this population in a prospective, randomized, placebo-controlled fashion unless there was data questioning the safety of statins in this population. Such data does not exist.

Nevertheless, there remains a large population of patients with non-ischemic heart failure who might benefit from treatment with statins, and who currently have no indication for statin therapy. Thus the SNIHF study was designed to address the potential benefit of statin therapy in patients with documented non-ischemic heart failure.

B. Study Design and Statistical Analysis

The study is designed as a multi-center, randomized, double-blind, placebo-controlled trial of simvastatin in adult subjects with documented non-ischemic cardiomyopathy. There will be two study groups, one of whom will receive simvastatin, initially at a dose of 10 mg once daily, increased to 20 mg once daily after 4 weeks. The other group will receive a matching placebo. After informed consent is obtained by the investigator at a specific site, subjects will be randomized to either placebo or study group based on a random number generated at the coordinating site. The subjects, their physicians, and the study investigators will be blinded to the subject assignments to simvastatin and placebo groups.

The primary outcome will be the percentage of patients in each group hospitalized for any cause at 24 months. Secondary outcomes will include the total number of hospitalizations in each study group, rate of hospitalization for heart failure, mortality, and change in ejection fraction at 24 months. Data from categorical variables such as rates of hospitalization and mortality will be analyzed using chi-square analysis. Continuous variables such as total number of hospitalizations and ejection fraction will be analyzed using an unpaired t-test.

The power analysis and calculation of sample size is based on the primary outcome, rate of all cause hospitalization at 24 months. Several large randomized clinical trials have suggested annual all cause hospitalization rates for NYHA class II and III heart failure subjects of approximately 15% to 30%. (28-31) The limited retrospective data that exists regarding the benefits of statin therapy in non-ischemic heart failure suggest a putative relative risk reduction of death of between 19% and 48%. (25,26) Assuming a roughly equivalent benefit in terms of rates of hospitalization, we postulate the simvastatin group to have a 20% relative risk reduction in the rate of hospitalization at 24 months. With a projected 20% annual hospitalization rate in the placebo group, the calculated sample size for each group will be 589 subjects. At the conclusion of the study, the results will be adjusted to account for the contribution of change in LDL and total cholesterol in each group.

Subjects in the study drug group who discontinue simvastatin, whatever the reason, will still be analyzed as part of the study drug group. Similarly, subjects in the placebo group who develop an indication for treatment with statins will also be analyzed in their initial study group. In other words, the analysis will be on an intention to treat basis.

C. Study Procedure

Subjects will meet with a research investigator at the time of enrollment in the study to obtain informed consent and to schedule follow up visits and phlebotomy sessions. All subjects in the study will have their blood drawn for study purposes at baseline prior to enrollment in the study to check liver function tests, fasting lipid panel and creatinine level (2 gold top vacutainer SST tubes, a total of 6cc of whole blood at each session). In addition, prior to enrollment all subjects will have a transthoracic echocardiogram to verify ejection fraction <40% and to rule out primary valvular heart disease. Lastly, prior to enrollment an investigator blinded to the subject's group assignment will determine their NYHA functional class.

Subjects will meet with a blinded investigator at 1 month, 3 months, 6 months, and then subsequently at 6 month intervals up to 24 months. At each visit, the study investigator will assess whether the subjects have been hospitalized since their prior visit, check compliance with the study medication, and report on any adverse events. In addition, subjects will have their blood drawn at each follow up visit to monitor liver function tests for study purposes. A fasting lipid panel will be repeated at 24 months.

Staff conducting all laboratory assays and the cardiologists reviewing the echocardiograms will be blinded to the subject's study group assignment. Monitoring of liver function is with greater frequency than in clinical practice, but this is necessary to ensure the safety of the study drug in this population. Among subjects hospitalized during the study, 2 independent cardiologists blinded to the subject's study group will determine whether or not the subject was admitted for worsened heart failure. Data from each blood draw will be examined by an independent reviewer blinded to the subject's study group assignment, who will then instruct the subject to discontinue the study medication if there is a significant elevation in transaminases (>2.5 times upper limit normal).

Each subject in the study will be followed for a period of 24 months after enrollment, and the study drug will be continued throughout this period unless contraindicated or discontinued due to side effects. We estimate that the study will need to run for approximately 5 years to enroll sufficient subjects. After 24 months, all subjects will have a repeat transthoracic echocardiogram, and again will meet with an investigator blinded to the subject's study group assignment to determine NYHA functional class. All adverse events, including reasons for discontinuing study medications, will be reported by the investigators and will monitored by an independent data safety monitoring board, who will review the preliminary study results at 6 months and 1 year.

D. Study Drugs

Simvastatin (ZOCOR, Merck USA) is an HMG-CoA reductase inhibitor that is structurally related to lovastatin. It is currently FDA approved for the treatment of coronary heart disease, hypercholesterolemia, homozygous familial hyperlipidemia, and in stroke and transient ischemic attack (TIA), prophylaxis. In this study, simvastatin will be used for a novel, non-FDA approved indication: heart failure. Typical dosage for hyperlipidemia ranges from 5 mg to 80 mg orally, once daily in the evening. Starting doses for hyperlipidemia are typically 20 mg to 40 mg orally, once a day. In the treatment of coronary artery disease, starting dose is typically 40 mg once daily. In this study, initial dosing will be 10 mg orally once a day in the evening, with a plan to reach goal dose of 20mg orally once daily, after 4 weeks of therapy

Simvastatin is administered orally as a prodrug, which is subsequently hydrolyzed in the liver to its active form. Peak serum levels of active drug occur 1 to 2 hours after oral administration and excretion is primarily via the biliary tract.

Simvastatin is associated with a low incidence of side effects. The most frequent adverse reactions are abdominal pain (up to 22%), headache (6.4%), constipation (5.7%), nausea (4.4%), dyspepsia (2.9%), diarrhea (2.9%) and fatigue (2.7%). Roughly 3% to 5% of subjects experience myalgias and transient elevations of CPK 3 times above upper limit of normal that does not require discontinuation of therapy. (2,4,5) More severe elevations of CPK >10 times upper limit of normal, myopathy, and rhabdomyolysis have each been reported in less than 0.1% of subjects treated with simvastatin in the clinical trials such as the Heart Protection Study. (3) In terms of hepatotoxicity, elevations in transaminases greater than 3 times the upper limit of normal, requiring discontinuation of the medication were reported in 1% to 2% of subjects in clinical trials. (2-5) Rates of hepatotoxicity have been elevated with concomitant use fibric acid derivatives, gemfibrozil and niacin. Simvastatin is a potential teratogen and is not safe for use during breast feeding and lactation.

E. Medical Devices

No medical devices will be used during this study

F. Study Questionnaires

No questionnaires will be used during this study

G. Study Subjects

Eligible subjects include adults aged greater than 21 years, with a diagnosis of non-ischemic cardiomyopathy, an ejection fraction <40% documented by echocardiogram, MUGA scan or cardiac catheterization, who have NYHA class II or class III symptoms, and are able to give informed consent. A diagnosis of non-ischemic cardiomyopathy will have been established either by cardiac catheterization demonstrating no significant coronary artery disease (defined as <60 % stenosis of at most one vessel), or with age <30 years at time of enrollment. Eligible subjects are required to have been optimally medically managed by a cardiologist, and treated with a stable dose of beta-blocker, diuretic, and ace-inhibitor or angiotensin receptor blocker (unless contraindicated) for 3 months prior to enrollment of the study.

Subjects will be excluded if they have prior any history of MI, percutaneous coronary intervention, CABG, or ischemia documented as the etiology of their heart failure. Subjects who have uncontrolled hypertension (defined as SBP>160 or DBP>100), or primary valvular heart disease will also be excluded. In addition, subjects who had previously been treated with any HMG CoA reductase inhibitor in the 6 months prior to the study will be excluded.

Subjects will be excluded if they have significant liver disease, defined as elevation of transaminases greater than 2.5 times upper limit normal or baseline INR>1.5 (unless on anticoagulation with warfarin), prior allergic reaction or history of myositis with any HMG-CoA reductase inhibitor. Subjects taking fibric acid derivatives, gemfibrozil, or niacin will be excluded from the study based on

higher rates of hepatotoxicity when these drugs are combined with any HMG-CoA reductase inhibitor. Pregnant and lactating women will be excluded due to potential teratogenicity of statins in pregnancy. Additional exclusion criteria included chronic renal insufficiency (estimated creatinine clearance by Cockcrauft-Gault formula <50 cc/min), subjects who had class IV symptoms within the past 3 months or need for inotropic support within the past 3 months, a history of chronic obstructive pulmonary disease, or a history of active substance abuse.

H. Recruitment of Subjects

Subjects will be recruited at 12 heart failure centers across the country. The study will be advertised with flyers at each heart failure center, and in addition eligible subjects will be identified through their heart failure physicians and referred to the study. The subject's heart failure physician must agree to the patient's participation in the study and discuss the study with them. Subsequently, an investigator will meet with the subject to discuss the study and obtain informed consent.

I. Confidentiality of Study Data

All study data will be strictly confidential. On entering the study, each subject will be given a 6 digit code and subsequently all identifying data will be removed from the active study file, and the study investigators will be blinded to all patient information including study group assignment. Patient identifying information corresponding to the subject's code will be kept in a secure, locked location at the coordinating site. The data safety and monitoring board will have access to identifying patient information in order to contact patients who have adverse events.

J. Potential Conflict of Interest

There are no conflicts of interests in the study. None of the investigators hold stock in or have received payments for lectures or endorsements from Pfizer, USA.

K. Location of Study

The study will be a multi-center trial, carried out at Columbia University Medical Center, the coordinating center, and 11 other participating heart failure centers across the United States. IRB approval for the protocol will be obtained from the institutional review board of each participating center.

L. Potential Risks

Participation in the study carries the risk that simvastatin may not have any beneficial effects in heart failure and could potentially worsen heart failure symptoms, hospitalization rate, and mortality rate from heart failure, although the currently available retrospective data suggests that this is not the case. In addition, risks of participation in the study include side effects of taking simvastatin (described in detail in the study drug section) including abdominal pain, constipation, diarrhea, dyspepsia, fatigue, headache, hepatotoxicty with abnormal liver function tests, myalgias, myopathy and rhabdomyolysis.

M. Potential Benefits

All subjects will have a screening echocardiogram and have a fasting lipid panel at no cost at the beginning and end of the study. The study postulates that simvastatin will improve subjects' symptoms of heart failure, decrease hospitalization rates and possibly reduce mortality, but this remains uncertain. In

addition, the subjects' LDL and total cholesterol may be lowered by participating in the study. However, there may in fact be no benefit from participating in the study.

N. Alternative Therapies

In this study, simvastatin will be used for a novel indication, heart failure, in addition to, rather than in place of, conventional therapies for NYHA class II and class II heart failure. Approved alternative therapies for NYHA class II and II heart failure include beat-blockers, ACE-inhibitors, ARBs, diuretics, digoxin, spironolactone and eplirinone. Patients will not be precluded from taking any of these alternative therapies during the course of the study; indeed, eligibility criteria for the study require that patients be on stable doses of b-blockers, ACE-inhibitors/ARBs and diuretics prior to enrollment, unless contraindicated.

O. Compensation to Subjects

Apart from paying all costs for study medications, follow up visits and lab testing, no specific compensation will be offered to subjects for participation in the study

P. Costs to Subjects

Subjects will not incur any additional costs as result of participating in the study. All costs for study medications, study follow up visits, and lab testing will be paid for by the study

Q. Minors as Research Subjects

No minors will be involved as research subjects in this study

R. Radiation and Radioactive Substances

No radiation or radioactive substances with be used during the study

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