The Use Of Intracoronary Ultrasound To Assess A Novel Strategy For Treatment Of Restenosis: Rapamycin Inhibition Of Coronary Artery Stent Restenosis

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A. Study Purpose

It is estimated that more than 400,000 Americans and 800,000 patients internationally undergo a percutaneous coronary interventional procedure each year(l). Abnormal vascular smooth muscle cell (SMC) proliferation and migration from the arterial media to the intima is involved in restenosis following percutaneous transluminal coronary angioplasty and in coronary stenting, occurs in 40-50% and 20% of patients within six months of the procedure, respectively. (2, 3) Rapamycin, a macrolide antibiotic and immunosuppressive agent, has been shown to inhibit smooth muscle cell proliferation and migration by interrupting regulators of the cell cycle. Preliminary data indicate that rapamycin also significantly inhibits intimal hyperplasia after balloon injury in the porcine model of restenosis. Therefore, in this proposal we will test the whether rapamycin inhibits stent restenosis owing to neointimal hyperplasia and whether rapamycin has a safety and tolerability profile of elevated risk relative to control patients.

B. Study design

This study is a randomized trial of to study the effect of rapamycin on coronary restenosis after stent placement. Detection of restenosis by intracoronary ultrasound will be used to assess the degree of restenosis.

All patients undergoing cardiac catheterization will be given informed consent prior to the procedure after conferring with their primary care physician or cardiologist as to the appropriateness of the patients ability to enroll. Patients will be divided into those having a stent placement vs. those having no interventional procedure and then randomized to receive rapamycin vs. no rapamycin. Patients in the stent group will be included if they have relatively poor immediate post-stent improvement in luminal diameter and/or are diabetic as these groups have been shown to progress more rapidly to restenosis. In the intervention group there will be three arms: no drug, rapamycin given as a loading dose of 1 mg/kg IM at the time of the procedure, followed by a dose of 2mg/kg/day x 7 days. In the non-intervention group patients will either receive a maintenance dose of rapamycin or no drug.

The patients will undergo repeat catheterization 6 months after the initial procedure or sooner depending on any repeat ischemic symptoms to determine the degree of restenosis.

C. Selection of patients

a. Inclusion criteria

a) Patients referred for cardiac catheterization at the cath lab at CPMC

b. Exclusion criteria

b) previous PTCA, stent, atherectomy
c) use of immunosuppressive agent, excluding prednisone or its derivatives
d) history of malignancy
e) history of liver disease
f) use of other investigational drugs known sensitivity to a macrolide antibiotic (i.e., erythromycin, azithromycin and clarithromycin

D. Study procedures

After shaving the right femoral region, an 8- French introducer will be inserted via an arteriotomy and through this a coronary guide will be passed retrograde over an 0.028" guide wire to the aortic root. All patients will be heparinized throughout the procedure. The ostium of the left coronary artery will be engaged and intracoronary nitroglycerin will be given and angiographic assessment will be accomplished via injection of radiocontrast agent during fluoroscopic visualization. Intracoronary imaging of any stenotic lesion requiring stent placement will be performed using a Hewlett-Packard Sonos intravascular ultrasound system. Care will be taken to ensure that similar regions will be analyzed between baseline and follow-up studies.

Lumen diameter, media thickness and neointimal thickness will be measured and patients will be included if they have relatively poor immediate post-stem improvement and/or are diabetics. The lumen-vessel wall and the intima-media interface will be traced by planimetry. The minimal luminal diameter and percent stenosis as well as acute luminal gain (MLD after treatment minus XILD before treatment) will be calculated by two observers.

Balloon catheter placement as well as placement of a Palmaz-Schatz stent will occur. At the conclusion, hardware will be removed and patients will be monitored for local bleeding and adequacy of limb perfusion.

a. Efficacy evaluation:

i. Primary endpoint:

a) non-stented patients: patients will be observed for adverse reactions or sideeffects of the rapamycin

b) stent group: patients will be evaluated after 6 months for the development of restenosis and the degree of intimal hyperplasia or earlier depending on ischemic events