A pilot study of cilostazol to improve quality-of-life and long term patency after open or endovascular revascularization for peripheral artery disease

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Background

Cilostazol is considered a cAMP (phosphodiasterase) inhibitor and is the only medication approved for use in peripheral arterial disease (PAD) patients to reduce claudication symptoms. Contemporary data has demonstrated Cilostazol to improve patency after endovascular interventions in multiple randomized trials and retrospective studies in both critical ischemia and claudication patients.[1-5] Recent meta-analysis showed decreased restenosis, target vessel revascularization and major amputation in patients receiving Cilostazol.[6] Cilostazol has also been shown to improve adverse outcomes after coronary stent implantations.[7]Cilostazol was also shown to be equivalent to warfarin anticoagulation in a small, randomized trial for femoral-popliteal bypass for graft patency.[8]

Peripheral vascular graft or angioplasty/stent failure, especially early, is caused by intimal hyperplasia and smooth muscle activation and proliferation. No human studies have shown a role of Cilostazol in curtailing these, but animal research provides insight into potential therapeutic strategies to reduce early graft or angioplasty/stent failure. In one animal model, Cilostazol was associated with decreased intimal hyperplasia in a vein graft.[9] Cilostazol reduces smooth muscle constriction and proliferation in animal models and also promotes angiogenesis in non-primate models.[10-12]

Cilostazol has been shown to be safe for long term use in patients with vascular disease.[7, 13] Cilostazol is contraindicated for use in patients with congestive heart failure due to decreased survival associated with use of other cAMP inhibitors in patients with Class III/IV CHF. No direct studies for Cilostazol have been undertaken in this regard. Cilostazol is also contraindicated in patients with allergic response to the drug, bleeding diathesis, intracranial bleeding or active bleeding peptic ulcer disease. It is not approved for use in pregnancy due to fetal defects and also shown to be excreted in milk.

Cilostazol use after peripheral revascularization has been sporadic and there has been no research to estimate patient quality of life with use of Cilostazol after open or endovascular lower

extremity revascularization. Moreover, prior randomized trials, as mentioned above, have all been performed in Japan, therefore results may not be generalizable to North American population.

Methods

We propose to study the effect of Cilostazol on patient quality of life (measured using standard QOL assessment tools in PAD patients (EQ-5D and EACH Qc) and relation of these to patency after lower extremity infra-inguinal bypass and endovascular interventions (angioplasty with or without stent placement) in a stratified randomized trial. Secondary endpoints would be limb salvage, minor (distal to calcaneus) and major amputation, claudication symptoms and distance and ischemic rest pain, stroke or other cardiovascular events, and overall survival. Adverse outcomes would also be collected, including - bleeding, need for blood transfusion, medication reaction (allergic or bleeding episodes), and cardiopulmonary failure.

This is a prospective investigator initiated single-center open-label, non-placebo controlled pilot study. All patients meeting the inclusion criteria would be screened for eligibility and after informed consent, randomization would be performed to either the Cilostazol treatment (drug group) or the non-Cilostazol treatment (control group) groups, stratified for endovascular or open interventions, using a closed envelope randomization technique. Eligible patients would be consented prior to surgery or within 48 hours of index procedure. Patients on Cilostazol prior to surgery would still be eligible and medication discontinued if randomized to control group. Cilostazol will be provided to patients randomized to the treatment arm free of charge for three months. . If you are randomized to the treatment arm (receiving Cilostazol) we will provide you with Cilostazol 100 mg, twice a day, free of charge for a period of three months. Patients who have renal impairment (problems with their kidneys) will be given 50 mg, twice a day instead of 100 mg, twice a day. Cilostazol has a half- life of 13 hours, therefore a washout period will not be necessary. Concurrent medication use based on comorbidities including diabetic, anti-hypertensive medications, lipid lowering agents would be prescribed based on standard practice and not dependent on study group or enrollment in the study.

Also concurrent use of single or dual antiplatelet therapy (aspirin with or without ADP receptor blocker or similar medication) would be used at discretion of treating physician. Patients who need to be on anticoagulation, with warfarin or other oral anticoagulants, for high risk revascularization or other comorbidities, would have single antiplatelet agent (as above) only for secondary prevention of thrombotic events. Cilostazol use in either group would not lead to a change in their antiplatelet/anticoagulation regimen.

Pre-operative demographic, medication use and co-morbidity data and operative data would be retrieved from EMR. Patient follow up would be based on our current standard protocol which includes duplex of the graft or intervened artery at 4-6 weeks and 3-6 months. Cilostazol will be provided to patients free of charge for three months. Restenosis is defined as stenosis>50% based on our current vascular laboratory criteria or based on arteriogram imaging if performed at discretion of treating physician. Clinical examination and medication use and other secondary and adverse outcomes would be evaluated and QOL questionnaires administered at above time points. Quality-of-life (QOL) questionnaires (EQ-5D and EACH Qc) will be administered at enrollment and each follow up visit.

Purpose

The primary purpose of this pilot study is to collect QOL data on patients undergoing peripheral revascularization in order to determine the sample size required for adequate powered trial of Cilostazol versus usual care without Cilostazol and its effect on QOL. Thirty patients, fifteen in each arm, will be recruited into the pilot study in order to obtain sufficient data needed to estimate the variance and within-subject correlation of the outcome measures.

Benefits/Risks

Benefits include: possible improvement in quality of life for patients suffering from claudication after revascularization, improvement in graft patency and decreased restenosis and potential amputation. Risks include possible allergic reaction to the drug.

Inclusion

1. Patents should be older than 35 years of age
2. Patients treated for atherosclerotic PAD
3. Able to provide informed consent
4. Lower extremity open or endovascular revascularization, including bypass (autogenous or prosthetic), angioplasty and/or stenting, with or without concomitant aorto-iliac intervention.

Exclusion

1. Known congestive heart failure Class III/IV, systolic, acute or chronic
2. Allergic reaction to phosphodiasterase inhibitors
3. Intracranial bleeding within 3 months or active bleeding peptic ulcer disease
4. Traumatic vascular injuries requiring revascularization

5. Pregnant or breast feeding women, or plan to get pregnant over the study period (for five years after enrollment)
6. Planned ipsilateral major amputation within 30 days of index procedure
7. Moderate to severe hepatic impairment

Analysis

Data will be collected and stored on a password protected secure server which only study team members can access. QOL instruments (EQ-5D and EACH Qc) will be scored from the baseline, 4-6 week and 3 month visits. Cross-sectional and change scores will be calculated to estimate effect size and variance of QOL outcomes measures. These data will be used to assess potential efficacy and to project sample size requirements for a future trial. Treatment arm differences in early (4-6 week) and late (3 month) month changes in QOL scores will be tested using two-group t-tests.

Follow-up graft patency will be assessed as a secondary outcome and will be measured early (within 14 day of intervention) and late (six weeks and three months) using duplex ultrasound. Treatment arm differences time to patency failure will be compared using Kaplan-Meier survival curves and log-rank tests. Information on the following tertiary outcomes will also be ascertained at six weeks and three months follow-up: (1) amputation, (2) death due to any cause, (3) clinical symptoms of claudication or rest pain (critical limb ischemia), and (4) stroke. Statistical comparison for differences between groups will not be performed for tertiary outcomes due to small sample size and power.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a separate master log. The master log will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be reported to the principle investigator and the Institutional Review Board by the study coordinator within seven business days of the event.

Financial reimbursement

No reimbursement will be provided to the patients or investigators for this study. All follow up is consistent with our current protocol in the care of these patients. Cilostazol will be provided to those patients randomized to the treatment arm free of charge for three months. At the end of the three month period, providers may choose to prescribe Cilostazol for patients if they want to continue the drug.

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