Evaluation of TNF-alpha Inhibition in Preventing Adverse Cardiac Outcomes after NSTEMI: A Randomized- Control Trial of Infliximab in Acute Coronary Syndromes.

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ICCR Proposal

Introduction: Approximately 1.5 million cases of myocardial infarction (MI) occur each year. These acute coronary syndromes (ACS) are typically classified as ST segment elevation MI (STEMI; where transmural infarction occurs), and non-STEMI (NSTEMI). Recent advances in interventional technologies and stenting of occluded infarct-related coronary arteries have resulted in improved overall survival for those suffering from STEMIs. Although much more prevalent, the same is not true for NSTEMIs. Data has not supported emergent catheterization of all patients with NSTEMIs, and treatment decisions have traditionally relied upon risk stratification to determine optimal care and the need for revascularization. When taken for angiography, it has been documented that these patients more frequently have multivessel disease, and a significant amount of residual ischemia. In short, patients who survive a NSTEMI have a worse overall long term prognosis, with a cumulative mortality at 1-2 years exceeding that of STEMI patients.

A growing amount of experimental evidence has shown that the ACS is associated with a significant inflammatory response, both locally and systemically, with increased plasma concentrations of several inflammatory markers. The largest quantity of data surrounds C-reactive protein (CRP), an inflammatory marker with an established prognostic relevance in subjects with coronary artery disease. Nevertheless, several other inflammatory cytokines are also reported to increase in subjects presenting with ACS. These observations suggest that inflammation plays a role in destabilizing atherosclerotic plaques, and enhancing the risk of coronary thrombosis. Thus, if coronary inflammation is a marker of plaque susceptibility to rupture, then patients with an acute coronary syndrome may have multiple vulnerable plaques.

One of these documented inflammatory cytokines is tumor necrosis factor-alpha (TNF-alpha). TNF-alpha has multiple effects on the immune system, including stimulating the release of multiple other inflammatory cytokines and chemokines, the upregulation of endothelial adhesion molecule expression, and the coordination of leukocyte migration to target organs. TNF-alpha has been implicated in many other rheumatologic illnesses (severe rheumatoid arthritis, crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriatic arthritis), and has recently been targeted for therapy with good results. The purpose of this study is to determine if similar immune modulation would result in improved outcomes for those patients presenting with NSTEMIs.

TNF-alpha inhibition has been evaluated in the presence of ACS, but with conflicting data. Clearly, circulating TNF-alpha levels correlate well with the development of atherosclerosis and the risk of MI. Published case reports of the association between TNF-alpha inhibition and myocardial infarction are conflicting. Some have implicated infusion of the TNF-alpha inhibitor *infliximab* with the development of myocardial infarction; a precaution listed in the product

literature. On the contrary, others have reported a protective effect of this treatment. Only animal data exists to evaluate the effect of TNF-alpha inhibition in models of acute MI. Gu et al. looked at myocardial injury following myocardial ischemia in dogs treated with TNF-alpha inhibitors. Anesthetized dogs underwent closed-chest balloon occlusion of the anterior descending coronary artery for 90 minutes, followed by reperfusion for 3 hours. Dogs randomly received a soluble TNF inhibitor (etanercept) or saline before occlusion. Collateral blood flow, infarct size, area of ischemic myocardium, and inflammatory markers were measured. They found that in addition to a significant reduction in all inflammatory markers, clinical ischemia was significantly lower in the treatment arm compared with the placebo group after adjusting for collateral blood flow ($P < 0.009$), with a mean reduction of 40%; 0.32 +/- 0.09 versus 0.53 +/- 0.09. Evaluation of this effect in humans has not been published to date.

Hypothesis: Inhibition of TNF-alpha during the acute coronary syndrome and the subsequent attenuation in local inflammation will reduce MACCE (Major Adverse Cardiac and Cerebrovascular Events), and prevent LV dysfunction over a 6 month follow up.

Study Design:

Patient Selection

Patients admitted to the Internal Medicine service regardless of admission diagnosis are considered to be potential candidates for this study. Patients will be considered eligible for participation after a diagnosis of NSTEMI is made and confirmed serologically with cardiac troponin assays. For those patients who do not go for cardiac catheterization, and instead, conservative (i.e. medical) management is warranted, consideration of inclusion will be made. Those not meeting predefined exclusion criteria will be approached regarding informed consent.

Intervention

Those meeting inclusion criteria will be randomized in a double-blind fashion to receive a one time IV-bolus infusion of infliximab at a dose of 5 mg/kg vs. placebo at the time of enrollment (diagnosis of NSTEMI).

Outcomes

Study participants without established outpatient Cardiologists will be followed at the CUMC cardiology clinic. They will be seen at 1 month intervals from discharge to 6 months and then once again at 1 year. Those with community Cardiologists will be contacted via telephone and questioned regarding recent medical follow up, medication changes, and current symptomology. Also, interval hospitalizations will be reviewed to determine the nature of the admission, the extent of the workup, relevant imaging and laboratory review, and discharge diagnoses.

Primary Outcome measures will be Major Adverse Cardiac and Cerebrovascular events (MACCE) at 6 months:

-Death: all cause mortality

-Myocardial infarction: repeat hospitalization for ACS with EKG documenting new STEMI/ Q wave infarction, or serologic evidence of MI in the absence of these findings

-Cerebrovascular accident: any radiographically confirmed ischemic or hemorrhagic stroke manifesting as a new neurological impairment

-Coronary Revascularization: subsequent PCI for any indication

-Congestive Heart Failure (CHF): new diagnosis of CHF with documented LVEF <40%

Study Design

-RCT; prospective, interventional, randomized, placebo-controlled, double-blinded, no possible crossover

-Data collection:
Clinical outcomes:
Death: hospital records, vital statistic registries
Myocardial infarction, CVA, revascularization: telephone follow up, hospital/ clinical records
CHF: telephone follow up, hospital/ clinical records, and TTE or nuclear imaging documenting LVEF < 40%

Sample Size
-Estimated 6 month incidence of MACCE after NSTEMI (based upon aggregate of published literature): 20%
-Effect Size set at 20% reduction (equivalent to a 4% decreased incidence at 6 months)
-For testing at p=0.05, approximations for 80% power suggest randomization of 3,000 patients (1,500 in each arm)

Statistical Analysis
-Chi-square test to evaluate the proportions of clinical outcomes observed between the infliximab and placebo arms (2 x 2 design) at different temporal endpoints.
-Kaplan-Meier curves to illustrate patterns of event free survival
-Multiple Regression Analysis of baseline risk factors (i.e. DM, HTN, LDL, HDL, tobacco Hx, antecedent ASA use, antecedent HMG-CoA reductase inhibition), to determine the presence of potential confounders

Study Procedure: At the time of enrollment, after establishing the diagnosis of acute NSTEMI, patients will be randomized to either placebo, or a one-time infusion of the tumor necrosis factor-alpha inhibitor i*nfliximab*. This bolus dose will be given at a 5 mg/kg dose, administered as a slow intravenous infusion over a 2 hour period. In addition, all patients will receive medical therapy consistent with standard medical practice for the management of the acute coronary syndrome. Decisions regarding follow up evaluations, and subsequent therapies will be left to the outpatient Cardiologists.

Study Drugs: *Infliximab* is a chimeric monoclonal antibody that blocks the action of TNF-alpha by binding to it and preventing subsequent cell signaling. The drug was developed and is manufactured by Centocor, Inc. (Malvern, PA). Currently, the FDA has approved i*nfliximab* for treatment of severe rheumatoid arthritis, crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriatic arthritis. The interaction of *infliximab* with other drugs has not been studied. The most common side effects of *infliximab* are upper respiratory tract infections, urinary tract infections, cough, rash, back pain, nausea, vomiting, abdominal pain, headache, weakness and fever.

Side effects such as low or high blood pressure, chest pain, difficulty breathing, rash, itching, fever and chills may occur during or shortly after administration. These reactions could indicate an allergy to the drug. The development of any of these reactions occurring during administration of the study drug would result in discontinuation of the offending agent, and appropriate medical management. For the purposes of this trial, evaluation of those patients would continue on an intention-to-treat basis.

Infliximab is marketed in 100mg vials, at a cost of $622/ vial. At a dose of 5mg/kg, approximately 400 mg would be required per dose, at a cost of $2400 per subject in the study arm. In addition to the standard cost of care for NSTEMI, this study is anticipated to cost $3.6 million dollars.

Study Subjects: Study participants will include all patients between over 18 y.o. who are admitted to the Internal Medicine Service at CUMC regardless of admission diagnosis, and able to provide informed consent either themselves or via a health care agent. Those who experience a documented NSTEMI during their hospitalization will be evaluated for inclusion in this study.

Exclusion criteria will be:
- Hypersensitivity to infliximab, murine proteins or any component of the formulation
- Moderate to severe congestive heart failure (NYHA Class III/IV); cardiogenic shock
- Acute MI requiring emergent PCI (including STEMI)
- Renal insufficiency (Cr > 1.5)
- Severe infections (i.e., sepsis, abscesses, tuberculosis, HIV, and opportunistic infections)
- Active malignancy
- Acute hepatitis
- Demyelinating CNS disease
- Pregnancy

Recruitment of Subjects: Patients will be enrolled at the time of NSTEMI diagnosis, and emergent catheterization is felt not to be warranted

Confidentiality: Study subjects will be given unique identifying codes, to which all data will be linked. The study will be double blinded, such that only the objective review committee will have access to these codes for analytical purposes

Conflicts of Interest: None at this time

Location of the Study: All study patients will be recruited from those admitted to the Medical Service at CUMC.

Potential Risks: Potential risks include those specifically related to the administration of *infliximab* during an acute MI. Specific drug interactions with *infliximab* have not been evaluated. Also, although the overall incidence of infusion reactions to *infliximab* is reported to be 6%, the risk of severe allergic reactions to this murine protein is approximately 1%. With long term *infliximab* therapy, underlying malignancy and infection are of particular concern with immune modulation. Whether this same risk is associated with single-doses is not known.

Potential Benefits: Given the overall prevalence of CAD, and the limited benefit standard therapy offers those patients who have suffered a NSTEMI, there may be substantial individual benefits if, in fact, immune modulation can help reduce associated morbidity and mortality.

Alternative Therapies: none

Laboratory Testing: All cardiac troponin assays will be run at CUMC laboratories. To avoid potential confounders, and increase specificity, a cutoff for a positive result will be set arbitrarily at 1 μg/L.

Compensation: Patients will have been admitted for medical evaluation and treatment. This therapy will not cause any further inconvenience, and thus, no compensation will be offered

Cost to Subject: None

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