A Phase 2, Double-Blind Placebo-Controlled study of the Efficacy and Safety of Recombinant Human Insulin-Like Growth Factor 1 (IGF-1) in Subjects with Acute Renal Failure (ARF).

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A. Study Purpose and Rationale:

Acute renal failure, defined as a serum creatinine increase of greater than 50% above baseline, complicates approximately 1% to 5% of patients following cardiac surgery. Thirty-day mortality following cardiac surgery in patients with ARF is 63.7% compared with 4.3% in patients without ARF. other than supportive care, we currently have no effective treatment for this debilitating complication of common surgeries.

Insulin-like Growth Factor-1 (IGF-1) is a naturally occurring trophic factor for cells. Of interest to this study, IGF-1 has been shown in rat models to restore cellular architecture to kidneys on thin section microscopy when administered within 30 min of an ischemic or nephrotoxic event. Other studies have illustrated increases in creatinine clearance using IGF-1 in both rat and human models. Efficacy and safety has been established in humans when administered for up to 27 days in patients with chronic renal failure. only side effects were jaw pain, Bells palsy, papilledema, hypoglycemia, hypokalemia, and gingival hyperplasia.

B. Description of study design and study analysis

The proposed phase 2 study will involve approximately 50 patients for each the study as well as placebo group. The estimated duration of the study is one year; given the estimated amount of time- to acquire enough patients. Patients will be selected either during or following cardiac surgery who have become either oliguric, or anuric with active sediment in the urin. Patients in the treatment group will receive subcutaneous injections of 100ug/kg of IGF-1 twice daily for a total of 7 days. Neither patient nor the evaluating physician will know whether the patient is receiving IGF-1 or placebo. The data will be collected and analyzed centrally by the sponsoring agency. The data will then be assessed to evaluate disease free survival defined the percentage of patients who underwent dialysis by day 14. Dialysis was studied by first estimating the curves for the time to the first dialysis with. Kaplan-Meier methods. Other end points include a serum creatinine elevated greater than 50% of baseline, and mortality from complications directly related to ARF at the end of 21 days. Mean serum levels of creatinine are to be analyzed using a Students t test.

C. Description of Study Procedures

This will be a randomized, double blind, placebo-controlled clinical trial of IGF-1 vs. placebo. Subjects for the study will be selected from patients undergoing cardiac surgery at CPMC. To enroll a patient, a member of the staff at the study site will telephone an independent Study Randomization Center who will assign the patients in a double blind manner in a 1:1 ratio and then the information will be sent directly to the research pharmacist for dispensing of the IGF-1, or placebo. The principal investigator will meet with the patients thought to be at high risk for going on to renal failure and obtain their informed consent if agreeable. The data for each patient consists of routine blood and urin analysis and does not provide any additional burden to the patient.

D. Inclusion and Exclusion Criteria

a. Inclusion criteria for subjects

All subjects volunteering for participation in the study will be screened for conformance with its inclusion and exclusion criteria. Patients enrolled in the study were at least 18 years of age with a clinical diagnosis of acute tubular necrosis (ATN) due to recent ischemic or nephrotoxic insults. To limit the number of patients screened for the study and to optimize the risk benefit ratio of using the IGF-1, they will be stratified according to risk factors for having an increased risk of going on to have severe ATN requiring dialysis. These risk factors including advanced age, poor renal reserve (CR > 3 mg/dl), cardiac bypass, use of intraaortic balloon pump, and aortic cross clamping. The diagnosis of ATN to be based on the patients clinical history, physical examination, and laboratory values including presence of active sediment on urinalysis.

b. Exclusion criteria for subjects

Patients to be excluded from the study for intrinsic renal diseases other than ATN (vasculitis, or glomerulonephritis), marked chronic renal insufficiency with a serum creatinine of > 3mg/dl, previous renal transplantation, hypotension with SBP < 90mmHg, evidence of vascular obstruction, and evidence of postrenal obstruction. All patients regardless of gender, or race are to be considered for this study.

E. General information

a. Study Drug

IGF-l will be obtained from Genentech Inc. IGF-l is a peptide chain made with recombinant technology. Subjects will receive 100ug/kg administered subcutaneously twice daily for seven days. The funding for this study will be provided by grants from the NIH as well as Genentech. All personal patient fiJes are completely confidential with exception to data specifically pertaining to the study *which is to* be published.

No medical devices needed

b. Alternative Therapies

Extremely weak evidence exists for the use of either calcium channel blockers, or atrial naturietic peptide as treatments for ARF. There currently are n6 therapies which are accepted as a treatment for ARF in clinical practice.

c. Risks and Benefits

The risks to patients are minimal and the minor side effects of the IGF-1 appear to be reversible with discontinuation of the drug. ARF has a high mortality following cardiac surgery of up to 63%. If IGF-1 is an effective treatment it would be a great boon to both affected patients and to society.