An Interventional Trial in Established Chronic Renal Allograft Rejection

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A. Study Purpose and Rationale

Chronic renal allograft rejection accounts for the majority of renal allograft failures one year or more after transplantation (when non-renal-related deaths are excluded from analysis) and is one of the leading causes for repeat renal transplantation. Despite its name, this condition is a complex one with multiple etiologies including immunologic, nephrotoxic, and hemodynamic components.[1] This condition typically occurs at least six months after renal transplantation and is characterized clinically by progressive azotemia, usually associated with proteinuria, hypertension, and edema and is unresponsive to increases in immunosuppressive therapy. There is no effective therapy for this condition, but preliminary evidence suggests angiotensin converting enzyme inhibitors (ACE inhibitors) may be beneficial in this condition,[2] just as they have proved therapeutic in a wide range of other chronic kidney diseases, including diabetic nephropathy and nondiabetic proteinuric nephropathy.

Side effects of ACE inhibitors are well known and include anemia, angioedema/anaphylaxis, cough, hyperkalemia, hypotension, and worsening of renal function, especially in the setting of volume depletion. ACE inhibitors are contraindicated in cases of renal ischemia due to arterial stenosis and there is significant fear among many nephrologists that renal transplant recipients who receive ACE inhibitors are at great risk of acute graft failure, due to ischemia or to decreased tissue levels of cyclosporine in the setting of renal transplant artery stenosis (either surgical or immunologic). It is this fear combined with the promise of ACE inhibitors that have led to the difference in attitudes towards ACE inhibitors prescription among transplant nephrologists, from reluctance to enthusiasm.

In fact ACE inhibitors have safely been used for years in renal transplant recipients to treat posttransplant erythrocytosis, hypertension, and proteinuria, as recently demonstrated in two large retrospective reviews[3,4]. There has been one prospective open label trial of ACE inhibitors in twentyone patients with chronic renal allograft rejection that demonstrated stabilization of renal function and decreased proteinuria without any adverse effects[5], and the National Institutes of Health have sponsored a trial of an angiotensin-II receptor blocker in patient with established chronic renal allograft rejection.[6]

The hypothesis is that ACE inhibitors are safe and effective in the treatment of chronic renal allograft rejection. The purpose of the study is to evaluate this hypothesis using a representative ACE-inhibitor (taken only once a day for ease of administration), ramipril for a period of six months after the diagnosis of chronic renal allograft rejection is confirmed by tissue biopsy.

B. Study Design and Statistical Analysis

The study design is a prospective randomized placebo-controlled double-blinded trial to evaluate graft survival after six months of ramipril in patients with chronic renal allograft rejection. The primary endpoint will be progression of renal dysfunction as measured by percent change in serum creatinine. Secondary endpoints will include the incidence of side effects requiring discontinuation of therapy, including anemia, angioedema/anaphylaxis, cough, hyperkalemia, symptomatic hypotension, and worsening of renal function, determined by routine physical exams and blood tests, including hemoglobin, serum potassium, serum creatinine. These endpoints are measured on a monthly basis as part of the routine care of renal transplant recipients at this institution and, for the purposes of this study, we will specify hemoglobin < 10 g/dl, potassium > 6 mEq/L, doubling of serum creatinine, and symptoms of lightheadedness or weakness as evidence of serious side effects, in addition to any side effect severe enough to cause the patient's transplant nephrologist to discontinue the study drug.

The statistical analysis of the primary endpoint is to be performed using the simple Student's t-test. In order to enroll enough subjects to enable the study to have 80% power to detect a 30% difference between the two study groups with a 5% level of confidence, it will be necessary to enroll about 40 patients in each of the two arms of the study. This is a difficult estimate to make because the literature states that the rate of decline of renal function is quite variable in chronic rejection.[7,8,9] Nevertheless, it is estimated that patients in the placebo arm of the study will manifest an percent increase in creatinine ranging between fifty and one hundred percent.

C. Study Procedures

The procedures described in this study, from the identification of patients with chronic renal allograft rejection via clinicolaboratory features, to the confirmation of the diagnosis by biopsy, to the follow-up laboratory data obtained on a monthly basis, is all part of the routine clinical management of renal transplant recipients in this institution. Therefore the only components of the research study that are performed solely for the purposes of the study are the administration of drug and the requirement for contraception.

D. Study Drugs

Ramipril (Altace, Monarch Pharmaceuticals) is an angiotensin converting enzyme inhibitor that has been used for years in the treatment of hypertension and heart failure after myocardial infarction. For patients with hypertension and renal impairment the recommended starting dose is one 1.25 mg tablet administered once daily, increased to a maximum total daily dose of one 5 mg tablet administered once daily. In this trial the study drug (ramipril versus placebo) would be started at 1.25 mg daily after enrollment and titrated by the patient's primary care nephrologist at clinic sessions 2 and 4 weeks after enrollment to the maximum tolerated dose, no more than 5.0 mg daily.

The most significant side effects of the drug, as listed previously, include anemia, angioedema/anaphylaxis, cough, hyperkalemia, hypotension, and worsening of renal function. Other rarer side effects include neutropenia and hepatic failure, but routine monitoring for these side effects are not recommended except possibly in patients with collagen vascular disease. ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women in the second and third trimesters of pregnancy, so for the purposes of this study, patient will have to agree to use an effective method of birth control.

E. Medical Devices

None

F. Study Questionnaires

None

G. Study Subjects

a. Inclusion Criteria

- Must be at least eighteen years old.
- Must have received a kidney transplant at least one year prior to study entry.
- Must have a confirmed rise in creatinine, without obvious correctable cause, to a value at least 1.0 mg/dl above their serum creatinine baseline obtained between five and seven months following

- transplant. Any patient with a serum creatinine greater than 3.5 mg/dl should have a Doppler ultrasound renal arteriogram done to eliminate the possibility of renal artery stenosis.
- Must have been diagnosed with chronic rejection with confirmatory transplant renal biopsy (analyzed according to the Banff criteria) following kidney transplant and within six months prior to study entry.
- Must have been receiving a stable immunosuppressive medication regimen for one month prior to study entry that includes at least cyclosporine or tacrolimus and prednisone.
- Must agree to use a medically accepted method of birth control, if female of childbearing potential.
- Must agree to six months of follow up at our Clinical Transplant Unit after study enrollment.

b. Exclusion Criteria

- Simultaneous participation in another clinical trial that specifies diagnostic or therapeutic
- procedures during the period of the study.
- Serum creatinine greater than 5.0 mg/dl at the time of randomization.
- Absolute need for, or contraindication to, ACE inhibitors.
- Use of a known ACE inhibitor or angiotensin-II receptor blocker at the time of randomization or at any point during the study.
- Presence of other serious disease (e.g. malignancy, elevated liver function tests) such that participation would not be in the patient's best interest
- Pregnancy.

H. Recruitment of Subjects

Patients would be identified by their primary transplant nephrologist, who would agree that the patient is suitable for the study and ascertain that the patient is willing to discuss the study with the research team before the research team makes an attempt to contact the patient.

The Columbia Presbyterian Medical Center Research Pharmacy would be responsible for manufacture and packaging of placebo tablets in three dosage forms. It would be responsible for procuring the study drug (ramipril) in 1.25, 2.5, and 5.0 mg tablet forms. It would be responsible for blinding and randomizing all patients enrolled into the study.

I. Confidentiality of Study Data

All study subjects will be assigned a unique code number and date collected would be listed under this unique code number, without personal identifiers, and stored in a dedicated file cabinet in my office.

J. Potential Conflict of Interest

None

K. Location of the Study

Columbia Presbyterian Medical Center Clinical Renal Transplant Unit, located on the twelfth floor of the Presbyterian Hospital.

L. Potential Risks

The potential risks of treatment include all of the side effects listed above, namely anemia, angioedema/anaphylaxis, cough, hyperkalemia, hypotension, and worsening of renal function. Other rarer side effects include neutropenia and hepatic failure. It is expected that the incidence of side effects would be less than 10% based on the results of the two large retrospective reviews, and it is expected that these side effects would be reversible on discontinuation of the study drug.

There is a very small risk (<1%) of acute graft failure within 2 weeks of initiation of the drug. This outcome has not occurred among the trials published to date in hundreds of renal transplant recipients, and the ultrasound examination would be expected to detect renal artery stenosis before enrollment into the trial.

There is a risk that the study drug will not be effective in the treatment of this disease.

There is a risk that the study drug will be effective in the treatment of this disease, and so patients randomized to receive placebo will experience a poorer outcome as a result of enrollment into this study.

M. Potential Benefits

Patients enrolled in this study may or may not directly benefit as a result of participation in this study. The study is being performed because there are several reasons to hope that this drug will be a safe and effective treatment of chronic rejection, however, and we expect that the results of this study will help settle these issues and therefore benefit future patients with chronic renal allograft rejection.

N. Alternative Therapies

None

O. Compensation to Subjects

None

P. Costs to Subjects

The only potential cost to patients who enroll in this study is the cost of birth control in women of childbearing age who are not already taking a medically accepted form of birth control.

Q. Minors as Research Subjects

None

R. Radiation or Radioactive Substances

None

S. References

1. "Mechanisms of Chronic Rejection" By LC Paul, N Ferguson, K Al-Fakeeh, and H Benediktsson, Chapter 7 (pp. 177-200) in Kidney Transplant Rejection: Diagnosis and Treatment 3rd edition, edited by LC Racusen, K Solez, and JF Burdick, published by Marcel Dekker, New York, 1998.

2. "Is it time for ACE inhibitors in chronic allograft nephropathy?" by JB Lewis and JH Helderman, in American Journal of Kidney Diseases 35(1): 154-156, Jan 2000.

3. "ACE inhibitors and angiotensin II antagonists in renal transplantion: an analysis of safety and efficacy." By CE Stigant, J Cohen, M Vivera, and JS Zaltzman, in American Journal of Kidney Diseases 35(1): 58-63, Jan 2000.

4. 4. "Treatment of hypertension after renal transplantation: long-term efficacy of verapamil, enalapril, and doxazosin." By A Martinez-Castelao, M Hueso, V Sanz, J Rejas, J Alsina, JM Grinyo, in Kidney International Suppl 68:S130-4, Dec 1998

5. "Treatment of kidney transplants with chronic rejection using angiotensin-converting enzyme inhibitors." By D Paredes, R Sola, L Guirado, J Ibeas, I Agraz, D Vizcarra, and F Algaba, in Transplantation Proceedings 29:2587-2588, 1997.

6. "Prevention of kidney transplant rejection." Accessed online at www.clinicaltrials.gov in May, 2000.

7. "The late results of renal transplantation and the importance of chronic rejection as a cause of graft loss." By MC Foster, PW Wenham, PA Rowe, RP Burden, AG Morgan, RE Cotton, and RW Blamey, in Annals of the Royal College of Surgeons of England 71: 44-47, 1989.

8. "The variable nature of chronic declines in renal allograft function." By BL Kasiske, KL Heim-Duthoy, KL Tortorice, and KV Rao, in Transplantation 51 (2): 330-334, Feb 1991.

9. "Histopathologic findings associated with a chronic, progressive decline in renal allograft function." By BL Kasiske, RSN Kalil, HS Lee, and KV Rao, in Kidney International 40: 514-524, 1991

Consent Form

Study Title: An Interventional Trial in Established Chronic Renal Allograft Rejection

Study Purpose:

You are invited to participate in a research study to see how effective a drug called ramipril (Altace) is at slowing kidney transplant failure. You have been invited to participate in this trial because you have had a biopsy of you transplant kidney that has signs of chronic rejection. This is a common condition among kidney transplant patients, one that cause scarring and damage to the kidney. Over time, chronic rejection can lead to kidney failure, making it necessary for patients to start dialysis and possibly receive another kidney transplant. There is currently no accepted treatment of this disease, but a doctor would like to see whether ramipril can slow this disease and prevent kidney failure in patients with signs of chronic rejection. Ramipril is a member of a family of drugs known as angiotensin converting enzyme inhibitors, or ACE inhibitors, and these drugs are used most often in the treatment of hypertension (high blood pressure), but are also used to treat certain types of kidney and heart disease.

If you participate in the study you will receive either ramipril or placebo (an inactive sugar pill) at the time you enter into the study. You will have regular clinic visits and blood tests performed at two weeks, four weeks, and monthly from the time you enter the study to six months after you enter the study. The dose of the drug will be doubled at two weeks and again at four weeks by your doctor if he believes it is safe to do so. You will continue to be cared for by your regular doctor whether or not you choose to participate in this research study, and you will only be required to make one additional visit to the medical center (two weeks after beginning the pill) if you agree to participate in this study. This study will take place here at Columbia Presbyterian Medical Center and is expected to enroll eighty patients over two years.

You may be eligible for this study if you: Are at least eighteen years old. Have received a kidney transplant at least one year prior to study entry. Have been diagnosed with chronic rejection following kidney transplant and within six months prior to study entry. Have been receiving a stable immunosuppressive medication regimen for one month prior to study entry that includes at least cyclosporine or tacrolimus and prednisone. Agree to use a medically accepted method of birth control during the study. Agree to six months of follow up at our Clinical Transplant Unit after study enrollment.

You will not be eligible for this study if you: Are participating in another study with required tests or treatments. Absolutely must take ACE inhibitors. Cannot take ACE inhibitors. Have another serious disease or medical condition. Are pregnant.

Your participation in this study involves the following risks: an allergic reaction that could potentially become life-threatening or sudden worsening of your kidney function that could potentially lead to kidney failure. These risks are expected to occur rarely if at all, to no more than 1 out of every 100 persons. Other side effects that may occur include anemia, cough, dizzyness, high blood potassium levels, or worsening kidney function, but these side effects are expected to affect no more than 10 out of every 100 persons.

There is a risk that ramipril will not be effective in the treatment of this disease.

There is a risk that the ramipril will be effective in the treatment of this disease, but that you were assigned to receive placebo instead of the ramipril.

Study Benefits:

You may or may not benefit personally from this study. If ramipril is effective treatment for chronic rejection and you are among the patients assigned to receive ramipril, you will have benefited by having slowed the progression of your disease. If ramipril is not effective treatment or you are not assigned to receive ramipril, you will have still have contributed to society, because there is no accepted form of treatment for this disease, which is quite common after kidney transplant, and any information on new types of therapy would benefit future patients with this disease. At the end of the study after the results are known you may choose to take the treatment yourself based on the results of the study.

Alternatives:

There are no alternative forms of treatment available for this disease. Patients with the disease typically progress to complete kidney failure in a matter of months to years, but it is not possible to predict how quickly any one patient will progress to kidney failure.

Costs:

The only cost to you is the cost of making one additional visit to the Medical Center and having one additional set of blood tests performed two weeks after beginning the study. If you are a woman of childbearing age, you will also incur the additional cost of birth control.

Compensation:

There will be no compensation for participation in this study.

Compensation for Injury:

If you should require medical care (as determined by the medical staff) due to a research-related injury, the study sponsor, Monarch Pharmaceuticals, will cover the cost of such medical care. Such reimbursement may extend only to that portion of the medical bills which are not covered by your medical or hospital insurance.

Confidentiality:

Any information obtained during this study and identified with you will remain confidential. The Food and Drug Administration and the study sponsor, Monarch Pharmaceuticals, may have access to medical records related to this study.

Participation is Voluntary:

You participation in this study is completely voluntary. You can refuse to participate, or withdraw from the study at any time, and such a decision will not affect your medical care at Columbia-Presbyterian Medical Center, now or in the future. Signing this form does not waive any of your legal rights.

If your choose to withdraw early from the study or transfer your care elsewhere, you may be required to have a final set of blood tests and physical exam. If you experience serious side effects (as determined by your regular doctor), have become pregnant or have evidence of renal artery stenosis by ultrasound exam, you will not be allowed to continue participating in the study.

Questions:

If you have any questions, please ask, and we will do our best to answer them. If you have additional questions in the future you can reach Dr. Parag Shah at 212-305-2323.

If you have any questions on your rights as a research subject, you can call the Institutional Review Board at 212-305-5883.

Statement of Consent:

I have discussed this study with Dr. Parag Shah or members of his staff to my satisfaction. I understand that my participation is voluntary and that I can withdraw from this study at any time without prejudice. I have read the above and agree to enter this research study. Signing this form does not waive any of my legal rights.

I have been informed that if I believe I have sustained injury as a result of participating in a research study, I may contact the Principal Investigator, Dr. Parag Shah at 212-305-2323, or the Institutional Review Board at 212-305-5883, so that I can review the matter and identify the medical resources which may be available to me.

I understand that:

a) The Presbyterian Hospital will furnish that emergency medical care determined to be necessary by the medical staff of this hospital.

b) I will be responsible for the cost for the cost of such care, either personally or thorugh my medical insurance or other form of medical coverage.

c) No monetary compensation for wages lost as a result of injury will be paid to me by the Columbia-Presbyterian Medical Center, and:

d) I will receive a copy of this consent form.

Signatures:

Participant Date

Investigator Eliciting Consent Date