

Effect Of Ace Inhibitors On Chronic Renal Transplant Rejection

Stephen Seliger

A. Study Purpose

Chronic renal allograft rejection ("chronic rejection") remains a major cause of morbidity and mortality among renal transplant recipients. Although short-term graft survival in renal transplantation has improved dramatically over the last several decades, the rates of graft dysfunction and loss beyond the acute phase of one year have remained nearly unchanged, at about 9% per year. Most of these cases of chronic or late graft failure are caused by a clinical entity known as chronic allograft rejection, which is characterized by onset beyond one year after transplant, a gradual decline in renal function, and characteristic morphological features on renal biopsy. The course of chronic allograft rejection is typically a gradual rise in serum creatinine over the course of years with an eventual need for dialysis or repeat transplantation. Chronic allograft rejection is now a major cause of end-stage renal disease in the U.S.

It is generally agreed that immunological factors contribute to chronic rejection, and it has been observed that frequent episodes of acute rejection in the first year will increase the likelihood of developing chronic rejection later. However, unlike acute rejection, chronic rejection does not typically respond to increasing immunosuppressive therapy. Based on this observation, some have proposed that nonimmunological factors are contributing to this disease, and in particular hemodynamic factors. One hypothesis holds that hypertrophy and hyperfiltration at the level of the glomerulus contribute to chronic allograft rejection by causing progressive damage and scarring. Animal models of chronic rejection have demonstrated glomerular hypertrophy and hyperfiltration in affected kidneys. Studies in humans have suggested that glomerular hyperfiltration may be a cause of chronic rejection in some patients. Systemic hypertension, which frequently accompanies chronic rejection, is also believed to contribute to the progression of the disease, and therapy to reduce blood pressure may slow the course of the disease.

If the hemodynamic factors of systemic hypertension and glomerular hyperfiltration contribute to the pathogenesis and progression of chronic allograft rejection, then it follows that medications which counteract these processes might be beneficial. The class of anti-hypertensives known as angiotensin-converting enzyme inhibitors (ACEI) is known to reduce both systemic hypertension and glomerular hyperfiltration. Large prospective randomized controlled studies of ACEIs have demonstrated a protection against the progression of renal disease in diabetics with overt nephropathy, and in other types of chronic renal insufficiency. Short-term studies in patients with chronic allograft rejection have shown a reduction in proteinuria with ACEIs, which may indicate a reduction in glomerular hyperfiltration. To date, however, no study has examined the impact of long-term ACEI therapy on patients with chronic allograft rejection. This study will attempt to determine the effect of ACEI therapy, as compared with other anti-hypertensive therapy, on the progression of renal insufficiency in patients with known chronic allograft rejection.

B. Study Design

This study will be a randomized, double-blind, placebo-controlled trial of the effects of the ACE inhibitor lisinopril on the progression of renal disease in chronic allograft rejection. Subjects will be selected among eligible patients at the Renal Transplant Outpatient Clinic at Presbyterian Hospital. Eligible patients will include those with confirmed chronic allograft rejection (see Recruitment method). Eligible subjects who enroll will be randomized in a 1:1 ratio to either a treatment arm (Lisinopril, 10mg per day) or a control arm (identical appearing placebo). Patients who are hypertensive will be treated in a step-wise fashion with other anti-hypertensives on an open-label basis to maintain a goal blood pressure

(see Study drugs). Patients will be followed for a total of three years without crossover or until a primary endpoint is reached. Patients will be evaluated every three (3) months for monitoring of renal function, electrolytes, clinical status, and blood pressure, or more frequently if needed for titration of antihypertensive medication (see Study procedures). The primary endpoint is a doubling of a patient's baseline serum creatinine or a requirement for dialysis. The secondary endpoints are overall survival and degree of proteinuria. In addition, the following clinical features at study entry will be analyzed for predictive value: serum creatinine, type of transplant graft (cadaveric vs. living donor), the prior use of specific biological therapy for acute rejection, and race.

Upon completion of the study, data will be analyzed on an intention-to-treat basis using a chi-squared analysis to compare the proportion of patients in each group who have reached the primary endpoint. In addition, we will construct cumulative survival curves for the two groups using the Kaplan-Meier method, using the same primary endpoint; differences in the survival curves will be assessed by the log-rank method. The effect of the baseline clinical features on the primary endpoint will be analyzed for their effect on the primary endpoint using a multiple regression model.

C. Study Procedures

Prior to randomization, routine laboratory measures of electrolytes, renal function, liver and cardiac function, and urine protein will be obtained, along with a detailed history and physical exam. All patients will receive a renal ultrasound to exclude the possibility of renal pelvic or uretral obstruction. After randomization, all patients will be evaluated every 3 months routinely for repeated measures of blood pressure, renal function, electrolytes, and evaluation of symptoms (especially potential adverse side effects) and physical exam. No subjects are expected to experience any pain or discomfort from these procedures.

Prior to randomization, there will be a 2 month screening period during which any current ACEIs will be discontinued. Patients who are hypertensive will be placed on a calcium-channel blocker, amlodipine (see study medications) at a low dose, and subsequently titrated to a goal BP of 150/90. An additional anti-hypertensive, metoprolol, will be added and likewise titrated for those patients still above the goal BP. Finally, for those patients who are not controlled on the above medications, antidiuretic, furosemide, will be added. After randomization, patients will receive either lisinopril or identical-appearing placebo. Patients may need additional follow up visits to maintain blood pressure at a goal of systolic 110-140 and diastolic 70-90. In addition, patients will receive dietary counseling from nutritionists on maintaining a protein-restricted diet.

There will be two groups of physicians participating in this study: Group #1 will be blinded to randomization, and will manage the patients' blood pressure as described above; Group #2, who will be blinded not only to the randomization but also to the patients' identities and use of open-label anti-hypertensives, will evaluate patients' need for dialysis and progression of renal disease. Patients will be enrolled in the study over a 2 year period, and each patient will be followed for 3 years or until the primary endpoint is reached.

D. Study Drugs

- Lisinopril (Prinivil, Merck) 10mg PO qd
- Known side effects: cough(3.5%)
 - hyperkalemia
 - hypotension(1.2%)
 - headache (5.7%)
 - angioedema
- Amlodipine (Norvasc, Pfizer) start at 2.5 mg PO qd, titrate up to 10mg PO qd
- Known side effects: edema (1. 8-10%)

- headache (7.3%)
- Dizziness (1.1-3.4%)
- fatigue (4.5%)
- Metoprolol (Toprol XL, Astra) 50 ing PO qd, titrate up to 400 mg PO qd
- Known side effects: bradycardia (3%)
 - depression (5%)
 - tire dness/dizzine ss (10%)
 - wheezing (I %)
- Furosemide (Lasix, Hoechst-Roussel) 40mg PO qd, up to 160 mg PO qd
- Known side effects: orthostatic hypotension
 - tinnitus
 - rash
 - pancreatitis

E. Medical Devices

No experimental medical devices will be used.

F. Study Subjects & Recruitment Method

a. Inclusion Criteria:

1. Chronic allograft rejection by renal biopsy
2. One year or greater after renal transplant (cadaveric or living donor)
3. Age 18-65
4. Use of cyclosporin in first year post-transplant
5. Serum Creatinine 1.5-4.0

b. Exclusion Criteria:

1. Systolic Blood pressure <120 or diastolic <80
2. Pregnancy
3. congestive Heart Failure (NYHA Class III, IV)
4. bradycardia
5. renovascular hypertension
6. routine use of non-steroidal anti-inflammatory drugs
7. obstructive lung disease
8. persistent hyperkalemia
9. Insulin- dependent diabetes mellitus
10. chronic cough
11. allergy or intolerance to any of the study medications
12. any medical condition which would limit patient's life expectancy to 3 years or less.
13. An inability to maintain regular follow-up.

Eligible subjects will be identified by their nephrologists, who will contact the patients during a routine visit to discuss their interest in entering this study. Women and minorities will be encouraged to enter this study.

G. Confidentiality

Appropriate methods will be taken to ensure confidentiality of the study data and identity of the study subjects. A unique code number will be used to identify subjects, and subject data will be secured on a computer system available only to investigators.

H. Location

This study will be conducted at CPMC in the renal transplant clinic on PH 14th floor; investigators will be from the Division of Nephrology,

I. Risks and Benefits

Potential risks to participants include the risk of any side effects of the study medications. In particular, although rare, potentially life -threatening angioedema has been documented to caused by ACEI therapy. Finally, there is the risk that ACEIs may exacerbate chronic allograft rejection, although there is no data at this time to suggest that this may happen.

Potential benefits to participants include receiving regular intensive blood pressure control, which may improve the prognosis of chronic rejection.

J. Alternative Therapies

At this time, there is no specific alternative therapy for chronic rejection.