Effects of Losartan on renal function in renal transplant recipients with antibodies to the angiotensin receptor: a randomized, double-blind, placebo-controlled trial

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A. Study Purpose and Rationale

Episodes of acute renal allograft rejection are a major risk factor for graft loss.[1] Most episodes of acute rejection are mediated by cellular mechanisms, but about one third of episodes of acute rejection are mediated by antibodies.[2]Many of these antibodies are directed against donor HLA antigens, and recently tremendous progress has been made in treating these patients with plasmapheresis, IVIG, tacrolimus and MMF.[3] However, some patients experience humoral rejection mediated by non-HLA antibodies - these patients often fail to respond to treatment and frequently lose their grafts.[4]

A recent study suggests that many of these episodes of non-HLA antibody mediated acute rejection may be due to antibodies to the angiotensin II type 1 (AT1) receptor. AT1 antibodies bind to the second extracellular loop of the receptor and affect several intracellular signaling pathways. AT1 antibodies increased the DNA binding activity of NF-KB. AT1 antibodies also induced transcription factor activator protein 1 activity. AP1 and NFKB regulate the gene for tissue factor, which initiates the extrinsic coagulation pathway. Biopsies taken during episodes of acute rejection mediated by AT1 antibodies show pronounced endothelial and epithelial staining for tissue factor.[5]

Sixteen patients in the study had an episode of acute rejection mediated by AT1 antibodies. Nine patients were treated with standard therapy including IVIG and plasmapheresis, while seven others were treated with standard therapy plus 100 mg of losartan daily. The study was not randomized or blinded, and the number of patients involved was too small to allow for firm conclusions. However, graft survival at 12 months in patients treated with losartan was 80%, compared with 20% in patients given standard treatment.[6]

B. Study Design

This is a prospective, multi-center, randomized, double-blind, placebo-controlled interventional trial to investigate whether losartan affects renal function in renal transplant recipients with AT1 antibodies.

C. Study Subjects

Subjects will be approached by their nephrologists for participation. After informed consent has been obtained by the investigators, adult renal transplant patients at 15 large transplant centers will be tested for AT1 antibody prior to transplant and two weeks post-transplant. Patients who undergo ABO

[1] Pascual M, Theruvath T, Tatsuo Kawai et al. Strategies to improve long-term outcomes after renal transplantation. NEJM 2002;346:580-590.

[2] Racusen L. Antibody-mediated rejection in the Kidney. Transplantation Proceedings 2004;36:768-769.

[3] Bohmig G and Regele H. Diagnosis and treatment of antibody-mediated kidney allograft rejection.Transplant Int. 2003;16:773-787.

[4] Ingelfinger J. Agonistic autoantibodies and rejection of renal allografts. NEJM. 2005;352;6:617-619.

[5] Dragun D, Dominik N, Brasen J et al. Angiotensin II Type 1-Receptor Activating Antibodies in Renal-Allograft Rejection. NEJM. 2005;352;6:558-569.

[6] Dragun et al.

incompatible transplants, multi-organ transplants, or who have known contraindications to ARB or ACEI, including anaphylaxis, angioedema, or cough, will be excluded from further study.

D. Study Procedure

Those who test positive at either point will be randomized to receive either 100 mg losartan daily plus standard treatment, or placebo plus standard therapy. Standard therapy includes IVIG, plasmapheresis, tacrolimus and mycophenolate mofetil in the event of an episode of acute humoral rejection. Losartan or placebo will be administered in a double-blind fashion. Patients will begin losartan or placebo starting two weeks post-transplant for one year.

E. Study Drug

Patients with hypertension, diabetes, or other clinical indications for treatment with ACE inhibitors or ARBs could be prescribed an ACE inhibitor at their clinician's discretion. Several smaller studies have demonstrated that combination therapy with ACEI and ARB is safe and well tolerated in renal transplant recipients.[7] Possible serious side effects include anaphylaxis and hyperkalemia. Post-transplant patients are closely followed, with weekly to monthly assessment of serum creatinine. Potassium will be followed at these times, and patients with serum potassiums above 5.8 or those who experience anaphylaxis, angioedema, or intolerable cough on ACEI necessitating unblinded administration of ARB will be discontinued from taking the study drug but included in an intention to treat analysis. All adverse events and toxicities will be reported for ongoing review to the NIH, IRB, FDA and an independent data and safety monitoring board.

F. Statistical Analysis

Study subjects will be risk stratified by center and cadaveric vs. living donor transplant prior to randomization. Serum creatinine will be assessed at one year as this is predictive of long-term graft survival.[8] The study is designed to detect a 25% difference in serum creatinine at one year between the two arms with 80% power and an alpha of 0.05. Accrual will end when 75 patients have been randomized to each arm. The trial will be conducted in fifteen large transplant centers – each of which perform about 200 transplants per year – to ensure adequate accrual within one year.

Mean serum creatinines for the two arms will be compared using a two-tailed unpaired t-test, followed by multiple regression analysis to facilitate narrower confidence intervals. The analysis will use previously validated covariates such as age, sex and race of recipient and donor, prior transplantation, pre-transplant blood transfusions, titer of serum panel reactive antibody, whether the patient received dialysis prior to transplant, diabetes, duration of cold ischemia, degree of HLA mismatch, and delayed graft function (Hariharan).

G. Alternatives

In the event of an episode of acute humoral rejection, one potential alternative therapy is immunoadsorption. However, this treatment is experimental, has only been used in small numbers of patients, is only available in a few select research centers, and is typically used as a salvage therapy when all other treatment options have failed. There is no randomized data to support its use (Bohmig).

H. Confidentiality of Study Data

[7] Paul LC. Renoprotective efficacy of antihypertensive drugs in chronic renal allograft nephropathy. Graft. 1999;2:146-148.

[8] Hariharan S, Mcbride M, Cherikh W

Study data will be coded and stored in a secure location in compliance with HIPAA and IRB regulations.

I. Compensation and costs to subjects

None.

J. Radiation or Radioactive Substances

None.