Tacrolimus (Pan Graf) in Live Related Renal Transplantation: An Initial Experience of 101 Recipients in India


ABSTRACT

Background. Success of modern transplantation is in large part due to the successful development of effective immunosuppressive agents. The safety and efficacy of tacrolimus in transplantation is well established. However, tacrolimus (Pan Graf, Panacea Biotec Ltd, India) has only been available in India for the last 2 years. This study was conducted to assess the safety and efficacy of tacrolimus in live related kidney transplantation. We report an initial experience of tacrolimus as de novo therapy in a live related renal transplantation program.

Materials and Methods. One hundred one consecutive recipients of a live renal allograft were commenced on triple immunosuppression consisting of tacrolimus, mycophenolate mofetil or azathioprine, and steroids. The dose of tacrolimus was adjusted to keep trough levels at 10–12 ng/mL in the first 3 months, 8–10 ng/mL in the next 3 months, and 5–8 ng/mL thereafter. All patients were followed up for a period ranging from 4 weeks to 24 months. The effect of this regimen on the incidence of graft rejection, graft survival, patient survival, and new-onset diabetes mellitus was evaluated. Any evidence of graft dysfunction was evaluated using a graft biopsy.

Results. There were 89 male and 12 female patients with mean age of 32.08 years. The incidence of acute rejection was 3.96%; 21.05% developed new-onset diabetes mellitus. Six patients were diabetic prior to transplantation and 9 patients were hepatitis C virus (HCV)-positive; 77.7% of HCV-positive patients and 15.1% of HCV-negative patients developed posttransplantation diabetes mellitus. The patient survival rate at the current follow-up was 92.07%. No graft was lost due to rejection.

Conclusion. Tacrolimus is a safe and effective immunosuppressant in live related renal transplantation.

TACROLIMUS, a calcineurin inhibitor, is derived from soil organism Streptomyces tsukubaensis found in Japan. It was first used as an immunosuppressive agent in 1994 for liver transplantation and in 1997 for kidney transplantation. Cyclosporine acts by binding cyclophilins, whereas tacrolimus acts by binding FK506-binding proteins (FKBPs). The net effect of tacrolimus is to inhibit T-cell function by preventing the synthesis of interleukin (IL)-2 and other important cytokines.1,2

The main difference between tacrolimus and cyclosporine, other than the actual immunophilin each binds to, is the relative potency, with tacrolimus being 100 times more potent than cyclosporine on a molar basis. Many studies have been performed since the introduction of tacrolimus, as an induction immunosuppressive agent, as an alternative in cyclosporine-failure cases, and in comparison with cyclosporine.
Tacrolimus has only recently been available for clinical use for transplantation in India. There have not been any documented studies on the use of tacrolimus in India. This study was conducted to assess the safety and efficacy of tacrolimus in live related kidney transplantation in India on 101 consecutive patients.

MATERIALS AND METHODS

One hundred one consecutive renal transplant recipients were included in this ongoing study after obtaining written informed consent. The age of the patients ranged from 12 to 60 years. There were 89 men and 12 women. Nine patients were hepatitis C virus (HCV) positive prior to transplantation and 6 patients had diabetic nephropathy leading to renal failure prior to transplantation. Recipients who were pregnant or receiving more than 1 organ transplant, recipients who were human immunodeficiency virus (HIV) positive or unable to tolerate tacrolimus orally or with a known hypersensitivity to tacrolimus or steroids, as well those receiving any other investigational prophylactic immunosuppressants were excluded from this study.

Immunosuppression consisted of tacrolimus (0.15 mg/kg) and azathioprine (1.5–2 mg/kg) or mycophenolate mofetil (500 mg twice a day). All patients received perioperative intravenous corticosteroid therapy. Oral steroids were started on the first postoperative day at a dose of 20 mg and were gradually tapered to 7.5–10 mg during the next 6 months. Nine patients opted for induction therapy with daclizumab, 2 patients with basiliximab, and 1 patient who was undergoing a second transplantation with a panel-reactive antibody (PRA) of >90% was given induction therapy with antithymocyte globulin for 5 days.

Tacrolimus levels were determined using the Abbott IMx Tacrolimus II assay (Abbott Laboratories, Abbott Park, Ill, United States), a procedure based on the microparticle enzyme immunoassay (MEIA) technology. The dose of tacrolimus was adjusted according to levels performed biweekly and kept at 10–12 ng/mL for the first 3 months, 8–10 ng/mL for the subsequent 3 months, and 5–8 ng/mL subsequently.

Full blood counts, blood sugar, and renal and liver function tests were done daily in the first week, then biweekly for the first 2 months, and weekly thereafter in the third month. Any consistent evidence of a fasting blood sugar >120 mg/dL was taken as evidence of posttransplantation diabetes mellitus.

All episodes of graft dysfunction were investigated with a color duplex scan, drug levels, DTPA, and a graft biopsy. Biopsy-proven acute rejection episodes were treated using 3 pulses of methylprednisolone. Polyclonal antibody was used when the rejection was steroid-resistant.

Demographic details, medical history, surgical details, donor and recipient HLA matching, PRA levels, posttransplantation blood steroid-resistant. Epileptic patients who were pregnant or not able to tolerate tacrolimus orally or with a known hypersensitivity to tacrolimus or steroids, as well as those receiving any other investigational prophylactic immunosuppressants were excluded from this study.

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Demographic details, medical history, surgical details, donor and recipient HLA matching, PRA levels, posttransplantation blood investigations, and biopsy results (if performed) were documented. Endpoints of the study were patient survival, graft survival, and treatment failure.

RESULTS

Donor and Recipient Characteristics

A total of 101 patients were included in the study, of which 89 were male and 12 were female. Mean age of recipients was 32.08 years with a range of 12 to 60 years. The mean age of the donors was 43.03 years with a range of 21 years to 66 years (Table 1). Thirty-eight mothers, 19 wives, 19 brothers, 17 fathers, 5 sisters, 1 son, and 1 husband defined the relationship with the recipient. The mean number of HLA mismatches at the A, B, and Dr loci was 2.24. Ninety-seven donors had a single renal artery, 3 donors had 2 renal arteries, and 1 donor had 3 renal arteries. The mean warm ischemia time was 20.79 minutes (range, 14–42 minutes). All grafts had good primary function.

Drug Dosing and Levels

Patients being given immunosuppressive therapy consisted of 2 groups: 32 patients received a combination of tacrolimus, azathioprine plus steroids, and 69 received tacrolimus, mycophenolate mofetil plus steroids. Four patients in the tacrolimus/azathioprine group were given induction therapy with daclizumab, and 1 patient with antithymocyte globulin for 5 days.

One patient in the tacrolimus/mycophenolate group was given induction therapy with basiliximab and 5 patients with daclizumab. The dose of tacrolimus was adjusted according to levels done biweekly and patients were maintained at blood trough levels of 10–12 ng/mL in the first 3 months. The mean dose of tacrolimus required to keep the prescribed trough levels in these patients was 4.24 mg/d (range, 0.5 mg/d–12 mg/d).

Efficacy and Safety

Episodes of biopsy-confirmed acute rejection were seen in 4 patients (3.96%). Among these, 1 had evidence of Banff Type Ib rejection, 2 had Banff Type Ila rejection, and 1 had Banff Type III rejection. All patients were given 3 pulses of methylprednisolone. Three of 4 patients responded to steroids, whereas the patient with Banff Type Ib rejection, despite having a lower grade of rejection, went on to develop steroid-resistant rejection and responded to a 7-day course of antithymocyte globulin.

Concerning renal function, the mean serum creatinine level at the time of discharge was 1.33 (range, 0.5–2.3 mg%) and at the time of the present analysis was 1.007 mg% (range, 0.5 mg%–2.2 mg%).

Patient mortality during the study period was 8, including 4 who died of fulminant chest infections; 1 was HCV-positive prior to transplantation and died of sepsis with liver failure at 10 months posttransplantation; 2 patients died of meningitis (cryptococcal in 1 and tuberculosis (TB) in other); and no cause of death was known in 1.
Twelve other patients had infectious episodes: herpes zoster in 6 patients and chickenpox in 1, both of which responded to acyclovir; Urinary tract infections that responded to antibiotics occurred in 2; acute gastroenteritis in 1; histoplasmosis in 1; and 1 patient developed cytomegalovirus (CMV) pneumonia.

Currently 93 patients are in follow-up. No graft was lost due to rejection. Our current graft and patient survival rates are 100% and 92.07%, respectively.

Posttransplantation Diabetes Mellitus

Twenty of 95 patients (21.05% patients) who had no pretransplantation history of diabetes developed posttransplantation diabetes mellitus. Seven of these 20 patients were HCV-positive prior to transplantation; 77.7% of HCV-positive patients and 15.1% of HCV-negative patients developed posttransplantation diabetes mellitus. Eight of these 20 patients had to be admitted to the hospital for control of blood sugar and currently all 20 are controlled on insulin.

DISCUSSION

The 5-year follow-up of the Phase 3 U.S. study of tacrolimus by Vincenti et al showed that the incidence of treatment failure at the 5-year follow-up was significantly lower than cyclosporine. The median serum creatinine level was significantly lower with a tacrolimus-based regimen. Single-center, randomized study with 6 years follow-up, on 115 patients who were given tacrolimus compared with 117 patients given cyclosporine microemulsion showed the former patients displayed significantly better graft survival rates (81% versus 60%, respectively) and greater renal function as well as a better cardiovascular profile posttransplantation. A study of more than 1000 renal transplant recipients by Sonoda et al using tacrolimus-based immunosuppression demonstrated patient and graft survival rates of 98.4% and 94.8% at 1 year, 98.0% and 92.6% at 2 years, and 97.6% and 90.4% at 3 years, respectively. Their acute rejection rates were 32.5%. Margreiter demonstrated biopsy-proven acute rejection incidence of 19.6% with an excellent cardiovascular profile with tacrolimus-based immunosuppression. The results from our study showed 92.07% patient survival and 100% graft survival after live related renal transplantation using a tacrolimus-based protocol. However, our acute rejection rate was 3.96%, which is lower than that reported in the literature. This may be due to the fact that most of our grafts were from well-matched live donors. Also, our mean follow-up was less; rejection rates may increase as our follow-up increases.

Posttransplantation diabetes mellitus is an important risk factor for the development of cardiovascular disease and may adversely impact patient and graft survival. Margreiter reported that the incidence of posttransplantation diabetes mellitus was higher among the tacrolimus group (8.0% versus 3.7%; \( P = .032 \)), but the difference diminished, becoming statistically insignificant if those with preexisting diabetes were excluded (4.5% versus 2.0%, tacrolimus versus cyclosporine microemulsion, respectively). Our incidence of diabetes mellitus was 21.05%. However, in the non-HCV-positive patients, the incidence was only 15.1%, which agrees more with that reported in the literature. The association of HCV and posttransplantation diabetes mellitus is well known.

One big worry with this degree of immunosuppression has always been infection, especially in our setting. Our study demonstrated a fairly acceptable incidence of posttransplantation infections. This may be because of the lower dose of steroids that this regimen allowed and the regular drug monitoring.

In conclusion, tacrolimus is a safe, effective immunosuppressant in living-related renal transplantation. It shows excellent graft and patient survival and is associated with a low incidence of acute rejection episodes. Tacrolimus has a safe cardiovascular profile and is associated with an acceptable incidence of infectious complications.

REFERENCES