Generic Tacrolimus (Pan Graf) in Renal Transplantation: An Experience of 155 Recipients in India


ABSTRACT

Background. The safety and efficacy of tacrolimus in transplantation are well established. However, tacrolimus (Pan Graf) has only been available in India for the last 2 years. We conducted this study to assess the safety and efficacy of tacrolimus in living related kidney transplantation. Herein we have reported our experience with tacrolimus as de novo therapy in a living related renal transplant program.

Materials and Methods. One hundred fifty-five consecutive recipients of living donor renal allografts were included in this study after consent and ethical clearance. Immunosuppression consisted of tacrolimus, mycophenolate mofetil or azathioprine, and steroids. The dose of tacrolimus was adjusted according to levels done on a regular basis. All patients were followed for periods ranging from 3 to 33 months. All episodes of graft dysfunction were evaluated by a graft biopsy. We evaluated the effects of this regimen on the incidence of graft rejection, graft survival, patient survival, and new onset diabetes mellitus. Six patients were diabetic prior to transplantation and 9 patients were hepatitis C virus (HCV) positive.

Results. There were 137 male and 18 female patients. The incidence of acute rejection was 3.87%; 17.93% developed new onset diabetes mellitus; and 77.7% of HCV-positive patients and 14.07% of HCV-negative patients developed posttransplantation diabetes mellitus. The patient survival at the current follow-up was 94.19%.

Conclusion. This generic form of tacrolimus is a safe, effective immunosuppressant in living related renal transplantation.

TACROLIMUS, a calcineurin inhibitor, is derived from soil fungus Streptomyces tsukubaensis, found in Japan. Tacrolimus acts by binding FK 506-binding proteins (FKBPs). The immunosuppressive effect of tacrolimus inhibits T-cell function by preventing synthesis of interleukin-2 (IL-2) and other important cytokines. Many studies have been performed since the introduction of tacrolimus as an alternative for cyclosporine-failure cases and also as a maintenance agent compared to cyclosporine. We conducted this study to assess the safety and efficacy of tacrolimus in living related kidney transplantation in India on 155 consecutive patients. We have published our experience with generic tacrolimus, which we have been using for the past 3 years with excellent rejection rates and an acceptable rate of new onset diabetes mellitus (NODM).4

MATERIALS AND METHODS

One hundred fifty-five living donor renal transplant recipients were included in this ongoing study after obtaining written informed consent. We initially recruited patients with hepatitis C virus (HCV) on tacrolimus, but have currently stopped this because of the high incidence of NODM. The ages of patients ranged from 9 to 65 years. They consisted of 137 men and 18 women. Nine

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patients were HCV positive prior to transplantation and 1 patient was HBsAg positive. Six patients had diabetic nephropathy leading to renal failure prior to transplantation. Recipients who were pregnant or receiving more than one organ transplant, who were HIV positive or unable to tolerate tacrolimus orally, or had a known hypersensitivity to tacrolimus or steroids, as well those receiving any other investigational prophylactic immunosuppressant 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, which was gradually tapered to 7.5 to 10 mg over the next 6 months. Twenty-eight patients opted for induction therapy: 25 with 2 doses of daclizumab and 2 with 2 doses of basiliximab. One patient who was undergoing a second transplantation with a panel-reactive antibody (PRA) of more than 90% was given induction therapy with antithymocyte globulin for 5 days.

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

Full blood counts, blood sugar, as well as renal and liver function tests were performed daily in the first week and then biweekly for the first 2 months and weekly thereafter in the third month. Any consistent evidence of a fasting blood sugar more than 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. A biopsy-proven acute rejection episode was treated with 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 investigations, and biopsy results (if performed) were documented. The study endpoints were patient survival, graft survival, and treatment failure.

RESULTS

One hundred fifty-five patients included in the study had an overall mean age of 32.08 years (range, 9–65 years). The overall mean age of the donors was 43.06 years (range, 9–65 years). The number of HLA mismatches at the A, B, and DR loci was 2.09. All grafts had good primary function. One hundred eleven patients received a combination of tacrolimus, mycophenolate mofetil, and steroids, while 44 received tacrolimus, azathioprine, and steroids. Four patients in the tacrolimus/azathioprine group were given induction therapy with daclizumab, and 1 patient with antithymocyte globulin for 5 days. Two patients in the tacrolimus/mycophenolate mofetil group were given induction therapy with basiliximab and 25 patients with daclizumab. The mean dose of tacrolimus required to keep the prescribed trough levels in these patients was 4.80 mg/d (range, 0.5–12 mg/d).

A biopsy-confirmed acute rejection episode was diagnosed in 6 patients (3.87%), including 2 Banff type Ia rejections, 3 Banff type Ib rejections, and 1 Banff type III rejection. All acute rejection episodes were treated with 3 pulses of methylprednisolone with 4 of 6 patients responding while 2 were steroid resistant, responding to a 7-day course of antithymocyte globulin.

Currently 146 patients are being followed with a mean serum creatinine of 1.11 mg% (range, 0.5–2.8 mg%). Nine patients died during the course of this study (Fig 1): 4 suffered fulminant chest infections, 1 who was HCV positive before transplantation of sepsis and liver failure at 10 months posttransplantation, 3 of meningitis, and 1 of undetermined cause.

Twenty-six patients (17.93%) who had no pretransplantation history of diabetes developed posttransplantation diabetes mellitus, including 7 who were HCV positive prior to transplantation; 77.7% of HCV-positive patients and 14.07% of HCV-negative patients developed posttransplantation diabetes mellitus. Currently all are controlled on insulin. Twenty-six episodes of infections were observed and responded to appropriate therapy, including herpes zoster in 6 patients and chicken pox in 2, both of whom responded to acyclovir; urinary tract infection that responded to antibiotics in 9; acute gastroenteritis in 7; histoplasmosis in 1; and cytomegalovirus (CMV) pneumonia in 1. Patient survival at the end of the study period was 94.19%.

DISCUSSION

Using tacrolimus-based immunosuppression, Sonoda et al demonstrated patient and graft survivals 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. Their acute rejection rate was 32.5%. Margeiter demonstrated a 19.6% incidence of biopsy-proven acute rejection with an excellent cardiovascular profile with tacrolimus-based immunosuppression. Our experience with 101 patients on tacrolimus-based therapy had shown an acute rejection rate of 3.96%. This has not
altered significantly with our current experience. However, our acute rejection rate is much lower than that reported in the literature, possibly due to the use of grafts from well-matched live donors. Also, our mean follow-up time is less; the rejection rate may rise as follow-up increases.

Posttransplantation diabetes mellitus is an important risk factor for the development of cardiovascular disease; a higher incidence has been reported with tacrolimus. Our rates have more or less stabilized since we stopped using tacrolimus in HCV-positive patients. The association of HCV and posttransplantation diabetes mellitus is well known.6

Our major concern using this degree of immunosuppression has always been infection, especially in our setting. However, we were able to use small doses of steroids with a fairly acceptable incidence of posttransplantation infections. In conclusion, this generic form of tacrolimus was safe and effective to provide immunosuppression in a living related renal transplant program. It achieved excellent graft and patient survivals and was associated with a low incidence of acute rejection episodes.

REFERENCES