Tacrolimus (Pan Graf) as de Novo Therapy in Renal Transplant Recipients in India


ABSTRACT
The safety and efficacy of tacrolimus in transplantation is well established. However, tacrolimus has only recently been available in India. We report an initial experience using tacrolimus as de novo therapy in a living related renal transplant program. Fifty-two consecutive recipients of living renal allografts were treated with tacrolimus, mycophenolate mofetil, or azathioprine and steroids. The dose of tacrolimus was adjusted to keep trough levels at 10 to 12 ng/mL in the first 3 months, 8 to 10 ng/mL in the next 3 months, and 5 to 8 ng/mL thereafter. Any evidence of graft dysfunction was evaluated by graft biopsy. The effect of this regimen on the lipid profile as well as the incidence of posttransplant diabetes mellitus was evaluated in an Indian population. All patients were followed for periods ranging from 6 to 72 weeks (mean $= 29$ weeks). The incidence of acute rejection was $3.84\%$; $17.3\%$ developed posttransplant diabetes mellitus. Graft and patient survivals at the current follow-up were $100\%$ and $96.26\%$. In conclusion, tacrolimus is a safe and effective immunosuppressant in a living related renal transplant program.

Tacrolimus (Pan Graf) has only recently been available for clinical use in transplantation in India. This is a derivative of a soil fungus Streptomyces tsukubaensis. Tacrolimus exerts potent inhibitory effects on T-lymphocyte activation. It binds to the intracellular protein FKBP-12. The tacrolimus FKBP-12 complex inhibits the activity of the calcium- and calmodulin-dependent protein phosphatase calcineurin, which interrupts signal transduction pathways in T cells. This blocks synthesis of lymphokines such as interleukin 2 (IL-2) and gamma interferon, which are vital for cell-mediated immunity.$^{1,2}$

Cadaveric renal transplantation is still in its infancy in this country. Most renal allografts are from living related donors. Since there are a scarcity of data regarding the use of tacrolimus in renal transplantation in India, this study was performed to assess the safety and efficacy of tacrolimus in a living related renal transplant program.

MATERIALS AND METHODS
Fifty-two consecutive renal transplant recipients were enrolled in this ongoing study. All donors were evaluated according to a standard protocol that included a digital subtraction angiogram to assess the renal vascular anatomy.

Recipient who were pregnant or receiving more than one organ transplant. Recipients who were HIV-positive or unable to tolerate oral tacrolimus or those with a known hypersensitivity to tacrolimus or steroids as well as those receiving any other investigational prophylactic immunosuppressant were excluded from the study. Tacrolimus levels were determined by the Abbot IMx Tacrolimus II assay (Abbot Laboratories, Abbot Park, Ill, USA). This procedure is based on the microparticle enzyme immunoassay (MEIA) technology.

There were 46 males and six female patients, five of whom were HCV-positive prior to transplantation and one had diabetic nephropathy leading to renal failure. Immunosuppression was commenced on day minus one with tacrolimus (0.15 mg/kg) plus azathioprine (1.5 to 2 mg/kg) or mycophenolate mofetil (500 to 750 mg twice a day). Steroids were given intraoperatively and then on the first postoperative day at a dose of 20 mg, which was rapidly tapered to 10 mg at the end of 6 months. Three patients opted for...

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This ongoing study is funded by Panacea Biotec after ethical clearance by the Ethics Committee of the All India Institute Of Medical Sciences.

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induction therapy with daclizumab; two patients with basiliximab; and one patient who was undergoing a second transplant with a panel-reactive antibody level of more than 90%, anti-thymocyte globulin for 5 days. The dose of tacrolimus was adjusted according to levels done biweekly and was maintained between 10 and 12 ng/mL for the first 3 months, 8 and 10 ng/mL for the subsequent 3 months, and 5 and 8 ng/mL subsequently.

Blood sugar and renal and liver function tests were done daily in the first week and then biweekly for the first 2 months and weekly thereafter in the third month. The lipid profile was assessed at the end of the first month, at 3 months, and at the end of 6 months posttransplantation. Any consistent evidence of a fasting blood sugar more than 120 mg/dL was taken as evidence of posttransplant diabetes mellitus.

All episodes of graft dysfunction were investigated with a color duplex scan, drug levels, and a graft biopsy. All biopsy-confirmed bouts of rejection were treated by three pulses of intravenous methylprednisolone. Failure to respond to this led to the use of a polyclonal antibody.

RESULTS

The 52 enrolled patients included 46 men and six women. The mean age of recipients was 37 years (range 12 to 60 years). The donors were 33 women and 19 men. The mean donor age was 41.4 years (range 23 to 65 years). Nineteen mothers, 12 wives, 10 brothers, 8 fathers, 2 sisters, and 1 son defined their relationship to the recipient. The mean number of mismatches at the A, B, and Dr loci was 3.8. Forty-eight donors had a single renal artery; two donors had two renal arteries, and one donor had three renal arteries. All grafts had good primary function.

Immunosuppression consisted of tacrolimus, azathioprine, and steroids in 30 patients and tacrolimus, mycophenolate mofetil, and steroids in 22 patients. Two patients in the tacrolimus azathioprine group were given induction therapy with daclizumab, and one patient with anti-thymocyte globulin. Two patients in the tacrolimus mycophenolate group were given induction therapy with basiliximab and one patient with daclizumab. Currently the mean serum creatinine is 1.1 mg% (0.58 mg% to 2.7 mg%).

Acute rejection was observed in two patients (3.85%): one had evidence of Banff type Ib and the other Banff Type IIa rejection. The second patient responded to three pulses of methylprednisolone while the other, despite having a lower grade of rejection, went on to develop steroid-resistant rejection, which responded to a 7-day course of anti-thymocyte globulin.

Nine patients developed posttransplant diabetes mellitus (80% in HCV-positive patients and 8.5% in HCV-negative patients). Four of these nine patients were HCV-positive prior to transplantation. Eight of these nine patients had to be admitted in hospital for blood sugar control; currently all nine are controlled on insulin.

Twenty-three patients had their lipid profile analyzed on the day of transplantation, as well as 1, 3, and 6 months posttransplantation (Table 1). There was no significant difference in the lipid profile at enrollment, 1 month, 3 months, and 6 months posttransplantation. Tacrolimus appeared to have no significant impact on the lipid profile at the end of a 6-month follow-up.

Infectious episodes were seen in six patients, including herpes zoster in two patients that responded to acyclovir and urinary tract infections that responded to antibiotics in the other two.

One patient died of a fulminant chest infection 9 months posttransplantation, while one patient who was HCV-positive prior to transplantation died of sepsis and liver failure at 10 months posttransplantation. Currently 50 patients are on follow-up. The mean dose of tacrolimus required to keep the prescribed trough levels in these patients was 5.4 mg/d (range = 1.5 to 15 mg/d). No graft was lost due to rejection. Our current graft and patient survivals are 100% and 96.26%, respectively.

DISCUSSION

In a study of more than a 1000 renal transplant recipients 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 study included non–heart-beating donors as well as ABO-incompatible donors. The acute rejection rate was 32.5%. Margreiter also observed an acute rejection incidence of 19.6% with an excellent cardiovascular profile. Vincenti et al demonstrated low rejection rates and no increased incidence of adverse effects associated with long-term immunosuppression. The results of our study show excellent patient and graft survivals after living related renal transplantation using a tacrolimus-based protocol. However, our acute rejection rate was lower, possibly due to the fact that most of our grafts were well matched and the donors were younger. Also our mean follow-up is less; the rejection rates may increase as our follow-up progresses.

A factor of concern with immunosuppressive medications is the incidence of hyperlipidemia. Sonoda et al demonstrated a low usage of antihyperlipidemic medications among patients on tacrolimus. A drawback to the ongoing

### Table 1. Lipid Profile of Patients on Tacrolimus (n = 23)

<table>
<thead>
<tr>
<th></th>
<th>Cholesterol (150–210 mg/dL)</th>
<th>Triglycerides (&lt;160 mg/dL)</th>
<th>HDL (30–95 mg/dL)</th>
<th>LDL (70–120 mg/dL)</th>
<th>VLDL (15–35 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>178 ± 27.3</td>
<td>155 ± 53.7</td>
<td>46 ± 3.13</td>
<td>101 ± 31.4</td>
<td>31 ± 10.71</td>
</tr>
<tr>
<td>1 mo</td>
<td>198 ± 43.6</td>
<td>217 ± 49.2</td>
<td>46 ± 2.4</td>
<td>102 ± 42.15</td>
<td>45 ± 8.38</td>
</tr>
<tr>
<td>3 mo</td>
<td>178 ± 10</td>
<td>181 ± 67.2</td>
<td>48 ± 3.83</td>
<td>94 ± 23.96</td>
<td>36 ± 13.41</td>
</tr>
<tr>
<td>6 mo</td>
<td>185 ± 26.87</td>
<td>186 ± 50.92</td>
<td>47 ± 3.15</td>
<td>100 ± 23.18</td>
<td>37 ± 10.24</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.
study was our shorter follow-up but the results seemed to suggest no significant difference. No patient is currently on antihyperlipidemic medications. In a study from the United States, conversion from cyclosporine to tacrolimus was associated with a reduced total cholesterol level and decreased number of patients requiring antihyperlipidemics.5

Posttransplant diabetes mellitus is an important risk factor for the development of cardiovascular disease, which may adversely impact patient and graft survival. Our incidence of diabetes mellitus was 17.3%. However, among non-HCV-positive patients, the incidence was only 8.5%, which is more consistent with the literature. An association of hepatitis C virus and posttransplant diabetes mellitus is well known.7

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

REFERENCES