ABSTRACT

Background. Tacrolimus has been increasingly used for liver transplantation during the last decade. The drug has immunological advantages in short- to medium-term follow-up. However, data on longitudinal follow-up are lacking.

Aim. The aim of the present report was to examine the impact of tacrolimus in primary adult and pediatric liver transplantation (LTx) patients.

Material and method. One thousand consecutive primary LTx patients were performed under tacrolimus between August 1989 and December 1992 were followed up until August 2004. Mean follow-up was 13.4 ± 0.92 (range, 11.7–15) years. There were 600 males and 400 females with a mean age of 42.6 ± 20.2 years. There were 166 children (age 18 years or younger) and 834 adults, of whom 204 were older than 60 years (seniors).

Results. Four hundred ninety-seven (49.7%) patients died in the follow-up period. The overall 15-year actuarial patient survival rate was 51.4%. The survival rate for children was significantly better (81.3%) compared with adults (47.5%) and seniors (36.4%) (P = .0001). One hundred fifty-one patients received a second LTx, 22 patients received a third LTx, and 4 patients received a fourth LTx. Over all 15 years the actuarial graft survival rate was 46.1%. At last follow-up, 69.1% of patients were off steroids. The majority of late deaths were due to age-related complications, recurrence of disease, and De novo cancers.

Conclusion. The data on longitudinal follow-up have shown actuarial survival for children to be significantly better than in adults and seniors. Graft loss from immunological causes are rare even with long-term follow-up.

TACROLIMUS (FK506, Prograf, Fujisawa Healthcare Inc, Ill, USA), a potent immunosuppressive agent, was approved a decade ago by the Food and Drug Administration for liver transplantation (LTx). There are several reports to suggest that tacrolimus is associated with reduced rate and severity of rejection.1–4,19 It also can reverse early chronic rejection; in addition, chronic rejection in primary LTx is a rarity under tacrolimus.5–7 Our institution was the first to use the drug in LTx beginning 1989,8 initially for liver allografts failing under cyclosporine and then for primary LTx.1,5,9 Ten years ago, we reported the first 1000 consecutive primary LTx under tacrolimus with a mean follow-up of 39.5 months (range, 18–59 months).10 Subsequently we updated the follow-up in September 1999 with mean follow-up of 93 months (range, 72–113 months).11 Here we report a longitudinal mean follow-up of 13.4 years (range, 11.7–15.0 years) in the same population.

The aim of the present study was to report patient survival, graft survival, causes of death, and causes of retransplantation, with adverse events and current renal
function, liver function, and immunosuppression in the patients who are alive.

MATERIAL AND METHOD

One thousand consecutive primary LTx performed under tacrolimus-based immunosuppression between August 1989 and December 1992 were included. There were 600 males and 400 females with a mean age of 42.6 ± 20.2 years at the time of transplantation. There were 166 children (age 18 years or younger); of the remaining 834 adults, there were 204 patients older than 60 years of age (seniors). The details of the population and the primary diagnoses have been described previously.10,11 Patients were followed up until August 2004, with the mean follow-up of 13.4 ± 0.92 (range, 11.7–15.0) years.

RESULTS

Patient Survival

Four hundred seventy-nine (47.9%) patients died during the follow-up period. Their causes of death are listed in Table 1. The overall 12-year actuarial patient survival rate was 53.9% and the 15-year (Kaplan-Meier) survival was 51.4% (Fig 1). The 15-year actuarial survival for children was significantly better (81.3%) compared with adults (47.5%) and seniors (36.4%) (log-rank \( P = .0001 \); Fig 2).

Graft Survival

During the entire follow-up period, 151 patients received a second liver allograft, 22 patients a third transplant, and 4 patients a fourth liver allograft. The overall 12-year actuarial graft survival rate was 47.6% and the actuarial 15-year graft survival rate was 46.1%. The etiologies for retransplantation are summarized in Table 1.

Liver Function

The mean total bilirubin was 0.7 ± 1.1 (median, 0.6) mg/dL. The mean aspartate aminotransferase (AST) was 49 ± 178 (median, 30) u/L, and the mean alanine aminotransferase (ALT) was 38 ± 34 (median, 28) u/L and the gamma glutamyl (GGTP) was 120 ± 247 (median, 46) u/L.

Current Maintenance Baseline Immunosuppression

Tacrolimus. At last follow-up the mean dose of tacrolimus was 2.8 ± 2.5 mg/d with a mean whole blood trough concentration of 4.2 ± 2.5 (median, 3.7) ng/mL.

Prednisone. In our study group, 69.1% of patients are off Prednisone, 76% are on a dose of ≤5.0 mg/d, 22% are on 6–10 mg/d, and 4% are on >10 mg/d.

Cyclosporine. Seven patients are on cyclosporine instead of tacrolimus.

Azathioprine. Forty-five patients (9%) are on adjunctive Azathioprine with calcineurin inhibitor in doses ranging from 25 mg/d–75 mg/d.

Table 1. Causes of Death and Retransplantation

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Sepsis</td>
<td>146 (30.4)</td>
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<tr>
<td>Cardiovascular</td>
<td>61 (12.7)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>32 (6.6)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>59 (12.3)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>40 (8.3)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>14 (2.9)</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>12 (2.5)</td>
</tr>
<tr>
<td>PTLD</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Recurrence of disease</td>
<td>14 (2.9)</td>
</tr>
<tr>
<td>Other</td>
<td>53 (11.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>32 (6.6)</td>
</tr>
<tr>
<td>Total</td>
<td>479</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Causes of retransplantation</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary nonfunction</td>
<td>59 (39)</td>
</tr>
<tr>
<td>Hepatic artery thrombosis</td>
<td>44 (29.1)</td>
</tr>
<tr>
<td>Disease recurrence</td>
<td>16 (10.5)</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>10 (6.6)</td>
</tr>
<tr>
<td>Biliary complications</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (7.2)</td>
</tr>
<tr>
<td>Total</td>
<td>151</td>
</tr>
</tbody>
</table>

Fig 1. Patient survival and graft survival after LTx.
Mycophenolate mofetil. Thirty-seven (7.4%) patients are receiving mycophenolate mofetil (MMF) mainly for drug-induced nephrotoxicity.

Rapamycin. Fifteen patients (3%) are receiving Rapamycin to reduce calcineurin inhibitor–related nephrotoxicity.

Renal Function
The mean serum creatinine level in surviving patients was 1.7 ± 1.8 (median, 1.2) mg/dL with mean blood urea nitrogen (BUN) of 26 ± 17 (median, 19) mg/dL. During the follow-up period, 42 patients underwent kidney transplantsations and 26 patients were on chronic dialysis.

Posttransplantation Lymphoproliferative Disorder
Forty-three (4.3%) cases of posttransplantation lymphoproliferative disorder (PTLD) were observed, 25 (3%) in adults and 18 (10.8%) in children.

De Novo Cancers
The rate of de novo cancers in adults continued to increase since we last reported 7 years ago. Nonmelanotic skin cancers were reported in 35 (4.2%) adult patients and melanotic skin cancers with other noncutaneous cancers occurred in 65 adult patients (7.8%).

DISCUSSION
This is the first long-term longitudinal report on a large post-LTx population from a single center under tacrolimus-based immunosuppression. The present report confirms our initial observations, because the majority of deaths beyond 1 year after successful LTxs are related to age, recurrence of primary disease, and de novo malignancies. Graft loss and death from immunological causes (acute or chronic rejection) remain extremely rare under tacrolimus. Of 204 patients older than 60 years of age at the time of transplantation, 76 (30.3%) are currently alive. Whereas of 166 pediatric patients, 135 (81.3%) are currently alive with the same follow-up. The majority of indications for primary LTxs do not recur after LTxs. Of interest, even after 12 to 15 years of follow-up about 30% of patients still remain on small doses of Prednisone, although almost all of them were weaned off at least once at some point after LTx. This also confirms our previous report in children and adults. In adults the rate of de novo cancers has continued to increase with time since our first report, whereas the rate of PTLD is relatively static. Fortunately with better understanding, earlier diagnosis, and development of better antiviral agents, survival after PTLD has improved.

In conclusion, children continue to fare better than adults and seniors after LTx. Age-related complications, recurrence of disease, and de novo cancers are the major causes of death beyond 1 year in adults. Graft loss from acute or chronic rejection is rare in LTx patient under tacrolimus-based immunosuppression.

ACKNOWLEDGMENT
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