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Long-term use of FK506 in living related liver transplantation

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Abstract FK506 (Tacrolimus) was used with steroids to treat 61 pediatric patients who received living related partial liver transplantation. Fifty-two recipients survived and 9 died between 6 months and 3 years after transplantation. In the surviving patients, oral doses of Tacrolimus were tapered from 0.298 ± 0.277 mg/kg daily at 1 month after transplantation to 0.078 ± 0.054 at 24 months after transplantation. The 12 h trough levels of Tacrolimus were 12.6 ± 7.1 ng/ml and 4.1 ± 2.4 at 1 and 24 months after transplantation, respectively. The percentage of recipients free from steroids was 77%, 97%, and 94% at 6, 12, and 24 months after transplantation, respectively. Liver allograft rejection was encountered in seven recipients, five of whom were treated by steroid pulse therapy and a dose increase of Tacrolimus; the remaining two required OKT3. However, there was no episode of rejection that required retransplantation. Infectious complications encountered in 34 patients included 12 bacterial, 3 fungal, and 19 viral infections. Two recipients died one of fungal pneumonia and one of Epstein-Barr virus-associated lymphoproliferative disorder. Regarding adverse reactions of Tacrolimus, hypertension was observed in 28 patients, diabetes mellitus in 3, pancreatitis in 3, convulsion in 1, tremor in 12, itching in 5, and pigmentation in the oral mucosa in 2. Slightly increased values of creatinine were observed in most of the patients; however, an abnormal increase of serum of serum creatinine (> 1.0 mg/dl) was confined to the complicated cases. Improvement of somatic growth was observed in 21 patients (62%) and 13 (75%) at 12 and 24 months after transplantation, respectively. The long-term use of Tacrolimus is highly effective in terms of its immunosuppressive potential and reduced adverse reaction. Steady growth development can be expected in pediatric recipients free from steroids.

Key words FK506 · Tacrolimus
Liver transplantation

Introduction

Since FK 506 (Tacrolimus) was introduced to clinical organ transplantation in 1989 [1], it has been used widely in clinical therapy programs at transplantation institutes throughout the USA and Europe. Several reports have demonstrated its efficacy, particularly in pediatric patients, because of its immunosuppressive potency and relatively low toxicity [2, 3]. On the other hand, living related liver transplantation (LRLT) has been performed in several institutes in the world as a new modality to resolve the problem of graft shortage in pediatric liver transplantation [4, 5]. This report summarizes our experience with the long-term use of Tacrolimus in pediatric recipients of LRLT.

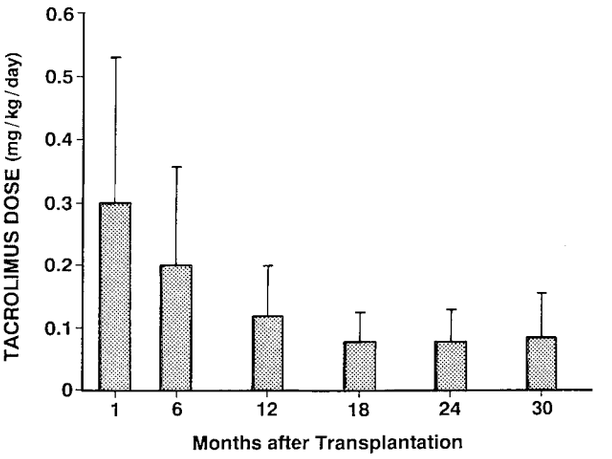

Fig. 1 Changes in oral dosage of Tacrolimus

Materials and methods

During the period between June 1990 and March 1993, we performed 61 LRLT on 61 pediatric patients (21 male and 40 female, ranging from 3 months to 17 years of age) with end-stage liver disease (48 biliary atresia, 2 Budd-Chiari syndrome, 2 progressive intrahepatic cholestasis, 3 liver cirrhosis of unknown etiology, 2 Wilson disease, 1 protoporphyria, 1 fulminant hepatitis, 1 tyrosinemia, and 1 type IV glycogen storage disease). The donors were 21 fathers and 40 mothers with an average age of 33 years. Thirty-nine lateral segmentectomies, 21 left lobectomies, and 1 right lobectomy were performed for graft harvesting. The follow-up period ranged from 6 to 39 months.

Immunosuppression

Continuous intravenous infusion of Tacrolimus at a dosage of 0.06 mg/kg daily was started soon after the operation. When oral intake began, the oral dosage of 0.15 mg/kg every 12 h overlapped the intravenous administration for 1–2 days. Optimal 12-h trough levels were found between 10 and 20 ng/ml in whole blood, and the oral dosage of Tacrolimus was adjusted to maintain the optimal trough level for the first month after transplantation. Afterwards, the oral dosage of Tacrolimus was not increased to maintain the optimal trough levels, unless the patient developed rejection. In addition, when the patients evidenced stable hepatic function in spite of low trough levels, we gradually decreased the oral dosage.

Methylprednisolone (20 mg/kg) was given during the operation. The dose of steroid was tapered from 2 to 0.5 mg/kg daily over the first period of 7 days. The steroid was discontinued 6 months after transplantation, unless the patient developed rejection.

Results

All donors could be discharged from the hospital 10–17 days after the harvesting operation. They all ultimately returned to their normal life-styles. Fifty-two recipients are still alive. Six patients died of early postoperative complications (two vascular complications, one cardiac failure, one pulmonary and renal failure, and two multiple organ failures). Two patients died of infectious complications, which were *Candida pneumonia* and Epstein-Barr virus (EBV) associated lymphoproliferative disorder. One patient died of accidental aspiration asphyxia 6 months after transplantation.

Seven patients developed eight episodes of allograft rejection. Six episodes were treated successfully with a steroid bolus and/or an increased dose of Tacrolimus. The remaining two episodes required OKT3 following treatment with the steroid bolus and an increased dose of Tacrolimus.

Oral doses of Tacrolimus in the 52 surviving patients were decreased gradually (mean $\pm$ SD = 0.298 ± 0.227 mg/kg daily, 0.119 ± 0.083, and 0.078 ± 0.054 at 1, 12, and 24 months after transplantation, respectively, (Fig. 1). The 12 h trough levels of Tacrolimus in whole blood decreased gradually (mean $\pm$ SD = 12.6 ± 7.1 ng/ml, 6.0 ± 2.8, and 4.1 ± 2.4 at, 1, 12, and 24 months after transplantation, respectively; (Fig. 2). Figure 3 shows the changes in the number of recipients no longer receiving steroid treatment. At 6 months after transplantation, 42 of 52 patients were free from steroids, and all 25 surviving patients were free from steroid at 18 months after transplantation. One patient developed allograft rejection 20 months after transplantation and required steroid administration thereafter.

Twelve patients developed bacterial infections, including three cholangitis, four regional peritonitis, one panperitonitis, one abscess formation, and three wound infections. All patients except one were treated successfully by the administration of sensitive antibiotics. One patient with refractory cholangitis required retransplan-

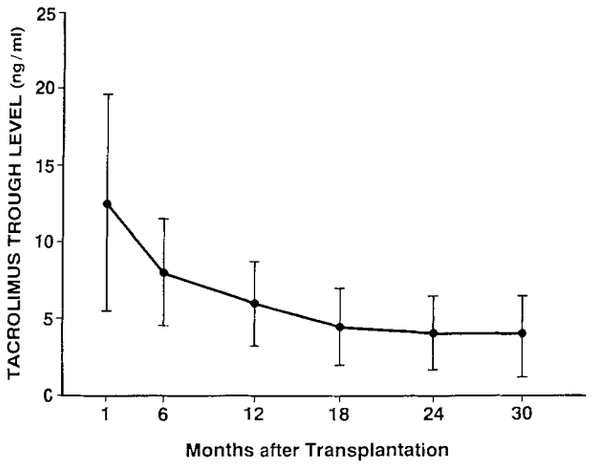

Fig. 2 Changes in Tacrolimus trough levels in whole blood

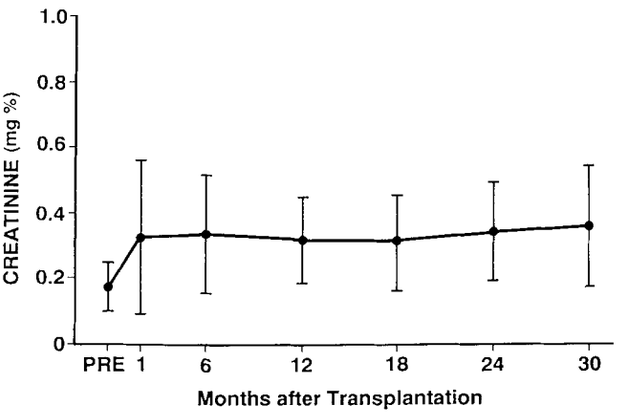

Fig. 4 Changes in serum creatinine levels

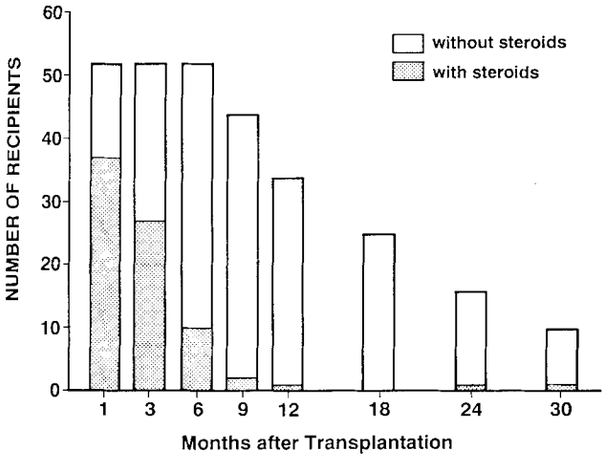

Fig. 3 Changes in number of recipients with or without steroid treatment

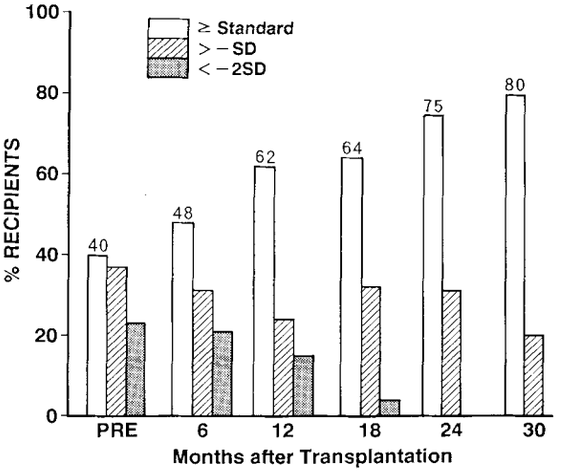

Fig. 5 Changes in the percentage of recipients over standard body weight (*-SD* under 1 standard deviation, *-2SD* under 2 standard deviations)

tation. Three patients developed fungal infections involving *Candida pneumonia*, *C. laryngitis*, and *Candida* wound infection. The patient with *C. pneumonia* died. Nineteen patients developed viral infections, including five cytomegalovirus (CMV) hepatitis, two CMV peritonitis, three EBV hepatitis, three EBV enteritis, one EBV peritonitis, one herpes simplex virus hepatitis, three skin involvement with herpes zoster virus, and one EBV-associated lymphoproliferative disorder. All patients except one were treated successfully with reduced immunosuppression and antiviral drugs. The one patient with the EBV-associated lymphoproliferative disorder died.

Figure 4 shows the changes in serum creatinine levels. Compared with the preoperative values, slightly increased levels were noted after transplantation, but these were still within the normal range. An abnormal increase of serum creatinine (> 1.0 mg/dl) was observed in a few patients; however, it was confined to the complicated cases, and the situation improved after successful treatment of the complications. Hypertension was observed in 28 patients (54%) who required one or two antihypertensive drugs during the first postoperative month, but treatment did not continue beyond the third month. Diabetes mellitus was observed in three patients, two of whom required insulin administration. All three patients were treated successfully with a reduction of the Tacrolimusdose. Acute pancreatitis with hyperamylasemia was observed in three patients, who were treated successfully with medical therapy and reduction of the Tacrolimus-

dose. One patient developed convulsion with high fever, but she recovered completely without any residual neurological signs. Tremor was observed in 12 patients (23%), itching in 5 (10%), and pigmentation of the oral mucosa in 2.

Figure 5 shows the percentage of recipients over standard body weight, those under 1 standard deviation (-SD), and those under 2SD: 60% of the recipients presented with failure to thrive and were -SD preoperatively. After transplantation, the percentage of patients over standard body weight increased gradually (62% and 75% at 12 and 24 months after transplantation, respectively).

Discussion

In the present series of 52 surviving patients, the oral dose of Tacrolimus could be decreased to around 0.1 mg/kg daily and the 12-h trough levels in whole blood were down to around 5 ng/ml by 18 months after transplantation. In addition, steroid administration was discontinued in most of the surviving patients at 12 months after transplantation. It is hypothesized that this reduced immunosuppressive treatment with a low dose of Tacrolimus and without steroids might contribute to the reduction in adverse reactions, lower rate of lethal infectious complications, and improved growth development in these pediatric patients. On the other hand, this reduced immunosuppressive treatment was calculated based on the superiority of LRLT with respect to histocompatibility [4, 5]. We conclude that the long-term use of Tacrolimus is highly effective regarding its immunosuppressive potential and reduction in adverse reactions, and steady growth development can be expected in pediatric patients free from steroid administration.

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