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Rejection and tacrolimus conversion therapy in paediatric liver transplantation

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Abstract Rejection and efficacy of rescue therapy with tacrolimus were evaluated in 50 children who underwent primary, ABO-compatible, liver transplantation. Six patients who died within the first week and one child who underwent retransplantation from an ABO-incompatible donor were excluded from the study. No patient or graft were lost due to rejection. We observed 48 episodes of rejection in 33 patients. Fourteen patients required conversion to tacrolimus for steroid-resistant rejection with resolution of rejection. One of these children developed PTLD. Other indications for conversion were neurotoxicity and hirsutism. One patient developed blindness of unknown origin after the conversion. Other side effects of tacrolimus were minor and resolved by lowering the dose. Five patients developed rejection after conversion; all achieved resolution with either steroid therapy or increase of tacrolimus dose. In conclusion, our study confirms that tacrolimus is an effective rescue therapy for paediatric liver transplantation.

Key words Liver transplantation · Rejection · Tacrolimus · Human · Child

Introduction

After solid organ transplantation in pediatric patients, rejection is more frequent and often more difficult to treat, compared to adult patients [7]. Several observations indicate that after liver transplantation, children are more immunoresponsive than adults [7, 8]. Based on these findings and on clinical experience, all the paediatric recipients after liver transplantation should be assiduously monitored for rejection and appropriate aggressive treatment should be promptly instituted once rejection occurs. Tacrolimus (Prograf®) is the only new immunosuppressive drug that can successfully replace cyclosporine in preventing allograft rejection after liver transplantation [6]. The immunosuppressive efficacy of tacrolimus first became clinically apparent when it was successfully used to treat rejection episodes resistant to high doses of steroid and OKT3 treatment [4]. Several reports showed that acute rejection responded more favourably than chronic rejection to the rescue therapy with tacrolimus [3]. Conversion to tacrolimus is most likely to be successful if treatment is initiated before hyperbilirubinaemia becomes pronounced [6].

At our institution, the standard immunosuppressive regimen is based on cyclosporine microemulsion (Neoral®) and low dose steroids. In cases of acute rejection resistant to steroids boluses, we have adopted a policy of switching early to the tacrolimus immunosuppressive regimen. We report the efficacy and the impact on patient and graft survival of the early conversion to tacrolimus in cases of steroid-resistant rejection after paediatric liver transplantation.

Materials and methods

Patients

Between November 1997 and May 1998, 50 children underwent primary liver transplantation from ABO-compatible donors. The diagnostic indications for hepatic transplantation are listed in Ta-

Table 1 Diagnostic indications for liver transplantation

Diagnosis	No. patients
Biliary atresia	36
Familial cholangiopathies	3
Metabolic diseases	2
Cryptogenic	2
Neonatal hepatitis	2
Miscellaneous other diagnoses	5
Total	50

Table 2 Clinical data of patients with steroid-resistant rejection

Patients converted to tacrolimus	14/43 (33%)
Median time after transplantation (days)	28
Biochemistry per conversion	
Total bilirubin (mg/dl)	2.7 ± 1.3
ALT (IU/l)	75 ± 57
GGPT (IU/l)	286 ± 143
Median time since conversion (months)	13
Patients alive after conversion	14/14 (100%)

ble 1. Six of the 50 patients (12%) underwent retransplantation. Eighteen cases had been performed with full-size livers, five with reduced-size livers and 32 with split-livers. Among split-livers, 29 were left lateral segments (segments II and III), two were left lobes (segments I–IV) and one was a right lobe procured from a paediatric donor. The techniques of organ procurement, preservation and transplantation are reported elsewhere [2, 9]. At the time of transplantation, median age was 1.7 years (range 2 months to 19 years), and median weight was 10.5 kg (range 3.4–62 kg).

Immunosuppression

Maintenance immunosuppression consisted of oral cyclosporine at a dose of 10 mg/kg per day and low dose prednisone. The target plasma level of cyclosporine was 250–350 ng/ml during the first 2 weeks after transplantation, 200–300 ng/ml from week 3 to week 12, 150–200 ng/ml from month 4 to month 12, and 50–150 ng/ml thereafter.

Diagnosis and treatment of rejection

When clinical or biochemical suspicion of acute cellular rejection was raised, a liver biopsy was taken and histologically confirmed acute cellular rejection was treated with a steroid bolus, with a maximal dose of 45 mg/kg administered in 3–6 days. If no improvement in biochemistry was observed and the liver biopsy taken after steroid treatment was still positive for rejection, patients were converted to tacrolimus for steroid-resistant rejection. Other reasons for conversion to tacrolimus were immunosuppression toxicity or inadequate levels of cyclosporine.

After cyclosporine was suspended, tacrolimus was administered orally (0.15 mg/kg every 12 h), and the dose was adjusted according to whole blood levels. The target whole blood level was 10–15 ng/ml during the first 3 months after transplantation, and 5–10 ng/ml thereafter.

Results

After a median follow-up of 10 months (range 1–20 months), 80% of the patients were alive with functioning grafts. Six deaths occurred within the first postoperative week, and these patients were excluded from the study. The causes of death in this group were primary non-function ($n = 2$), cardiorespiratory insufficiency after retransplantation ($n = 2$), sepsis ($n = 1$) and neurologic complication ($n = 1$). One child underwent retransplantation from an ABO-incompatible donor and was excluded from the study. Another four patients died 17 days, 18 days, 39 days and 13 months after transplantation; causes of death were sepsis ($n = 1$), pneumonitis ($n = 1$), gastrointestinal haemorrhage ($n = 1$) and neurologic complication ($n = 1$), respectively.

Overall, we observed 48 episodes of rejection in 33 patients (78%), with a median time to first rejection episode of 14 days. At liver biopsy, 46% of the rejection episodes were classified as mild acute rejection, 38% as moderate and 26% as severe rejection.

Fourteen patients (33%) required conversion to tacrolimus for steroid-resistant rejection, at a median time of 28 days after transplant (Table 2). At the time of conversion, the degree of rejection was moderate to severe in all cases. No patients showed histologic evidence of chronic rejection. All patients had a complete response to rescue therapy, with an improvement of biochemistry evident by the first week and normal levels of total bilirubin and liver enzymes reached within an average of 1 month.

One of these patients developed a monocucleosis-like syndrome, correlated to an Epstein-Barr virus infection, 2 months after transplantation. Tacrolimus dosage was lowered and patient underwent tonsillectomy, with resolution of the clinical picture 3 months later.

One patient was converted to tacrolimus for suspected neurotoxicity. This was a 2-month-old baby urgently transplanted for fulminant hepatitis of unknown origin with encephalopathy. After transplantation, due to the worsening of the neurological picture, the patient was converted to tacrolimus with no improvement. The child died 13 months after transplantation; serial CT scans had shown progressive massive cerebral atrophy.

Another patient was converted to tacrolimus for severe hirsutism, and experienced resolution of this side effect. Seventeen days after the conversion, this child developed acute blindness of unknown origin. At that time, tacrolimus whole blood concentration was in the therapeutic range. EEG and MR were normal, while a marked reduction of ERG and VECP were observed, associated to bilateral atrophy of the papilla. Suspecting tacrolimus toxicity, the drug was discontinued and the patient was reconverted to cyclosporine with only partial recovery.

Table 3 Latest follow-up mean values of liver enzymes and kidney function of the 16 patients converted to tacrolimus

Parameter	Mean ± SD
Total bilirubin (mg/dl)	0.6 ± 0.2
ALT (IU/l)	37 ± 19
GGPT (IU/l)	59 ± 27
Serum creatinine (mg/dl)	0.5 ± 0.2
BUN (mg/dl)	53 ± 22

Except for this case, the adverse reactions associated with tacrolimus were minor and resolved by lowering the dose. In particular, we did not observe nephrotoxicity, hypertension, or hyperglycemia (Table 3).

Five patients (36%) experienced rejection after conversion to tacrolimus. All had undergone rescue therapy for steroid-resistant rejection. In one patient, tacrolimus was stopped after the diagnosis of PTLD. Fifteen days after tacrolimus withdrawal, he developed acute rejection; tacrolimus was re-administered, together with a steroid bolus, and the patient showed resolution of the rejection. The other four patients achieved clinical and biochemical resolution of their rejection episodes with either steroid therapy or an increased dosage of tacrolimus.

Discussion

The clinical efficacy of tacrolimus as rescue therapy in paediatric liver recipients has been documented by Egawa et al. [3]. In their series, tacrolimus was very effective in the patients who were converted for refractory acute cellular rejection, while only half of the children rescued for chronic rejection experienced biochemical improvement.

In our series, we adopted a policy of early conversion to tacrolimus for biopsy-proven steroid-resistant rejection and, so far, we have not observed any chronic rejection.

Egawa in his series documented a slow biochemical response to tacrolimus. This was not our finding. Total bilirubin and γ-glutamyl phosphotransferase normalised within 1 month after conversion. Moreover, we did not observed nephrotoxicity or hyperglycaemia, in accordance with other reports [1].

Hirsutism is a serious side effect of cyclosporine, particularly in children and adolescents, and it is an accepted indication for tacrolimus conversion. The patient that we converted for this reason developed acute blindness, with normal tacrolimus whole blood level. Even although the neurological and radiological pictures were not similar to those usually associated with tacrolimus neurological toxicity [11], and differ also from a case report of cortical blindness related to tacrolimus [10], we discontinued the drug, restoring cyclosporine-based immunosuppression. We observed only a partial response with a slight clinical and instrumental improvement.

Tacrolimus immunosuppression has been associated with a higher incidence of PTLD when compared to cyclosporine [12]. As reported elsewhere in this issue, in our series we did not observe a difference in terms of PTLD incidence between patients treated with cyclosporine or tacrolimus [5].

In conclusion, in our experience the policy of early conversion to tacrolimus for refractory rejection has been safe and efficient in the control of acute rejection. The impact of this approach on patients and graft survival, and the effect of tacrolimus on growth, need to be addressed after longer follow-up.

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