Transpl Int (1998) 11 [Suppl 1]: S275–S277

Tacrolimus for steroid-resistant liver rejection in children

P. Jara
M. J. Robledo
E. Frauca
M. D. Gonzalez-Filgueira
L. Hierro
A. de la Vega
C. Camarena
M. Martín-Ibáñez
J. Murcia
M. López-Santamaría
J. Larrauri
M. C. Díaz
M. Gámez

P. Jara (✉) · M. J. Robledo · E. Frauca · M. D. Gonzalez-Filgueira · L. Hierro · A. de la Vega · C. Camarena · M. Martín-Ibáñez · J. Murcia · M. López-Santamaría · J. Larrauri · M. C. Díaz · M. Gámez
Pediatric Hepatology and Liver Transplantation Unit, Hospital Infantil "La Paz", Paseo de la Castellana 261, E-28046 Madrid, Spain Tel. 358 38 35; Fax 358 25 45

Abstract Eighteen pediatric liver transplant recipients were converted from cyclosporine-based immunosuppression to tacrolimus for refractory rejection episodes affecting 21 grafts. Before conversion, steroid boluses were applied to all episodes followed by OKT3 monoclonal antibodies in 3 of them. Baseline biopsy showed cellular rejection in 18 patients and ductopenia in 3 cases. Thirteen episodes initiated within the first 2 postoperative weeks, and 8 occurred beyond the 21st day. A previous steroid-responsive episode of rejection was noted in 4 patients. Tacrolimus was administered by the oral route to obtain trough blood levels in the range 6–15 ng/ml. Reversal of rejection was obtained in 15 patients (71.4%). Complete normalization of liver function tests was achieved in 10 out of 12 patients who were followed for more than 6 months. A refractory evolution affected 6 patients (28.5%). Significant factors predictive for tacrolimus-resistant rejection were identified as ductopenia on baseline biopsy, previous episodes of acute rejection, late onset rejection (beyond 21st posttransplant (day), and a longer time of evolution of rejection prior to conversion.

Key words Pediatric liver rejection · Tacrolimus

Introduction

Refractory liver rejection has been reported in 2–10% of pediatric recipients under primary cyclosporine-based immunosuppression [8, 9]. Chronic rejection was proved through protocolized serial biopsies in 15% of children surviving more than 2 months and most of them evolve directly from early episodes of acute rejection [3]. Tacrolimus exerts a potent immunosuppressive effect through the inhibition of cytokine production. The relationship of adverse effects to blood concentrations and the availability of drug monitoring, together with successful experiences dealing with children, encouraged the use of tacrolimus as a rescue therapy. The aim of the present study was to assess the efficacy of tacrolimus as a therapy for steroid-resistant rejection and to identify the factors predictive for response.

Patients and methods

In the period in which tacrolimus has been available for rejection rescue therapy, from 1992 to December 1996, 135 pediatric orthotopic liver transplantation (OLT) procedures were performed at our center. A cyclosporine-based primary immunosuppression was applied in all cases. It consisted of steroids, cyclosporine, and azathioprine during the first 15 days, followed by prednisolone plus cyclosporine. The lowest steroid dose was sought, but withdrawal was not attempted. A liver biopsy was routinely performed to determine the cause of graft dysfunction episodes. Diagnosis of rejection was based on histopathological findings. Sixty-two episodes of rejection occurred in 50 grafts, 39% of them ($n = 24$) did not resolve after steroid boluses. The study on the efficacy of tacrolimus was centered on 21 cases where tacrolimus was used for a minimum period of 14 days.

The subjects of the study were 18 children aged from 6 months to 15 years (mean 4 years). The original indication for OLT was biliary atresia ($n = 7$), acute liver failure ($n = 3$), progressive familiar intrahepatic cholestasis ($n = 3$), α-1-antitrypsin deficiency ($n = 2$), type I tyrosinemia ($n = 2$), and Alagille's syndrome

($n = 1$). They were converted to tacrolimus for treatment of steroid-resistant rejection which occurred in 21 different grafts. Three episodes had also been refractory to OKT3 monoclonal antibodies. Eleven were whole livers and 10 were reduced-size grafts and there was 1 case of an ABO major or minor donor-recipient incompatibility in each group. The graft came from a retransplantation procedure in 11 patients, it was the second liver in 7 patients, the third in 3 patients, and the fourth in one patient. Chronic rejection had been the indication for regrafting in 3 patients.

Rejection initiated at a mean postOLT time of 26 (± 7) days. Thirteen cases started within the first 2 weeks (4–14 postOLT days). Onset of late episodes ranged from 30 to 120 postOLT days. In 81% ($n = 17$) rejection appeared for the first time. Four cases were recurrent episodes of rejection usually soon after an apparently steroid-responsive episode. When rejection began, liver biopsies showed signs of acute cellular rejection in 20 cases (mild in 10, moderate in 8, and intense in 2) with half of them showing regenerative signs of bile duct epithelium. One patient showed mild inflammatory portal infiltrate, fibrosis, and paucity of interlobular bile ducts. Eight patients underwent a second biopsy after the initial therapeutic approach. Among those, ductopenia was evident in two additional patients. Baseline liver function tests when tacrolimus therapy began were (mean ± SD) ALT: 386 ± 269 U/l (range 18–913), total bilirubin: 10.4 ± 7.3 mg/dl (range 1.4–27.5), and GGT: 644 ± 369 U/l (range 99–1368).

Tacrolimus was initiated on average 9.3 days (range 2–90) after the onset of the rejection episode. Starting at 0.15 mg/kg per 12 h, it was always given by the oral route. Dosage was modified when necessary to obtain trough whole blood levels ranging from 6 to 15 ng/ml (MEIA, Abbott Diagnostics or ELISA, Incstar). Response to therapy was defined if normal or near normal graft function was achieved during the follow up. In the case of a superimposed cause of graft dysfunction, a liver biopsy with an absence of signs of acute or chronic rejection was assigned as response. Liver retransplantation was indicated immediately in ongoing or progressive severe cholestasis, whether as the main dysfunction or associated with liver failure. A period of 4–6 months of follow up under tacrolimus was attempted in the case of ongoing moderate cholestasis. Wilcoxon and chi-squared tests were applied for a statistical analysis of factors predictive for response.

Results

Four children died, one during retransplantation for chronic rejection, one from systemic lymphoma, and two due to multiorgan failure after retransplantation (one for hepatic artery thrombosis and one for hepatic vein thrombosis).

Efficacy of tacrolimus

A refractory outcome of rejection was observed in 6 patients (28.5%) while 15 (71.4%) showed a full recovery. The worsening of liver function led to retransplantation in 5 patients who had been under tacrolimus therapy for 15 days, 16 days, 1 month, 2 months, and 4 months, respectively. The pathology of the explanted livers reported ductopenia plus arteriopathy in two cases and ductopenic chronic rejection in three cases, two of them with signs of a recently superimposed portal vein thrombosis. ReOLT was indicated, but not yet performed, in another patient due to cholestasis unresponsive to 5 months of therapy; intrahepatic cholestasis followed by moderate ductopenia was observed in successive biopsies 1 and 5 months after tacrolimus conversion.

Fifteen patients had a satisfactory recovery from rejection. Twelve patients achieved normal or near normal graft function. Cure of rejection was ascertained through histological studies (explanted liver or autopsy) in the other 3 patients who maintained graft dysfunction or had recurrent disturbances due to other causes (CMV hepatitis, hepatic artery thrombosis, and hepatic vein thrombosis). One month of follow up was available in all responders. At that time, total bilirubin had fallen to normal values in 9 patients and values were over 5 mg/dl in only 1 patient affected by hepatic artery thrombosis. At the 6th month follow up, bilirubin was normal in all 12 patients and ALT had become normal in 6 patients. Four out of the 6 patients displaying high ALT at this point underwent biopsies that showed scattered foci of centrolobular necrosis or mild portal fibrosis. Only 2 patients maintained ALT disturbances in further follow ups. Successive episodes of rejection under tacrolimus therapy were not observed.

Factors predictive for response

The grade of baseline graft dysfunction measured as total bilirubin and ALT values when tacrolimus was initiated did not predict the outcome, although there was a trend toward higher ALT values in the group of non-responders. The length of time elapsed since the onset of rejection until tacrolimus was initiated was significantly longer in non-responders. Episodes of rejection that consisted of a recurrence and those occurring after the 3rd postOLT week had a significant risk of being tacrolimus resistant. All 3 patients who showed ductopenia in baseline biopsy did not respond (Table 1).

Discussion

The incidence of graft failure due to rejection has been 6.6% in our recent series when tacrolimus has been available for rescue therapy. This includes two patients who were withdrawn from tacrolimus therapy due to grand mal seizures some days after conversion, and one patient who was diagnosed at retransplantation and never received tacrolimus. During the initial period of study, three children were previously treated with monoclonal antibodies causing a delay in tacrolimus therapy that in the light of our results could determine the outcome.

Table 1 Factors predictive for response to tacrolimus (OLT orthotopic liver transplant)

	Responders (n = 15)	Non-responders (n = 6)	*P* value
First rejection episode	15 (100%)	2 (33%)	< 0.01
Recurrent episodes	0	4 (66%)	
Onset of rejection beyond 21st postOLT day	3 (20%)	5 (83%)	0.02
Evolution of rejection until conversion, mean and range (days)	6 (2–17)	27 (6–90)	< 0.01
Ductopenia	0	3 (50%)	0.02
Baseline total bilirubin (mg/dl)	8.2 ± 6.6	11.8 ± 5.2	n.s.
ALT (U/l)	316 ± 283	528 ± 215	0.07

Attending the baseline histological picture, conversion to tacrolimus achieved full response in 83% of the acute and in none of the chronic rejection episodes in the present series. Absence of response in the presence of ductopenia was reported by Reding et al. [7], while acute rejection was rescued in 69% in those series, of which most patients had been previously treated with poly- or monoclonal antibodies without success. On the contrary, complete reversal of dysfunction was obtained in 25–73% of children showing vanishing bile duct syndrome according to other reports [2, 5]. Efficacy reached all children affected by acute rejection in these series.

Indications for retransplantation have to be analyzed carefully in tacrolimus-converted patients in order to avoid unnecessary deterioration. In our experience, baseline liver function tests did not predict outcome, but responders were normalized or showed bilirubin levels below 5 mg/dl within the 1st month of therapy. Predictive factors for response would also be of help, although more studies are necessary.

Tacrolimus rescue therapy has been associated with an increased risk of lymphoproliferative disorders (PTLD), reaching 28.3% in those who received both OKT3 and tacrolimus [6]. A rate of 18.9% was reported after tacrolimus conversion in young children [1]. Series of children receiving tacrolimus as primary immunosuppression are affected to a lesser extent [4]. In our experience, PTLD developed in one patient (5.5%), a low figure compared to the experience of other authors, probably in relation to the avoidance of OKT3 therapy prior to tacrolimus.

Acknowledgements Supported in part by FISSS Grant 96/0771

References

1. Cox KL, Lawrence-Miyasaki LS, Garcia-Kennedy R, Lennette ET, Martinez OM, Krams SM, Berquist WE, So SKS, Esquivel CO (1995) An increased incidence of Epstein-Barr virus infection and lymphoproliferative disorder in young children on FK506 after liver transplantation. Transplantation 59: 524–529
2. Egawa H, Esquivel CO, So SK, Cox K, Concepcion W, Lawrence L (1994) FK506 conversion therapy in pediatric liver transplantation. Transplantation 57: 1169–1173
3. Freese DK, Snover DC, Sharp HL, Gross CR, Savick SK, Payne WD (1991) Chronic rejection after liver transplantation: a study of clinical, histopathological and immunological features. Hepatology 13: 882–891
4. Inomata Y, Tanaka K, Egawa H, Uemoto S, Ozaki N, Okajima H, Satomura K, Kiuchi T, Yamaoka Y, Hashida T (1996) The evolution of immunosuppression with FK506 in pediatric living-related liver transplantation. Transplantation 61: 247–252
5. McDiarmid SV, Wallace P, Vargas J, Ament ME, Busuttil RW (1995) The treatment of intractable rejection with tacrolimus (FK506) in pediatric liver transplant recipients. J Pediatr Gastroenterol Nutr 20: 291–299
6. Newell KA, Alonso EM, Whitington PF, Bruce DS, Millis JM, Piper JB, Woodle ES, Kelly SM, Koeppen H, Hart J, Rubin CM, Thistlethwaite JR (1996) Posttransplant lymphoproliferative disease in pediatric liver transplantation. Transplantation 62: 370–375
7. Reding R, Wallemacq PE, Lamy ME, Rahier J, Sempoux C, Debande B, Jamart J, Barker A, Sokal E, Ville de Goyet J de, Moulin D, Clement de Clety S, Otte JB (1994) Conversion from cyclosporine to FK506 for salvage of immunocompromised pediatric liver allografts. Transplantation 57: 93–100
8. Salt A, Noble-Jamieson G, Barnes ND, Mowat AP, Rolles K, Jamieson N, Johnston P, Friend P, Calne RY (1992) Liver transplantation in 100 children: Cambridge and King's College Hospital series. Br Med J 304: 416–421
9. Yandza T, Gauthier F, Valayer J (1994) Lessons from the first 100 liver transplantations in children at Bicetre Hospital. J Pediatr Surg 29: 905–911