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Indications for Tacrolimus anti-rejection therapy in liver allograft recipients

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Abstract We reviewed our experience with conversion to Tacrolimus after 600 liver transplantations, performed from September 1988 to March 1995. Conversion to Tacrolimus as an anti-rejection therapy was implemented in 78 patients because of chronic ductopenic rejection ($n = 9$), early chronic rejection ($n = 5$), OKT3-resistant cellular rejection ($n = 12$), steroid-resistant cellular rejection ($n = 30$), late-onset cellular rejection ($n = 10$), cellular rejection in patients suffering from cyclosporin malabsorption ($n = 5$) and uncomplicated cellular rejection ($n = 7$). Control of rejection was achieved in 72 of 78 patients (92 %); 6 patients (18 %) were non-responsive. Patient and graft survival were 82 % and 77 %, respectively. Fourteen patients died almost exclusively from opportunistic infections. Out of the six patients who did not respond to Tacrolimus treatment, four underwent successful retransplantation and two died from infections associated with a poor graft function. Overall, graft loss with or without patient death occurred in 6 of 9 patients undergoing chronic rejection, in 3 of 12 patients with OKT3-resistant cellular rejection, in 6 of 30 patients suffering from steroid-resistant cellular rejection and in one patient each suffering from late-onset or uncomplicated cellular rejection. In severe steroid-resistant cellular rejection, successful Tacrolimus rescue therapy corresponded to a significantly lower preconversion total serum bilirubin when compared to failures (9.9 ± 6.8 mg % vs. 22.2 ± 7.3 mg %, $P < 0.05$). Conversion to Tacrolimus was a reliable treatment option in liver allograft rejection. However, failures occurred in the OKT3- and steroid-resistant cellular rejection groups, and only in a subgroup of patients suffering from chronic rejection was a permanent benefit observed. Implementation of a conversion early in the course of a rejection episode may result in a further improved outcome. Predictive parameters, e. g. the total serum bilirubin in steroid-resistant cellular rejection, are still needed to select those patients who would profit rather from a retransplantation.

Key words Tacrolimus conversion therapy · Liver allograft rejection · Chronic ductopenic rejection

Introduction

Earlier reports on conversion to Tacrolimus from cyclosporin A (CsA)-based regimens have demonstrated its potency in the treatment of liver allograft rejection [3, 4, 18]. A marked ability of Tacrolimus to reverse ongoing rejection even with evidence of ductopenic changes has been observed in those patients converted for persistent cellular, or during an early stage of chronic rejection [2, 4]. Treatment failures have been reported af-

ter conversion during clinically manifest chronic ductopenic rejection and to a lesser extent for steroid-resistant and OKT3-resistant cellular rejections [2, 7, 12]. Prior OKT3 courses and excessive preconversion total serum bilirubin levels were identified as putative risk factors for patient and graft survival. It was concluded that a less stringent selection for rescue therapy, i.e. its implementation early in the course of a rejection episode and prior to an OKT3 application, should result in an improved overall outcome. Herein, we report our experience with 78 patients converted for various types of liver allograft rejection, comprising uncomplicated cellular rejection episodes, as well as patients suffering from vanishing bile duct syndrome (VBDS).

Material and methods

Patient selection

From September 1988 to March 1995, 600 liver transplantations were performend in 546 patients. In 478 transplantations, immunosuppression consisted of cyclosporin-based immunosuppressive regimens. As part of different trials, after a total of 122 transplantations, patients received Tacrolimus in order to evaluate its properties as a primary immunosuppressive agent. After Tacrolimus had become available to our centre in May 1990, it was used as a rescue agent in 78 cases until August 1995. Conversion from cyclosporin-based immunosuppressive regimens to Tacrolimus was implemented after informed consent had been obtained. The course of the patients was followed on an inpatient basis during the first 4 weeks posttransplant, or on a routine clinical and outpatient basis later on.

Liver transplantation

Grafts had been preserved using almost exclusively Belzer's University of Wisconsin solution. In two cases each, Euro Collins' and Bretschneider's HTK solution were applied. The surgical procedure was performed using a standardized technique, comprising a veno-venous bypass and completion of all four vascular anastomoses prior to reperfusion. In all but 53 cases requiring a bilio-digestive anastomosis due to the underlying disease, the biliary reconstruction was performed as a side-to-sidecholedochocholedochostomy [15].

Primary immunosuppression

Primary immunosuppressive protocols consisted either of conventional triple therapy, of our standard quadruple drug induction regimen entailing an antithymocyte or antilymphocyte globulin preparation (ATG; Fresenius, Bad Homburg, Germany) [16], or of another sequential quadruple drug protocol using a monoclonal anti-interleukin 2 receptor antibody (BT563; Biotest GmbH, Dreieich, Germany) [14].

Except for ATG or BT563 treatment, an almost identical immunosuppressive regimen was applied irrespective of the primary protocol group. Cyclosporin was started after surgery as a parenteral dose of 1–2 mg/kg body weight (BW) twice a day. If clinical course and protocol cholangiography on posttransplant day 5 allowed capping the T-tube drainage, cyclosporin was switched to an oral intake of 5 mg/kg BW twice a day. Subsequent dosing was adjusted according to whole blood levels, aiming at 600 and 900 ng/ml as measured by a polyclonal FPIA (TDX-assay, Abbott). Methylprednisolone was given prior to reperfusion and directly after transplantation at a dose of 500 mg i.v. each.

Prednisolone was begun as a single oral dose of 1 mg/kg BW, which was tapered to 20 mg/day during the first month. Parenteral administration of azathioprine was started at 25 mg/day until 1 week after transplantation; on posttransplant day 7 the dosage was increased to 1–2 mg/kg BW orally. Intake was reduced or interrupted according to peripheral white blood counts. ATG was started intra- or postoperatively at a dose of 5 mg/kg BW per day and given for 7 days in a continuous infusion over 6 h. BT563 was administered i.v. for 12 days at a daily dose of 10 mg.

Rejection episodes

Rejection episodes were suspected in cases of scant production of light bile or biochemical graft dysfunction as defined by rising serum levels of bilirubin or hepatic enzymes (> 50 % above initial values) without evidence of mechanical causes or infection [11]. Doppler ultrasonography was done if indicated to rule out hepatic artery or portal vein thrombosis. If suspicion of a vascular complication prevailed, diagnosis had to be confirmed by angiography. Bile leakage or biliary obstruction were excluded by cholangiography. Screening for infectious disorders entailed the collection of routine specimens for culture and microscopy, quantification of fungal and viral titres in blood, direct immunofluorescence for *Legionella* in blood and urine and the search for cytomegalovirus antigen in blood by the polymerase chain reaction [17].

Core liver biopsies were obtained on posttransplant day 7 or when rejection was suspected. The histopathological grading of acute or cellular rejection was classified as listed below:

Mild (grade I): mild periportal mononuclear infiltrate with minimal endothelialitis and focal duct damage involving less than 50 % of the bile ducts

Moderate (grade II): moderate periportal mononuclear infiltrate extending beyond portal field confines, or focal duct damage involving more than 50 % of the bile ducts

Severe (grade III): the same alterations as described for grade II plus severe injuries (arteritis, central ischaemic damage, confluent necroses, paucity of bile ducts)

A diagnosis of chronic or ductopenic rejection relied largely on the evidence of cholestasis with an interlobular and septal duct loss. Other histological criteria were the absence of findings concordant with viral hepatitis, obliterative arteriolar lesions and portal tract fibrosis with linkage between central veins and portal triads. Distinction between early chronic and chronic rejection was based on the extent of lymphocytic bile duct damage or loss. A bile duct loss limited to less than 25 % of the sample triads without cholestasis or lobular changes was categorized as an early chronic rejection. Findings indicative of a chronic rejection were a bile duct loss of 50 % or more, lymphocytic damage in the remaining ducts and hepatocanalicular cholestasis. Corresponding to an onset prior to or after posttransplant day 90, cellular rejection episodes were classified as early- or late-onset rejections, respectively.

Treatment of rejection

Initial therapy consisted of a 3-day course of high-dose steroids, i.e. 500 mg/day methylprednisolone intravenously. Steroid-resistant episodes were treated for another 5–10 days with 5 mg/day of

monoclonal OKT3 antibody. Conversion to Tacrolimus was applied in OKT3 non-responders, or as soon as a chronic ductopenic rejection was suspected irrespective of prior OKT3 treatment. A direct switch to Tacrolimus for steroid-resistant cellular rejection was considered in late-onset episodes and in patients with a persistent CsA malabsorption in spite of a capped T-tube drainage. After gaining more experience with Tacrolimus, we were more apt to implement a direct conversion for steroid-resistant or even uncomplicated cellular rejection. Rescue therapy was started with continuation of oral steroids and administration of oral Tacrolimus. Initial dosing ranged from 0.07 to 0.1 mg/kg BW twice a day. Further adjustments were related to toxicity and response or graft function.

Evaluation of outcome

Outcome was evaluated in terms of response or non-response and success or failure. Response was considered positive if a cellular rejection was reversed or if progression of bile duct loss in chronic rejection was at least interrupted, thereby improving liver function. Repeat biopsies were performed unless the clinical course had been unambiguous. Success or failure were determined with regard to both patient and graft survival.

Statistical evaluation

Data were expressed as mean ± standard error of the mean. Comparisons between groups were made by the Wilcoxon rank-sum test for continuous variables and by the chi-square test for categorical variables. Differences were considered statistically significant at $P < 0.05$.

Results

Patient characteristics

Of 600 patients transplanted between September 1988 and March 1995, 78 underwent Tacrolimus rescue therapy after the drug became available to our centre in May 1990. In 478 transplantations, CsA-based regimens had been administered as primary immunosuppression (Table 1). Indications for transplantation in the 78 patients converted to Tacrolimus included 15 patients with hepatitis C virus (HCV) disease, 10 patients with hepatitis B virus (HBV) disease, 7 patients with primary sclerosing cholangitis, 7 patients with primary biliary cirrhosis, 7 patients with Klatskin tumours, 6 patients with fulminant liver failure, 6 patients with alcoholic cirrhosis and 20 patients with various other indications. Forty-one patients were female and 37 were male, with a mean age of 49.1 ± 11.1 years.

Table 1 Primary immunosuppression in the study population compared to the whole series

Primary immunosuppression	$n = 522$	Tacrolimus rescue $n = 78$
Tacrolimus-based	122 (20.3 %)	
CsA-based	400 (66.6 %)	78 (13.1 %)
Triple	23 (5.7 %)	6 (7.7 %)
Quadruple (ATG/ALG)	234 (58.5 %)	48 (61.5 %)
Quadruple (BT563)	143 (35.8 %)	24 (30.8 %)

Table 2 Indications for conversion to Tacrolimus and outcome in terms of response and survival

Indication for conversion	n	Response		Survival	
		Yes	No	Yes	No
Chronic ductopenic rejection	9	5	4 (3)[a]	6 (3)[a]	3
Early chronic rejection	5	5		5	
OKT3-resistant cellular rejection	12	12		9	3
Steroid-resistant cellular rejection	30	28	2 (1)[a]	24 (1)[a]	6
Late-onset cellular rejection	10	10		9	1
Cellular rejection and CsA malabsorption	5	5		5	
Uncomplicated cellular rejection	7	7		6	1
Overall	78	72 (92 %)	6	64 (82 %)	14

[a] Number of retransplantations

Indications for conversion

The secondary diagnoses triggering off rescue therapy are shown in Table 2. The most common indications were chronic ductopenic rejection ($n = 9$), OKT3-resistant cellular rejection ($n = 12$), steroid-resistant cellular rejection ($n = 30$) and late-onset cellular rejection ($n = 10$). In the group of poor CsA uptake ($n = 5$), three patients had undergone liver transplantation and Whipple's procedure for Klatskin tumours [13]. In two patients, choledochojejunostomy for primary sclerosing cholangitis had been performed. Cycles of OKT3 had already been administered in five patients with chronic rejection and in one patient each of the late-onset and of the early chronic rejection group.

Outcome

After a median follow-up of 2 years (23.3 ± 14.5 months), 72 of 78 patients or 92.3 % were responsive, and six patients or 7.7 % were non-responsive. Patient survival was observed in 64 patients (82.1 %) and graft survival in 60 patients (77.0 %). Non-responsiveness was evident in 4 of 9 patients in the chronic rejection group and in 2 of 30 patients in the steroid-resistant cellular rejection group (Table 2).

There were 14 lethal cases: 3 of 9 patients suffering from chronic ductopenic rejection, 3 of the 12 OKT3 non-responders, 6 of 30 patients in the steroid-resistant

cellular rejection group and 1 patient each suffering from an uncomplicated or a late-onset cellular rejection (Table 2). In these patients, the average period of time elapsing from transplantation to the onset of rescue therapy and from the switch to patient death was approximately 4 months (122 ± 150 days; range: 10–454 days) and 3 months (78 ± 151 days; range: 7–526 days), respectively.

Patients died almost exclusively of infectious complications. The most common final diagnoses were *Pneumocystis carinii* and cytomegalovirus (CMV) pneumonia in five and four patients, respectively. Aspergillosis was the cause of death in two patients. One patient each died from recurrent primary disease, an aggravated HCV reinfection and a Klatskin tumour relapse.

Comparing those who, for chronic ductopenic rejection, were converted to Tacrolimus only ($n = 4$) to those who had in addition received at least one prior course of OKT3 ($n = 5$), a rather balanced pattern for the rejection response ($n = 2$ vs. $n = 3$) was found. Looking at the fatalities ($n = 3$), all had undergone a previous course of OKT3 and none had solely been on Tacrolimus. However, neither correlation was statistically significant.

Graft loss that was not related to patient death was observed four times (Table 2). Three patients underwent successful retransplantation for chronic ductopenic rejection and another for a hyperacute rejection in the postoperative course. Chronically rejecting grafts were lost 4–5 months posttransplant or 2–3 months postconversion.

Patients were converted to Tacrolimus on an intent-to-treat basis. Mainly during the earlier phase of our programme, prior to our initial experience with Tacrolimus or its availability, 15 patients received OKT3 alone for treatment of cellular steroid-resistant rejections. Ten patients recovered (67 %), while one patient died and four underwent retransplantation for refractory rejection. A further 19 patients had to be switched to Tacrolimus for progressive rejection after OKT3 therapy.

Table 3 Incidence of adverse events in the study population listed as de novo, persistent or improving in relation to the start of Tacrolimus therapy

Adverse events		De novo *n*	Persistent *n*	Improving *n*
Infections (all)		30	6	27
	CMV (PCR positivity[a])	10	1	4
	CMV pneumonia	3	2	1
	PCP	5		
	Legionella pneumonia	3		
	Fungal infections	5	2	5
	Bacterial cholangitis	5		12
	Urinary tract infection	3		7
	Bacterial pneumonia	3		3
	Peritonitis		1	1
	Tuberculosis	1		
Renal insufficiency (all)		18	11	10
	Serum creatinine > 1.5 mg/dl	12	3	2
	Haemodialysis requirement	6	8	8
Neurological disorders (all)		22	6	11
Minor	Tremor	19	4	5
	Mood changes	2		
	Somnolence	2		
	Headache	3		
	Peripheral neural disorders	1	1	
Major	Organic mental syndrome	4		1
	Psychosis	2		
	Seizures	2	1	
	Encephalopathy			5
	Personality disorder			1
	Dysarthria			2
	Ataxia			1

[a] Polymerase chain reaction (PCR) directed detection of CMV envelope in blood

Adverse events

Adverse events that occurred were mainly infection, renal insufficiency or neurological disorder and were pre-existent in a total of 51 patients (65 %). Their incidence could be split into three categories; those arising de novo, those that were persistent and those improving postconversion (Table 3).

De novo infections were observed in 30 patients (38 %) and nephrotoxic or neurotoxic effects were observed in 18 (23 %) and 22 cases (28 %), respectively. Persistence or even aggravation of pre-existent infectious complications were evident in 6 patients (8 %) and pre-existent renal insufficiency or neurological disorders were evident in 11 (14 %) and 6 patients (8 %), respectively. Improvement of prior disorders occurred in 27 patients (35 %) if they were of infectious nature, and in 10 (13 %) and 11 patients (14 %) if of renal origin or related to a neurological site, respectively.

De novo infection was mostly caused by opportunistic pathogens, i.e. CMV ($n = 13$), *Pneumocystis carinii* ($n = 5$) and *Legionella* ($n = 3$), as well as by fungi ($n = 5$). Aggravation of pre-existent infection after conversion was mainly related to those caused by CMV ($n = 3$). All these took a lethal course, in one patient each suffering from chronic ductopenic, OKT3-resistant cellular or severe steroid-resistant cellular rejection. Five pre-existent CMV infections improved postconversion, and bacterial cholangitis ($n = 12$) was the pre-existent complication improving most often during success-

Table 4 Comparison of preconversion laboratory values as a function of the indication for conversion to Tacrolimus in the groups where failures had occurred

	Bili (mg/dl)	aP (IU/l)	γ-GT (IU/l)	AST (IU/l)	ALT (IU/l)
Chronic ductopenic rejection					
Success	16.6 ± 11.0	727 ± 429	640 ± 195	88 ± 38	194 ± 83
Failure	13.7 ± 4.7	697 ± 444	602 ± 476	61 ± 53	100 ± 67
OKT3-resistant cellular rejection					
Success	12.3 ± 8.1	207 ± 93	320 ± 201	48 ± 35	124 ± 91
Failure	15.9 ± 6.3	263 ± 78	411 ± 237	79 ± 41	137 ± 38
Severe steroid-resistant cellular rejection					
Success	9.9 ± 6.8*	234 ± 147	340 ± 175	70 ± 52	114 ± 41
Failure	22.2 ± 7.3*	139 ± 173	299 ± 261	94 ± 48	147 ± 53

ful rescue therapy irrespective of the secondary diagnosis.

An isolated rise in serum creatinine above 1.5 mg/dl or a requirement for haemodialysis as a complication after the onset of Tacrolimus administration was evident in 12 and 6 patients, respectively. Eight patients undergoing haemodialysis had already done so prior to conversion. In another eight patients, the postconversion kidney function improved to an extent that haemodialysis was no longer necessary. No non-lethal case required haemodialysis for more than 8 weeks. However, renal insufficiency, as measured by a serum creatinine level ranging from 1.6 mg/dl to 3 mg/dl, was persistent in eight patients during long-term follow-up. A further four patients suffering from renal dysfunction were among seven patients (8.9 %) undergoing a reconversion to CsA-based immunosuppression either after dissolution of a rejection episode or after retransplantation due to VBDS ($n = 2$). An improvement in postconversion disorders was observed in six patients after reconversion, while one who reconverted due to an aggravated HCV reinfection died later on.

Neurological disorders were further divided into minor and major disturbances, observed in 22 (28 %) and 8 patients (10 %), respectively. Since the clinical picture was compounded by minor and major manifestations, only 14 patients (18 %) presented solely with minor changes. The most prominent de novo neurological complication after conversion to Tacrolimus was tremor ($n = 19$). It did not display a predilection for any of the secondary diagnoses and occurred in 7 of the 14 lethal cases. However, neurological evaluation in the moribund and critically ill was likely to be impeded by sedation or even relaxation for optimized ventilatory support. Both cases of somnolence were diagnosed in patients dying later of CMV and *Pneumocystis carinii* pneumonia. Among the neurological disorders improving during the rescue therapy, encephalopathy ($n = 5$) was most eminent. Its aetiology was metabolic, and it occurred in two successful rescue cases in the groups of chronic ductopenic and steroid-resistant cellular rejections, as well as in one patient suffering from cellular rejection in the CsA malabsorption group.

Laboratory findings

Preconversion laboratory parameters in the groups where failures had occurred were checked for a putative predictive potency (Table 4). A significantly elevated total serum bilirubin when comparing failures and the respective successful cases (22.2 ± 7.3 mg/dl vs. 9.9 ± 6.8 mg/dl; $p < 0.05$) was found in the group of steroid-resistant cellular rejection. Prior to conversion in chronic ductopenic rejection, total serum bilirubin levels were rather higher in patients profiting of the rescue therapy. Among OKT3 non-responders, the levels of total serum bilirubin, as well as alkaline phosphatase (aP) and γ-glutamyltransferase (γ-GT) activities had been elevated slightly though not significantly in those where rescue was about to fail.

Discussion

After 2 years of follow-up, patient and graft survival after conversion to Tacrolimus for various types of liver allograft rejection were 82 % and 77 %, respectively, with a response rate of 92 %. These figures exceeded earlier results from the United States multicentre trial, which generated 1-year survival figures of 72 % for patients and 50 % for grafts, as well as our previously reported experience after 33 conversions, where the 2-year data for patient and graft survival were 76 % and 70 %, respectively [7, 12]. While in the United States multicentre trial, patients suffering from chronic or OKT3-resistant cellular rejection had almost exclusively been enrolled, our earlier results have already reflected a more liberal use of conversion therapy. However, it could be concluded from these and other reports that a conversion to Tacrolimus earlier in the course of a rejection episode might be advisable [2]. Therefore, only 33 % of the patients in this study fulfilled the re-

quirements of the United States multicentre trial, while the remaining were suffering from steroid-resistant and late-onset cellular rejection, from cellular rejection during inadequate CsA uptake or even from uncomplicated cellular rejection. The improved outcome was largely due to a higher share of these less complicated rejection types, while the survival figures after conversion for manifest chronic ductopenic rejection, where a restricted impact of rescue therapy is a well-known feature, remained unchanged [2, 4, 8, 9, 19].

Opportunistic infections, i.e. *Pneumocystis carinii* and CMV pneumonia, account for most of the rescue failures. Although in 65 % of all cases undergoing conversion to Tacrolimus, many infectious, renal, and neurological complications had already pre-existed, all *Pneumocystis carinii* pneumonias were acquired de novo. It might be worthy of note that four of these five patients had undergone transplantation prior to a change in our perioperative prophylaxis from aerosolized Pentamidine to Bactrim. While the incidence of infections was not elevated in primary protocols entailing Tacrolimus, a rising rate was evident in the same study among those converted [11]. A distinct risk associated with conversion was also supplemented by another report indicating a *Pneumocystis carinii* pneumonia incidence of 12 % [8].

In spite of a liberalization of entry criteria, a substantial proportion of the patients were still high-risk cases, which is reflected by both the 51 patients (65 %) presenting with pre-existent infectious, renal or neurological disorders, and a time interval from onset of Tacrolimus conversion to patient death sometimes being as short as 1 week. In successfully converted patients, the benefit applied not only to control of rejection, but also to these pre-existing disorders. The general improvement might be associated with a gain in liver function or with previous drug-induced toxicity. Bacterial infections mainly and, herein, cholangitis may have been affected by less impaired non-specific defences and a normalization in bile flow [1, 5]. Kidney function was enhanced to an extent that in eight cases the former requirement for haemodialysis did not persist after conversion. Neurological disorders that were alleviated after conversion were predominantly metabolic, with a subsequent gain in liver and kidney function. Conversely, postconversion nephro- and neurotoxicity were experienced by 23 % and 28 % of the patients, respectively. Possible contributing factors such as infections or nephrotoxic antibiotics not being taken into account, the share of patients exhibiting renal dysfunction was considerably lower than the initial 80–90 % figures of previous rescue studies [6, 10]. Long-term toxicity was confined to mild renal insufficiency in eight patients. However, a reconversion to CsA-based immunosuppression was implemented in a further seven patients (9 %) mainly for renal dysfunction, resulting in an improved serum creatinine.

In our study, neither the bilirubin level nor serum activities of hepatocellular or canalicular enzymes were predictive of outcome of conversion in chronic ductopenic and OKT3-resistant cellular rejection. In cellular steroid-resistant rejection, the preconversion total serum bilirubin was significantly elevated in failures when compared to the respective successful cases. In all patients where a biopsy was obtained after conversion, rejection had resolved completely. In contrast to chronic rejection, the rise in serum bilirubin was likely to be due to an impaired hepatocellular function without a significant role of duct loss. Since the predictive potency was confined to failure and not to non-response, it raises the question of whether Tacrolimus will be able to overcome a given extent of graft damage only at the expense of severe overimmunosuppression.

In conclusion, implementation of a conversion to Tacrolimus early in the course of a rejection episode resulted in a further improvement in patient and graft survival. Failures occurred in the groups of OKT3-resistant and steroid-resistant cellular rejection, and only in a subgroup of patients suffering from chronic ductopenic rejection was a permanent benefit observed. Therefore, predictive parameters, e.g. the total serum bilirubin in steroid-resistant cellular rejection, are still required to identify those patients who would profit rather from a retransplantation.

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