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Rescue therapy with tacrolimus in simultaneous pancreas/kidney transplantation

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Abstract Tacrolimus has been effective both in primary and rescue therapy following steroid and OKT3-resistant acute rejection in liver and kidney transplantation. Due to the effects of tacrolimus on glucose metabolism, there has been concern about its use in simultaneous pancreas/kidney transplantation. We report on the results of six patients (three female, three male, age 35.2 ± 7.3 years) converted from cyclosporin A to tacrolimus following simultaneous pancreas/kidney transplantation in steroid-resistant acute rejection. Tacrolimus was induced 2.8 ± 1.7 months (range 1–4.8 months) after transplantation; follow-up was 3–18 months. Following conversion, creatinine levels declined in all patients [3.5 ± 1.2 mg/dl before conversion, 3.0 ± 1.9 mg/dl (n = 6) at three months, 1.4 ± 0.1 mg/dl at 1 year (n = 3)]. Before conversion, fasting blood glucose levels averaged 154 ± 33 mg/dl, with three patients receiving insulin. Three months later no patient required insulin, the mean glucose level being 107 ± 23 mg/dl (n = 6); at 1 year it was 92 ± 9 mg/dl (n = 3). One patient lost his pancreatic graft after 4 months due to a mycotic aneurysm. We conclude that conversion to tacrolimus is a safe and effective treatment in cases of steroid-resistant rejections following pancreas/kidney transplantation.

Key words Rescue therapy, tacrolismus, kidney/pancreas transplantation · Tacrolimus, kidney/pancreas transplantation · Kidney/pancreas transplantation, rescue therapy · Pancreas/kidney transplantation, tacrolismus, rescue therapy

Introduction

In simultaneous pancreas/kidney transplantation, acute rejection episodes occur twice as frequently as after kidney transplantation alone [13, 15]. Nearly 30 % of them are steroid-resistant [22].

Tacrolimus has been effective both in primary therapy and in rescue therapy for steroid and OKT3-resistant acute rejection episodes in liver and kidney transplantation [3, 6, 8, 10, 21]. Due to the presumed effects of tacrolimus on glucose metabolism, there has been concern about its use in simultaneous pancreas/kidney transplantation [3, 10, 14, 21]. The present study was designed to evaluate the safety and efficacy of tacrolimus in steroid-resistant acute rejections following simultaneous pancreas/kidney transplantation.

Patients and methods

Six patients (three female, three male) with a mean age of 35.2 ± 7.3 years (range 25–43 years) undergoing steroid-resistant acute rejection episodes after combined pancreas/kidney transplantation were converted from a cyclosporin-based immunosuppressive regimen to tacrolimus. All patients suffered from insulin-dependent diabetes mellitus and end-stage renal disease. The pancreas was placed with segmental duodenum into the iliac fossa

Table 1 Creatinine levels, fasting blood glucose, C-peptide, urinary amylase, HbA_1, dose of tacrolimus, and trough levels of tacrolimus before and after conversion to tacrolimus

	Before conversion (**n** = 6)	3 months (**n** = 6)	6 months (**n** = 5)	9 months (**n** = 4)	12 months (**n** = 3)	15 months (**n** = 3)	18 months (**n** = 2)
Creatinine (mg/dl)	3.5 ± 1.2	3.0 ± 1.9	2.0 ± 1.1	2.4 ± 1.9	1.4 ± 0.1	1.4 ± 0.2	1.4 ± 0.0
Blood glucose (mg/dl)	154 ± 33	107 ± 23	87 ± 7	90 ± 6	92 ± 9	88 ± 15	98 ± 8
C-peptide (ng/ml)	10.3 ± 5.2	6.2 ± 1.8	7.8 ± 1.8	4.8 ± 1.5	4.4 ± 1.8	3.7 ± 1.4	4.7 ± 0.3
Urinary amylase (U/l)	14177 ± 21575	4951 ± 4884	6001 ± 6685	9503 ± 8094	12522 ± 8785	9954 ± 6658	23878 ± 1761
HbA_1 (%)	7.5 ± 1.3	6.1 ± 0.9	6.2 ± 0.6	5.9 ± 0.8	5.0 ± 0.9	5.5 ± 1.0	6.0 ± 0.1
Dose of tacrolimus (mg/kg/per day)	0.14 ± 0.02	0.12 ± 0.04	0.09 ± 0.05	0.10 ± 0.07	0.09 ± 0.02	0.08 ± 0.06	0.08 ± 0.05
Trough tacrolimus level (ng/ml)		8.9 ± 1.6	6.7 ± 2.2	8.4 ± 3.2	9.0 ± 1.1	6.6 ± 2.4	6.7 ± 0.6

and drained into the bladder. The kidney was transplanted at the contralateral side. All grafts had been preserved with cold University of Wisconsin solution (cold ischemic time 30.5 ± 8.8 h, warm ischemic time 14.5 ± 3.5 min). Panel reactive antibody titer was 0 %. HLA mismatches, based on the summed mismatches at A, B, and DR loci, were 1.5 ± 1.0 (range 0–3). The immunosuppressive regimen consisted of prednisolone, cyclosporin A, and azathioprine. All patients were additionally treated with an antithymocyte globulin (ATG) induction therapy for 10 days. Cyclosporin trough levels were adjusted to 175–225 ng/ml for the first 3 months.

Rejection episodes were diagnosed by kidney biopsy in every case. The first rejection episode occurred after 56 ± 54 days (range 4–133 days). All patients suffered from interstitial rejection without any signs of vascular rejection. Pancreas biopsies were not performed. Acute rejection episodes were initially treated with methylprednisolone bolus therapy (day 1: 500 mg/day, days 2 and 3: 250 mg/day).

Three patients who experienced their first acute rejection episode had contraindications for OKT3 therapy (pre-existing coronary heart disease in two patients and elevated temperature of unknown origin in another patient) and were immediately switched to tacrolimus (15 ± 1 days after unsuccessful methylprednisolone pulse therapy).

Three patients had two rejection episodes. The first rejection episode was successfully treated with methylprednisolone in two cases, while one patient failed to respond to methylprednisolone and was successfully treated with OKT3 10 days later. These patients developed a second interstitial acute rejection that was diagnosed by kidney biopsy (39 ± 34 days after the first rejection, range 13–87 days). These second rejections were unsuccessfully treated with a 10-day course of OKT3 ($n = 2$) or methylprednisolone ($n = 1$); the patients were then switched to tacrolimus 19 ± 7 days later.

In all six patients, steroid- and/or OKT3-resistant rejection was proven by kidney biopsy.

Results

Tacrolimus was administered at 2.8 ± 1.7 months (range 1–4.8 months) after transplantation. Follow-up after conversion ranged from 3 ($n = 6$) to 18 ($n = 2$) months. Tacrolimus was administered orally with an initial dose of 0.14 ± 0.02 mg/kg body weight (bw) per day. Tacrolimus was maintained at trough levels of 7–10 ng/ml, at a dose of 0.12 ± 0.04 mg/kg bw per day at 3 months and of 0.09 ± 0.02 mg/kg bw at 1 year. The resulting trough levels were 8.9 ± 1.6 ng/ml at 3 months and 9.0 ± 1.1 ng/ml at 1 year.

One patient lost his pancreatic graft after 4 months due to a local infection at the site of operation. This patient had three revisions due to multiple abscess formation. The pancreatic graft had to be removed in order to treat a mycotic aneurysm with multiple septic embolization. After an increase in creatinine during this septic period, he regained normal creatinine levels (1 mg/dl) following removal of the septic focus.

Creatinine levels declined in all patients (Table 1) and no further acute rejection episodes were observed following conversion. Creatinine levels decreased from 3.5 ± 1.2 mg/dl before conversion to 3.1 ± 1.2 mg/dl within 14 days and to 2.9 ± 1.3 mg/dl at 1 month after conversion. In one patient the creatinine level increased after 3 months due to a biopsy-proven chronic rejection. A marked decrease was observed in fasting blood glucose levels at 3 months (Table 1). Before conversion three patients received insulin; from 3 months following conversion to the end of the follow-up, no patient required insulin therapy (except for the patient who lost his pancreatic graft). These results were confirmed by decreased HbA_1 levels following rescue therapy.

Following conversion two patients suffered from CMV infection during the first month, one patient had an oral candidiasis (after 9 months), and four patients suffered from urinary tract infections. Three of these patients had been pretreated with OKT3.

Discussion

Tacrolimus has proved to be effective both as primary therapy following liver and kidney transplantation and as rescue therapy for steroid- and OKT3-resistant acute

rejection episodes. Graft salvage rates of 71 %–85 % have been reported in steroid-resistant kidney transplantation [5, 7]. The use of tacrolimus, however, has been associated with a significant incidence of hyperglycemia and new-onset insulin-dependent diabetes mellitus [3, 6, 8, 10, 21]. These adverse effects have hindered its administration in combined pancreas and kidney transplantation. Recently, several single center studies, as well as one multicenter study, have been published concerning the use of tacrolimus in combined pancreas and kidney transplantation [1, 2, 16, 17, 19]. In the U.S. multicenter analysis, tacrolimus was successfully administered in simultaneous pancreas/kidney transplantation for induction and maintenance therapy ($n = 54$), for anti-rejection or rescue therapy ($n = 44$), or for other reasons ($n = 4$). Six month graft survival in the antirejection/rescue group was 90 % for the pancreas graft and 89 % for the kidney graft [4]. In the same study, the impact of steroid- or OKT-resistant rejections was not evaluated. The median average tacrolimus blood level used in the U.S. multicenter study was 11 ng/ml (range 6–30 ng/ml). Diabetogenicity was observed in five patients (8 %).

Burke et al. used tacrolimus rescue therapy in 13 pancreas/kidney recipients after steroid- and/or OKT3-resistant rejection [2]. All grafts were preserved and euglycemia was achieved in all patients using tacrolimus trough levels between 5 and 15 ng/ml.

Shaffer et al. reported two cases of steroid- and OKT3-resistant acute rejection [16]. The first patient was converted to tacrolimus with a concomitant steroid bolus and had stable kidney and pancreas function during 15 months of follow-up. The other patient was switched to tacrolimus after a 14-day course of OKT3. His kidney function improved 2 weeks after starting tacrolimus, but he developed another acute rejection under tacrolimus therapy 4 months later.

Teraoka et al. reported two cases of successful conversion to tacrolimus in steroid- and ATG-resistant acute rejection [19]. One of these patients developed an episode of pathological glucose tolerance while tacrolimus levels were elevated to 20 ng/ml. This problem resolved following dose reduction.

In our study we evaluated the therapeutic use of tacrolimus in steroid- and OKT3-resistant rejection in combined pancreas and kidney transplantation. In all six patients converted to tacrolimus, creatinine levels decreased markedly and no further acute rejection episodes were observed. Before transplantation all of our patients were insulin-dependent. At the time of conversion to tacrolimus, three recipients were receiving insulin, suggesting a rejection of the pancreatic graft as well. Those three patients had no concurrent infection. However, all patients had received steroid bolus therapy or OKT3 before. As both drugs are known to induce peripheral insulin resistance, a rejection of the pancreas graft cannot be proven without pancreas biopsies. Three months after the initiation of tacrolimus rescue therapy, no patient required insulin and no episodes of hyperglycemia were observed.

In an experimental study, high doses of tacrolimus impaired glucose tolerance in vivo; this effect, however, appeared to be reversible [20]. In liver transplantation, the insulin requirement diminished in tacrolimus-treated patients over time [9, 18].

One possible explanation for the absence of a diabetogenic effect of tacrolimus in our patients may be that, in contrast to other studies, trough levels were kept below 10 ng/ml [12]. Infectious complications after conversion to tacrolimus mostly occurred within the first month. This cannot be attributed to tacrolimus alone as most infections occurred after initial steroid pulse and OKT3 therapy. OKT3 treatment is known to cause a significant increase in CMV disease as well as in urinary tract infections [11].

In conclusion, our results indicate that tacrolimus is safe and effective in treating ongoing steroid- or antibody-resistant rejection episodes following combined pancreas and kidney transplantation if trough levels are kept below 10 ng/ml.

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