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ORIGINAL ARTICLE

Conversion from tacrolimus to cyclosporine A for new-onset diabetes after transplantation: a single-centre experience in renal transplanted patients and review of the literature

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Summary

Tacrolimus (TRL) increases the incidence of new-onset diabetes mellitus after transplantation (NODAT). Little is known about whether conversion from TRL to cyclosporine A (CsA) improves glucose metabolism in patients with NODAT. We retrospectively analysed glucose metabolism parameters in 54 TRL-treated renal transplant patients who developed NODAT. Thirty-four were converted to CsA whereas 20 patients continued TRL. After conversion, fasting plasma glucose decreased from 146 ± 64 to 104 ± 20 mg/dl ($P < 0.0001$) and HbA1c levels decreased from 6.8 ± 0.8% to 6.0 ± 0.6% ($P < 0.0001$) after 1 year of follow-up. The remission rate of NODAT reached 42% (95% confidence interval 24–59%) 1 year after conversion versus 0% in the control group ($P = 0.001$). Blood pressure and lipid levels were stable after conversion although the use of statins significantly increased ($P < 0.01$). The conversion was safe in terms of graft function and acute rejection episodes. The 1-year patient survival and graft survival rate were 100%. In conclusion, our results suggest a significant improvement of glucose metabolism after conversion to CsA in renal transplant patients with NODAT.

Introduction

The development of new-onset diabetes mellitus after transplantation (NODAT) is a serious and frequent complication in recipients of solid organ grafts. Cardiovascular morbidity and mortality [1], overall mortality, graft failure [2], sepsis and medical costs [3] are significantly increased in renal transplant recipients with NODAT. Although the true incidence of NODAT has been difficult to assess because of the heterogeneity of diagnostic criteria used, a large-scale retrospective study reported a cumulative incidence of NODAT of 9%, 16% and 24% at 3-, 12- and 36-month postrenal transplantation with a significantly increased risk with tacrolimus (TRL) as initial maintenance immunosuppressive medication (RR = 1.53) [2]. A meta-analysis of 16 randomized trials also reported a significantly higher incidence of NODAT in patients receiving TRL than with CsA (10.4% vs. 4.5%) after solid organ transplantation [4]. Recently, a randomized controlled trial showed an incidence of treated new-onset diabetes at 6 months of 8.9% in the cyclosporine A (CsA) group and 16.8% in the TRL group ($P = 0.005$) [5]. In addition to the classical risk factors known in the general population, immunosuppressive drugs play an important causal role in the occurrence of abnormalities in glucose metabolism. Corticosteroids are diabetogenic mainly by inducing insulino-resistance [6]. The calcineurin inhibitor (CNI) TRL inhibits insulin secretion by pancreatic β-cell cells [7]. The diabetogenic side-effect of TRL might contribute to the persistent high risk of

NODAT in spite of the use of modern and efficient immunosuppressive combinations that allow the use of low doses or even withdrawal of steroids. Although CsA is less diabetogenic than TRL, little is known about the ability of a conversion from TRL to CsA to improve glucose metabolism in patients with NODAT. Indeed, in renal transplant patients this question has only been addressed by two studies. However, the number of patients studied was small, and the study endpoint was not the reversal of diabetes but other measures of glycaemic control. In order to better assess the efficacy and safety of a conversion strategy, we retrospectively reviewed a cohort of 54 renal transplant recipients who developed NODAT while being treated with TRL. Thirty-four were converted to CsA, and the 20 patients who were maintained on TRL served as controls. In addition, we report a review of the literature on this issue.

Subjects and methods

To be included in this retrospective study, patients had to meet the following criteria: 1/having received an isolated kidney graft, 2/being treated with tacrolimus (Prograf®; Astellas Pharma) as main immunosuppressive agent and 3/having developed NODAT, with diabetes as defined by the 2003 diagnostic criteria of the American Diabetes Association [fasting plasma glucose (FPG) ≥126 mg/dl on at least two occasions] [8]. Only cases of NODAT that persisted beyond the first month were included. Two groups of patients with NODAT were identified. The first corresponds to patients converted from TRL to CsA (Neoral®; Novartis Pharma) because of *de novo* diabetes (converted group, $n = 34$). The second included patients who were not converted and continued TRL (control group, $n = 20$). In practice, the starting dose of CsA was between 3 and 5 mg/kg according to the immunological risk of the patient. During the first post-transplant year, TRL trough levels were targeted between 8 and 12 ng/ml and CsA trough levels between 100 and 200 ng/ml. The patients were retrospectively identified with our computer database and medical files at the outpatient clinic. We collected the following data: patient baseline characteristics on the day of transplantation, laboratory parameters including FPG, HbA1c, serum creatinine and urea, cholesterol [total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL)], triglyceride levels, CsA and TRL trough levels, several clinical parameters: weight, body mass index (BMI), blood pressure, dose of immunosuppressive, antihypertensive, lipid-lowering and glucose-lowering medications. The creatinine clearance was calculated with the Cockroft and Gault formula. The occurrence of acute rejection episodes was also recorded. Data were collected every 3 months for a period of 12 months. Data collection was initiated at the time of conversion (defined as t_0) up to 1-year later for the converted group and from the time of NODAT diagnosis (defined as t_0) up to 1-year later in the control group.

The aim of the study was to evaluate the efficacy and safety of a conversion from TRL to CsA in case of NODAT. The primary outcome was the proportion of patients with reversible NODAT between t_0 and t_{12} months, defined as FPG <126 mg/dl without administration of glucose-lowering medication.

Statistical analysis

Analyses were done on an intention-to-treat basis. Continuous data are expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) and categorical data as proportions with 95% confidence interval (CI). Comparisons between the two groups were done by the Wilcoxon rank sum test or the Fischer's exact test as appropriate. Parameters during time were compared by repeated measures ANOVA with treatment group as a between-subject factor in the model. All statistical tests were two-sided and the level of statistical significance was a *P*-value of the null hypothesis <0.05.

Results

Patient characteristics and treatments

Among the 281 patients with tacrolimus-based immunosuppression, transplanted between August 1997 and December 2005 and regularly followed in our centre, 54 patients (19.2% 95% CI 14.7–24.3%) developed NODAT according to the 2003 ADA criteria. Thirty-four were converted from TRL to CsA whereas 20 were maintained on TRL. The main patient characteristics relevant to NODAT are summarized in Table 1. The proportion of patients with insulin or oral hypoglycaemic therapies was statistically not different ($P = 0.082$) although there were numerically more patients treated with hypoglycaemic agents at baseline in the control group. There were no significant differences concerning FPG at baseline, but HbA1c was significantly lower in the control group ($P = 0.005$). This is probably due to the fact that the duration of NODAT at the time of inclusion (t_0) was shorter in the control group [median: 19 days (IQR: 5–92) after transplantation] as compared to 188 days (IQR: 107–276 days) for the conversion group.

Calcineurin inhibitors dose and trough levels as well as the prednisolone dose during the 1-year follow-up are shown in Table 2. The mean CsA starting dose was

Table 1. Baseline characteristics of patients.

	Converted group (n = 34)	Control group (n = 20)	P-value
Sex ratio (F/M)	12/22	12/8	NS
Age in years (mean ± SD)	50.7 ± 11.8	54.1 ± 11.6	NS
Hepatitis C status (+/–)	10/ 24	2/18	0.17
Body mass index (mean ± SD)	25.6 ± 4.7	25.6 ± 4.9	NS
Glucose-lowering therapy			
No	17 (50%)	6 (30%)	0.082
Oral	4 (11.8%)	8 (40%)	
Insulin	12 (35.3%)	5 (25%)	
Insulin + oral	1	1	
FPG (mg/dl)	146 ± 64	154 ± 47	NS
HbA1c (%)	6.8 ± 0.8	5.9 ± 1.1	0.005

NS, not significant; FPG, fasting plasma glucose.

Table 2. Immunosuppressive agents.

	t_0	+3 months	+6 months	+12 months	P-value
Converted group (n = 34)					
Mean CsA trough level (ng/ml)	–	190	164	149	<0.0001
Mean CsA dose (mg/kg/day)	3.9	3.4	3.0	2.8	<0.0001
Mean prednisolone dose (mg/day)	7.2	6.3	5.3	5.0	0.003
Control group (n = 20)					
Mean TRL trough level (ng/ml)	11.7	11.1	11.2	9.3	0.002
Mean TRL dose (mg/kg/day)	0.14	0.11	0.10	0.08	0.0002
Mean prednisolone dose (mg/day)	11.9	5.5	4.9	4.0	<0.0001

TRL, tacrolimus; CsA, cyclosporine A.
P-value corresponds to within-group comparisons.

3.9 mg/kg. One year after conversion, the average CsA through level was 149 ng/ml. In the control group, the average TRL trough level decreased from 11.7 ng/ml at inclusion to 9.3 ng/ml 1-year later (P = 0.002) The dose of prednisolone decreased during the 1-year follow-up from 7.2 to 5.0 mg/day in the converted group (P = 0.003), and from 11.9 to 4 mg/day in the control group (P < 0.0001). Steroids were completely withdrawn in seven out of 34 converted patients (21%) and in five out of 20 patients who remained on TRL (25%); (P = NS).

Efficacy of switch to CsA on diabetes

After 12 months of follow-up, 42% (95% CI 24–59%) of converted patients no longer had diabetes versus 0% in the control group (P = 0.001). In the converted group, insulin could be stopped in four out of 13 insulin-treated patients, and the dose reduced in seven patients [from 31 ± 17 units at conversion to 13 ± 12 units per day (P < 0.05) at 12 months]. In the control group, all the initially untreated patients had to start a hypoglycaemic treatment, mainly an oral agent but two patients had to start insulin. The detailed glucose parameters are shown in Table 3. In the converted group, FPG decreased from 146 ± 64 mg/dl at the time of conversion to 104 ± 21 mg/dl 12 months later (P < 0.0001). Most of the reduction occurred early after conversion. HbA1c levels decreased from 6.8 ± 0.8% to 6.0 ± 0.6% at 12 months (P < 0.0001). In the control group, while FPG decreased from 154 ± 47 mg/dl at t_0 to 124 ± 30 mg/dl 12 months later (P = 0.004), HbA1c levels increased from 5.9 ± 1.1% to 6.8 ± 1.5% at 12 months (P = 0.035). At 12 months, between-group comparisons showed that both FPG (P = 0.007) and HbA1c (P = 0.06) were lower in the in the converted group.

Safety issues

After conversion to CsA, creatinine clearance remained stable (56 ± 16 ml/min at t_0, 60 ± 20 ml/min at 12 months; P = NS) as did blood pressure and lipid levels, although the use of statins significantly increased after conversion (P < 0.01). BMI increased significantly in the

Table 3. Glucose metabolism parameters.

	t_0	+3 months	+6 months	+12 months	P-value
Converted group (n = 34)					
FPG (mg/dl)	146 ± 64	111 ± 26	106 ± 19	104 ± 21[a]	<0.0001
HbA1c (%)	6.8 ± 0.8	6.6 ± 1.0	6.1 ± 0.6	6.0 ± 0.6[b]	<0.0001
Control group (n = 20)					
FPG (mg/dl)	154 ± 47	121 ± 25	121 ± 42	124 ± 30[a]	0.004
HbA1c (%)	5.9 ± 1.1	6.4 ± 1.4	6.7 ± 1.0	6.8 ± 1.5[b]	0.03

FPG, Fasting plasma glucose.
P-value corresponds to within-group comparisons. Between group comparisons: [a]P = 0.007 at t + 12 months, [b]P = 0.06 at t + 12 months.

converted group (25.6 at t_0 vs. 26.7 at 12 months; $P < 0.0001$) and remained stable in the control group (25.6 at t_0 vs. 25.9 at 12 months; P = NS). There were three episodes of acute rejection in the control group and two episodes in the conversion group. In the converted group, rejection followed the conversion in one case and for the other case, rejection occurred 1 year after conversion. Graft and patient survival rates were 100% in both groups at 1 year.

Literature review

In addition to the present series, five reports on conversion from tacrolimus to CsA for adverse events in transplant recipients have been published in the literature [9–13]. Four of these have provided data on glucose metabolism which are summarized in Table 4. The four studies differ in terms of their diagnostic criteria for diabetes, the outcome measurements for the assessment of glucose metabolism, the type of solid organ transplanted, and were mostly of relatively small size and uncontrolled. Only two studies exclusively concerned renal transplant patients with NODAT [9,10]. Similar to our study, more than half of patients experienced either resolution or a significant improvement of diabetes after conversion from TRL to CsA in all previous reports. Nevertheless, our trial adds more arguments for a significant beneficial effect on glucose metabolism; first, we used accurate criteria for the diagnosis and the remission of NODAT and second, it is the largest retrospective cohort of transplanted patients converted to CsA for NODAT under TRL.

Discussion

In our retrospective study of renal transplant patients with NODAT, conversion from TRL to CsA was associated with a significant improvement of glucose metabolism. This strategy was efficient as reflected by a reversibility of diabetes in about half of the patients. On the other hand, in the control group (under TRL) no patient had a reversal of diabetes, although hyperglycaemia was adequately controlled by glucose-lowering medications.

Our study has several shortcomings that have to be acknowledged. It is a retrospective analysis that reflects a single-centre experience of the incidence and management of NODAT in TRL-treated renal transplant recipients during a 9-year period. The intervention was not randomly assigned and the sample of the cohort is modest Conversion was rapidly perceived by the physicians of the transplantation team as an efficient and safe approach to manage patients with NODAT. It explains why 50% of

Table 4. Trials of conversion from tacrolimus to cyclosporine.

Trial (ref.)	Organ type, (no. patients)	No. patients (converted/control)	Endpoint(s)	Results
Wyzgal *et al.* [9]	Kidney (20)	20/0	C-peptide secretion Insulin requirement	C-peptide increased from 4.8 to 11.2 ng/ml after conversion ($P < 0.05$) Insulin dose reduced from 46 to 6 IU/day, insulin stopped in 12 out of 15 patients
Oberholzer *et al.* [10]	Kidney (28)	8/20	Proportion of patients on glucose-lowering therapy	50% of converted patients versus 0% of controls could stop glucose lowering therapy
Abouljoud *et al.* [11]	Kidney (49) or Liver (108)	157/0 (37 conversions for NODAT)	Resolution or improvement of diabetes (combined endpoint)	Resolution or improvement of diabetes in 78% of 37 patients converted for NODAT
Dumortier *et al.* [12]	Liver (25)	25/0 (18 conversions for NODAT)	Resolution and improvement of diabetes	Resolution of diabetes in 22% and improvement in 60% of patients with NODAT
Ghisdal *et al.* (this study)	Kidney (54)	34/20	Resolution of diabetes	Resolution of diabetes in 42% (95% CI 24–59%) of converted versus 0% of control patients ($P = 0.001$)

NODAT, new-onset diabetes mellitus after transplantation.

patients in the converted group had no hypoglycaemic treatment at the time of conversion.

Interestingly, in our study, the observed 42% remission rate of diabetes corresponds to the approximately 50% increase in risk of NODAT associated with TRL immunosuppression [1] and suggests that most of the diabetogenic effect of TRL is reversible. These results do not provide a formal proof of a causal association between conversion and improved glucose metabolism, as spontaneous reversal of NODAT in TRL-treated patients has been previously reported [14]. However, our results suggest that conversion has contributed to the observed benefit: the maximum reduction in FPG and insulin requirements occurred rapidly after conversion, suggesting that TRL discontinuation had an important role in the observed improvement of glucose homeostasis. The fact that none of the patients in our control group normalized glucose metabolism in spite of a slightly lower maintenance dose of steroids is also in favour of a direct effect of conversion.

As expected, conversion to CsA resulted in the need for more antihypertensive drugs and more lipid-lowering medications. However, blood pressure and lipid levels remained very well controlled. Concerning CsA-induced hypercholesterolemia, we have recently shown that both total cholesterol and LDL-C was significantly lower when patients received CsA and atorvastatin therapy as compared to the values observed after conversion from CsA to TRL [15]. Conversion from TRL to CsA was safe as graft function remained stable during the follow-up period and only one acute rejection episode was directly associated with the change in CNI. The other acute rejection episode observed in the converted group occurred 12 months after the conversion and was probably caused by incompliance of the patient.

A recent review on the management of diabetes in TRL-treated patients with NODAT advocated aggressive lowering of both TRL and steroids [16]. However, the safety of this approach in terms of prevention of acute rejection has not been prospectively assessed and in our cohort, priority was given to the reduction and withdrawal of steroids.

Conclusions

In summary, our retrospective study and the literature review suggest that conversion from TRL to CsA is a simple, cost-effective and efficient strategy to improve glucose metabolism in renal transplant patients with NODAT that persists after minimization of steroids and TRL. The safety and efficacy of this intervention need to be confirmed in a prospective and randomized trial.

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Authorship

LG: performed study, collected data, wrote the paper; NBB: performed study, collected data; NB, LC, ADH: collected and analysed data; DA: analysed data, wrote the paper; KMW: performed study, analysed data, wrote the paper.

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