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ORIGINAL ARTICLE

Conversion to mammalian target of rapamycin inhibitors increases risk of *de novo* donor-specific antibodies

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Summary

In kidney transplantation, conversion to mammalian target of rapamycin (mTOR) inhibitors may avoid calcineurin inhibitor (CNI) nephrotoxicity, but its impact on post-transplant allo-immunization remains largely unexplored. This retrospective cohort study analyzed the emergence of donor-specific antibodies (DSA) in kidney transplant recipients relative to their immunosuppressive therapy. Among 270 recipients without pretransplant immunization who were screened regularly for *de novo* DSA, 56 were converted to mTOR inhibitors after CNI withdrawal. DSA emergence was increased in patients who were converted to mTOR inhibitors (HR 2.4; 95% CI 1.06–5.41, $P = 0.036$). DSA were mainly directed against donor HLA-DQB1 antigens. The presence of one or two DQ mismatches was a major risk factor for DQ DSA (HR 5.32; 95% CI 1.58–17.89 and HR 10.43; 95% CI 2.29–47.56, respectively; $P < 0.01$). Rejection episodes were more likely in patients converted to mTOR inhibitors, but this difference did not reach significance (16% vs. 7.9%, $P = 0.185$). Concerning graft function, no significant change was observed one year after conversion ($P = 0.31$). In conclusion, conversion to mTOR inhibitors may increase the risk of developing class II DSA, especially in the presence of DQ mismatches: this strategy may favor chronic antibody-mediated rejection and thus reduce graft survival.

Introduction

Over the last decade, kidney transplantation has become highly successful at treating end-stage renal disease. However, long-term graft outcomes are still limited by chronic allograft dysfunction (CAD). Pathogenesis of CAD is multifactorial, with both immune and non-immune factors contributing to the progressive loss of kidney function. In the latter case, long-term exposure to calcineurin inhibitors (CNI) causes chronic irreversible damages [1]. Thus, a key challenge is to develop non-nephrotoxic immunosuppressive strategies and mammalian target of rapamycin inhibitors (mTORi) have been assessed as possible candidates.

Many trials have evaluated the safety and efficacy of replacing CNI by mTOR inhibitors after kidney transplantation. In the CONVERT study, 830 recipients were converted from CNI to sirolimus, and glomerular filtration rate improved only in those patients with good kidney function at the time of conversion [2]. Furthermore, other studies confirmed that this beneficial effect occurred in patients converted before 6 months post-transplant [3–6]. In the ZEUS study [4], where patients were converted at 4–5 months after kidney transplantation, everolimus treatment was associated with improved renal function at 1 year despite an increased risk of acute rejection. In contrast, the ASCERTAIN trial [7] showed that conversion to

everolimus, with elimination or minimization of CNI, had no overall impact on allograft function. The benefits of conversion from CNI to mTOR inhibitor-based immunosuppression, therefore, remain uncertain.

Besides the toxicity of CNI regimens, the contribution of antibody-mediated rejection (AMR) to the development of CAD has also been increasingly recognized. AMR is triggered by humoral immunity, which is mediated by various types of antibodies, especially donor-specific anti-human leukocyte antigen (HLA) antibodies. Thus, allo-antibodies are a serious problem in clinical transplantation: donor-specific antibodies (DSA) that appear after renal allograft have been associated with acute rejection episodes [8–10], and a number of reports have also demonstrated that DSA are a marker for poor long-term graft outcome [11–16].

Despite these advances and their evident implications in CAD, few published studies have focused on the impact of this conversion on the development of post-transplant DSA and their potential influence on kidney allograft function. In the Postconcept study [17], conversion from cyclosporine to sirolimus at 3 months post-transplant did not increase the risk of emergence of anti-HLA antibodies. In contrast, Liefeldt *et al.* [18] showed for the first time that everolimus-based immunosuppression was associated with an increased risk for the development of DSA and AMR, and Kamar *et al.* [19] confirmed in a retrospective study a numerically increased incidence of DSA on a CNI-free everolimus-based immunosuppression: this finding though was not significant.

Thus, the main objective of this study was to assess the impact of conversion from CNI to mTOR inhibitors on post-transplant allo-immunization in our cohort of immunologically naïve kidney transplant recipients. We also wished to analyze whether the delay of conversion influenced immunization status in these patients.

Materials and methods

Patients

All patients (n = 462) who had received a kidney transplant from a living or deceased donor, at Grenoble Hospital, between January 1, 2005 and December 31, 2009 were assessed for inclusion into this retrospective study. All kidney transplantations were conducted with a negative current donor/recipient immunoglobulin G T-cell complement-dependent cytotoxicity cross-match. The patients, while on the kidney transplant waiting list, had been regularly screened for the presence of HLA antibodies using the same Luminex® technology (One Lambda Inc., Canoga Park, CA, USA). Of the total, 179 patients with pretransplant immunization were excluded from the analysis; 13 other recipients were also excluded: eight had lost their graft during the first days post-transplantation because of vascular complications, three patients died during the first 3 months, and two were lost to follow-up. The study thus included 270 patients, and the mean follow-up period was 3.8 years (range: 1.4–6.3).

Immunosuppression

Concerning induction therapy, rabbit antithymocyte globulin (rATG) was administered to 217 recipients (80.4%). 43 patients (15.9%) received an interleukin-2 receptor antagonist (IL2-RA) as they were considered to have an even more low immunological risk (first allograft without a previous immunological event). Ten patients (3.7%) did not receive an induction treatment because of an HLA-identical living donor.

All patients received corticosteroids until month 3 post-transplant except for 63 recipients (23.3%) who had early steroid discontinuation defined as withdrawal of the treatment before day 10 because of diabetes.

Among the 270 patients included, 56 (21%) were converted to mTOR inhibitors after CNI withdrawal at various times post-transplantation. The mean post-transplant time at conversion was 1.3 ± 0.8 years. Recipients who were selected for this conversion were patients with a stable renal function and a lower immunological risk (first allograft without previous rejection episode or immunological event such as transfusion or pregnancy). The main reason for this change in immunosuppression before 2009 was neoplasia. Thirty-seven recipients were converted before 2009 at a mean post-transplant time of 1.7 ± 1.4 years: 27 because of previous history of cancer, three because of BK virus nephropathy and seven because of post-transplant neoplasia. These patients did not have allograft biopsy before conversion. Since January 1, 2009, protocol allograft biopsies have been performed at 3 months post-transplantation in all recipients. Conversion has been then implemented only in patients who had no histological sign of rejection or borderline injuries in the protocol biopsy. Since 2009, 19 patients were converted at 3.5 months post-transplantation to avoid CNI nephrotoxicity. All these 19 recipients had protocol allograft biopsy before conversion, at 3 months post-transplantation: using Banff classification, 16 biopsies were normal (category 1) and three had interstitial fibrosis and tubular atrophy (category 5).

Conversion consisted of abrupt discontinuation of CNI, which was immediately replaced by mTOR inhibitors, either sirolimus (n = 47) or everolimus (n = 9).

No patient had HLA antibodies at the time of conversion to mTOR inhibitors. These 56 patients constituted the 'mTORi group', whereas the other 214 recipients constituted the 'CNI group' (tacrolimus: 197 recipients, cyclosporine: 17 recipients).

Detailed maintenance immunosuppression in the two groups is specified in Table 1.

Table 1. Baseline characteristics of all patients and of mTORi and CNI groups.

	All patients *n* = 270	mTORi *n* = 56	CNI *n* = 214	*P*
Age (years), mean ± SD	50.4 ± 14.3	51.9 ± 13	50 ± 14.6	0.360
Gender: male, *n* (%)	183 (67.8)	40 (71.4)	143 (66.8)	0.511
First renal allograft, *n* (%)	260 (96.3)	54 (96.4)	206 (96.3)	0.953
Primary etiology of nephropathy, *n* (%)				
Glomerular disease	95 (35.2)	24 (42.9)	71 (33.2)	0.178
Polycystic kidney disease	63 (23.3)	11 (19.6)	52 (24.3)	0.463
Chronic tubulo-interstitial nephropathy	31 (11.5)	6 (10.7)	25 (11.7)	0.840
Vascular nephropathy	21 (7.8)	6 (10.7)	15 (7)	0.357
Unknown	60 (22.2)	9 (16.1)	51 (23.8)	0.214
Immunological event: transfusion/pregnancy/transplantectomy, *n* (%)	120 (44.4)	92 (43)	24 (42.8)	0.986
Donor type: deceased, *n* (%)	241 (89.3)	50 (89.3)	191 (89.3)	0.994
Expanded criteria donor*, *n* (%)	76 (28.1)	17 (30.4)	59 (27.6)	0.680
HLA mismatches, mean ± SD				
Class I	2.3 ± 0.9	2.3 ± 0.9	2.4 ± 0.9	0.617
DQ	0.6 ± 0.6	0.7 ± 0.6	0.6 ± 0.6	0.166
DR	1.0 ± 0.6	1.0 ± 0.6	1.0 ± 0.6	0.728
Cold ischemia time (hours), mean ± SD	19.4 ± 29.5	18.7 ± 38.6	19.7 ± 38.6	0.317
Delayed graft function†, *n* (%)	50 (18.5)	11 (19.6)	39 (18.2)	0.808
History of acute pyelonephritis/CMV/BK virus infections, *n* (%)	58 (21.5)	11 (19.6)	47 (22)	0.707
Induction therapy, *n* (%)				
rATG	217 (80.4)	39 (69.6)	178 (83.2)	0.023
IL2-RA	43 (15.9)	17 (30.4)	26 (12.1)	0.001
None	10 (3.7)	0 (0)	10 (4.7)	0.100
Early steroid discontinuation‡, *n* (%)	63 (23.3)	12 (21.4)	51 (23.8)	0.705
Current immunosuppression, *n* (%)				
CNI§/MMF	177 (65.6)	0 (0)	177 (82.7)	
mTOR inhibitor¶/MMF	44 (16.3)	44 (78.6)	0 (0)	
CNI§/MMF/Prednisone**	14 (5.2)	0 (0)	14 (6.6)	
CNI§	11 (4.1)	0 (0)	11 (5.1)	
mTOR inhibitor¶/MMF/Prednisone**	7 (2.6)	7 (12.5)	0 (0)	
CNI§/Prednisone**	6 (2.2)	0 (0)	6 (2.8)	
CNI§/Azathioprine	6 (2.2)	0 (0)	6 (2.8)	
mTOR inhibitor¶/Prednisone**	5 (1.8)	5 (8.9)	0 (0)	
MMF dose (mg/day), mean ± SD	1066 ± 406	1079 ± 382	1053 ± 438	0.809
Banff category on screening biopsy at M3, *n*	56	19	37	
Category 1 (normal), *n* (%)	47 (83.9)	16 (84.2)	31 (83.8)	0.967
Category 3 (borderline injuries), *n* (%)	4 (7.1)	0 (0)	4 (10.8)	0.140
Category 5 (IF/TA), *n* (%)	5 (9)	3 (15.8)	2 (5.4)	0.201

CMV, cytomegalovirus; MMF, mycophenolate mofetil; IF/TA, interstitial fibrosis, tubular atrophy.

*Defined as donor age >60 years or between 50 and 60 years with two risk factors: hypertension, serum creatinine >250 μM, or a lethal cerebrovascular stroke.

†Defined as the necessity for at least one dialysis session during the first week post-transplant.

‡Defined as withdrawal of steroids before day 10 post-transplantation.

§Tacrolimus and cyclosporine were administered to obtain targeted blood trough levels of 4–8 μg/l and C2 levels of 350–450 ng/ml, respectively.

¶Everolimus and sirolimus doses were adjusted to maintain blood trough levels of 6–10 and 8–12 ng/ml, respectively.

**5 mg/day.

Everolimus and sirolimus doses were adjusted to maintain blood trough levels of 6–10 and 8–12 ng/ml, respectively. Tacrolimus and cyclosporine were administered to obtain targeted blood trough levels of 10–15 μg/l and C2 levels of 500–800 ng/ml during the first month, and then 4–8 μg/l and 350–450 ng/ml, respectively.

We noted 30% ($n = 17$) of mTORi discontinuations, because of low tolerance to the medication ($n = 8$) or

because of the emergence of HLA allo-antibodies ($n = 7$) or cellular rejection ($n = 2$) after conversion.

Follow-up time after conversion to mTOR inhibitors varied from 7.5 months to 5.8 years, with a mean value of 24.2 ± 16.7 months.

Post-transplant screening of anti-HLA antibodies

The post-transplant sera of patients were screened using the same solid-phase Luminex® technology. They were tested at 3, 6, 12 months and then every year post-transplant, and when clinically indicated (increased serum creatinine with clinical suspicion of rejection) for classes I and II HLA antibodies, using LAB-Screen Mixed Beads® (One Lambda Inc., Canoga Park, CA, USA). Samples that screened positive were then tested using single-antigen flow beads. Beads with normalized mean fluorescence intensity (MFI) value more than or equal to 1000 were defined as positive.

Allograft biopsies

Every rejection episode was biopsy proven, and all patients who developed post-transplant DSA underwent an allograft biopsy. Biopsies were analyzed by light microscopy, with histological changes graded according to the Banff 97 classification revised in 2007 [20] and a two-step indirect immunofluorescence method. Immunofluorescence was conducted on frozen tissue using an antibody specific to C4d (rabbit monoclonal antibody to human C4d, Biomeda).

Statistics

Categorical data were reported as frequency and percentage, and continuous data as mean ± standard deviation (SD) or median (first quartile–third quartile) when the distribution was not normal. Baseline characteristics of mTORi and CNI groups were compared using Student's *t*-test for continuous variables and the chi-square (or Fisher's exact test when appropriate) for categorical variables.

Univariate Cox's proportional hazards models were used to analyze the unadjusted association between patients' characteristics and the occurrence of DSA. We subsequently estimated the adjusted hazard ratios (aHR) of DSA occurrence with 95% confidence intervals (CI) using a multivariate Cox's proportional hazards model, by entering in the model variables that were associated with *P*-value of <0.15 in univariate analysis: age and sex of the recipients, number of DQ mismatches, type of induction therapy, early steroid discontinuation and current immunosuppression (mTOR inhibitor or CNI).

DSA-free graft survival curves were plotted using the Kaplan–Meier estimates. Patients were censored at 4 years post-transplantation or at time of DSA occurrence. *P*-values <0.05 were considered as significant throughout the study. Statistical analysis was performed with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Study population

Characteristics of the whole population, mTORi and CNI groups are reported in Table 1. Patients converted to mTOR inhibitors had higher proportion of IL2-RA treatment compared to the CNI group. All other characteristics were comparable between the two populations.

Timing and characterization of DSA development

During the follow-up, 28 patients (10.4%) developed DSA. All DSA were directed against donor HLA-DQB1 antigens, associated in four cases with reactivity against DRB1 antigens, and for one patient against class I. DSA MFI varied from 1106 to 17601 with a median value of 3435 (2153–5373). The mean time until *de novo* emergence of DSA after transplantation in our cohort was 1.9 ± 1.4 years, and the mean follow-up time after DSA had developed was 2.2 ± 1.6 years. Among the 56 patients of the mTORi group who were converted at a mean post-transplant time of 1.3 ± 0.8 years, 11 developed DSA, only after conversion as they had no antibodies before conversion. DSA appeared at a mean time of 0.9 ± 0.6 years postconversion.

Factors associated with the development of DSA

Univariate analysis revealed that patients who were converted to mTOR inhibitors had a significantly increased risk of developing DSA (HR = 2.5; 95% CI 1.17–5.33; $P = 0.018$) (Table 2). Adjusting on potential confounders (i.e., age, gender, DQ mismatches, type of induction therapy, and early steroid discontinuation) did not influence this result (HR = 2.4; 95% CI 1.06–5.41; $P = 0.036$) (Table 2). As expected, the presence of one or two DQ mismatches between the donor and recipient was another major risk factor for the emergence of DQ DSA (Table 2), with adjusted HR of 5.32 (95% CI 1.58–17.89) and 10.43 (95% CI 2.29–47.56), respectively ($P < 0.01$).

The CNI group received more ATG than the mTORi group: this may infer a protective role of ATG induction in DSA emergence, but multivariate analysis does not confirm this hypothesis (as shown in Table 2). The 'DSA-free graft survival' Kaplan–Meier curves for the two groups are shown in Fig. 1.

Post hoc subgroup analysis was conducted within the mTORi group according to the delay between transplanta-

Table 2. Factors associated with development of DSA on univariate and multivariate analysis.

	DSA + $n = 28$	DSA − $n = 242$	Univariate analysis			Multivariate analysis*		
			HR	95% CI	*P*	aHR	95% CI	*P*
Age (years), mean ± SD	45.7 ± 15.1	50.9 ± 14.1	0.98	0.96–1.01	0.14	0.98	0.95–1.01	0.12
Gender, *n* (%)								
Male	23 (82)	160 (66)	2.36	0.90–6.22	0.08	2.64	0.93–7.48	0.07
Female	5 (18)	82 (34)						
Donor type, *n* (%)								
Deceased	25 (89)	216 (89)						
Living	3 (11)	26 (11)	0.95	0.29–3.15	0.93			
Expanded criteria donor, *n* (%)	6 (21)	70 (29)	0.76	0.31–1.88	0.55			
DQ mismatches, *n* (%)								
0	3 (11)	118 (49)						
1	21 (75)	111 (46)	6.66	1.99–22.33	0.002	5.32	1.58–17.89	0.007
2	4 (14)	13 (5)	11.26	2.52–50.41	0.002	10.43	2.29–47.56	0.002
Immunological event (transfusion/pregnancy/ transplantectomy), *n* (%)	11 (39)	105 (52)	0.78	0.37–1.68	0.53			
Induction therapy, *n* (%)								
rATG	19 (68)	198 (82)						
IL2-RA	7 (25)	36 (15)	2.18	0.92–5.16	0.075	1.52	0.63–3.67	0.35
Early steroid discontinuation, *n* (%)	2 (7)	61 (25)	0.29	0.07–1.23	0.09	0.44	0.10–1.92	0.28
Current immunosuppression, *n* (%)								
mTOR inhibitor	11 (39)	45(19)	2.50	1.17–5.33	0.018	2.4	1.06–5.41	0.036
CNI	17 (61)	197 (81)						

*A Cox's proportional hazard model was developed by entering variables associated with a *P*-value <0.15 in the univariate analysis.

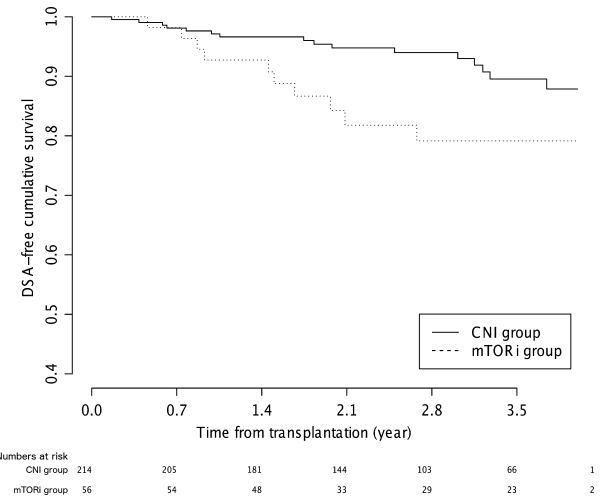

Figure 1 Kaplan–Meyer estimation of 'DSA-free graft survival' for the two groups.

tion and conversion. Using a cut-off point of 1 year post-transplant, we showed that early conversion is an important risk factor (HR = 4.54; 95% CI 2.02–10.22; $P < 0.001$) (Table 3, Fig. 2). In contrast, we did not observe any difference in the risk of DSA emergence between patients who were converted after this time point and recipients who were still treated with CNI.

The net increment in DSA in the mTORi group from the time of conversion to mTORi is shown on the Kaplan–Meier curves of Fig. 3, subdivided in two groups according to the interval between transplantation and conversion.

Clinical outcomes: rejection episodes and allograft function

Overall graft and patient survival rates were 97.3% and 98.2% in the mTOR inhibitor group, 97.6% and 98.6% in the CNI group, respectively.

Graft function, estimated from mean serum creatinine, did not vary significantly during the first year following conversion in the mTORi group, despite the development of DSA. This was evaluated by one-way ANOVA of measured creatinine levels at different times post-conversion (day 0, months 3, 6, 9, and 12). Mean serum creatinine before conversion was 145 ± 53 μM, whereas at 1 year post-conversion, it was 149 ± 58 μM ($P = 0.31$). Using the same statistical method, proteinuria in mTORi group numerically increased during our follow-up (0.03 ± 0.04 g/L before conversion, 0.34 ± 0.62 g/L 1 year later), but this was not significant ($P = 0.85$).

Renal function and proteinuria of CNI and mTORi groups did not vary differently during our follow-up ($P = 0.98$ for renal function and proteinuria): they were

Table 3. Subgroup analysis according to the interval between transplantation and conversion to mTORi.

			Univariate analysis		
Conversion to mTOR inhibitors	DSA +*n* = 28	DSA -*n* = 242	HR	95% CI	*P*-value
No conversion, *n* (%)	17 (7.9)	197 (92.1)			
Conversion before 1 year post-transplant, *n* (%)	9 (28.1)	23 (71.9)	4.54*	2.02–10.22	<0.001
Conversion after 1 year post-transplant, *n* (%)	2 (8.3)	22 (91.7)	0.82*	0.19–3.57	0.79

*Compared with patients without conversion.

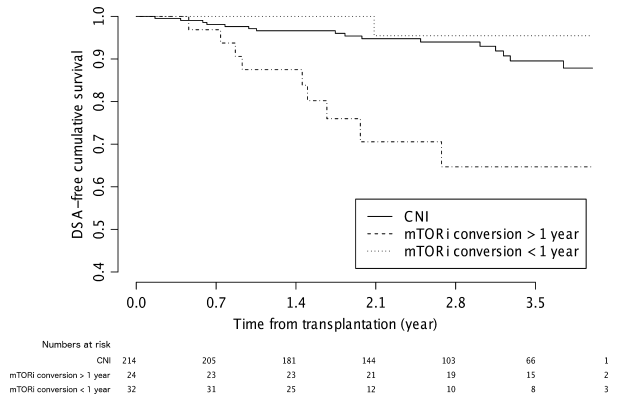

Figure 2 Kaplan–Meyer estimation of 'DSA-free graft survival' for CNI group and mTORi group subdivided according to the interval between transplantation and conversion.

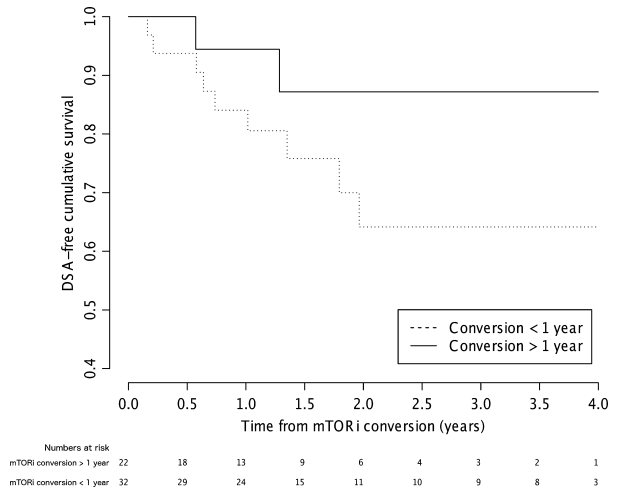

Figure 3 Kaplan–Meyer estimation of 'DSA-free graft survival' in mTORi group since the time of conversion to mTORi, subdivided according to the interval between transplantation and conversion.

compared by ANOVA of measured creatinine levels and proteinuria at different times post-transplantation (every 3 months from the day of transplantation until the end of our follow-up).

At our last follow-up, 26 cases (9.6%) of biopsy-proven rejection had been reported: 14 cellular rejections, 10 AMR, and two had both cellular and humoral lesions. Rejection episodes were more likely in patients converted to mTOR inhibitors compared to recipients still treated with CNI, but this difference did not reach significance (14.3% vs. 8.4%, $P = 0.185$). This was true for both AMR (7.1% vs. 3.7%, $P = 0.279$) and acute cellular rejection (7.1% vs. 5.6%, $P = 0.75$).

Among the 28 patients who developed de novo DSA, only 13 (46.4%) presented an acute or chronic antibody-mediated rejection during our follow-up. Renal function of these 28 patients deteriorated significantly from 6 months before DSA emergence until the end of our follow-up (one-way ANOVA, $P = 0.037$). Mean serum creatinine 6 months before DSA emergence was 141 ± 37 μM, whereas, at 1 year post-DSA, it was 176 ± 45 μM. Proteinuria of the same group did not vary significantly ($P = 0.072$).

Discussion

As of today, clinical trials that have focused on the benefits of replacing CNI with mTORi have provided contradictory results. Some studies [4] have shown that discontinuation of CNI with introduction of mTORi is associated with improved renal function, despite an increased risk of acute rejection, whereas other studies have reported similar rejection rates [21–25] but no substantial benefit on renal function [21, 22, 24, 26]. Despite these results, and evidence showing that early discontinuation of CNI or total avoidance can increase rejection episodes [27–30], the large randomized conversion trials [2, 17] have not shown a more important immunological risk, even in the late follow-up analysis. However, these multicenter trials were not designed to look for immunization even though in the 4-year results of the postconcept study, no difference was found between the two populations (sirolimus vs. cyclosporine) in terms of proportion of HLA antibody appearance. Specificity of the antibodies though was not analyzed and so it is impossible to conclude on the prevalence of DSA. The discovery and continuous optimization of Luminex® technology has per-

mitted the detection of low titer HLA antibodies that in the past were invisible. This probably explains why previous studies have not described results similar to ours.

One study of Liefeldt *et al.* [18] has focused on the impact of this conversion on post-transplant DSA. They showed that early conversion from cyclosporine to everolimus favors emergence of donor-specific HLA antibodies and AMR. Our results confirm their findings but differ somewhat: (i) The immunosuppressive regimen before conversion in our mTORi group and in CNI group is essentially based on tacrolimus, a drug considered more potent than cyclosporine; (ii) The vast majority of our patients (80%) received rATG as induction therapy; (iii) Our study population includes late conversions (after 1 year post-transplant) and these patients had no increased risk of DSA development. Overall, despite a strong induction protocol and maintenance by tacrolimus, we confirm that conversion to mTORi with CNI withdrawal is a risk factor for DSA development. Furthermore, our subgroup analysis suggests that early conversions (before 1 year post-transplant) are particularly concerned and that this strategy may be applied more serenely afterward.

Another element that distinguishes our analysis is the predominance of class II DSA, in particular against DQB antigens. The finding that DQB is a preferred target antigen agrees with observations made by other investigators [31–33] who have also reported class II DSA to be more closely related to renal dysfunction because of chronic AMR: this is confirmed by our results. These findings are not restricted to kidney transplantation, as a similar predominance of class II DSA associated with cardiac allograft vasculopathy and decreased graft survival has been documented in heart transplant patients [34]. As the follow-up of our study is limited, it does not allow us to see the long-term effects of the immunization process. We can only speculate that the prevalence of class II antibodies in our cohort will influence negatively graft survival with a higher proportion of mTORi-treated patients suffering in the future from chronic AMR.

The impact of HLA DQ mismatches between donor and recipient on the emergence of *de novo* DQ DSA is also highlighted by our study. This result shows the major interest of proper donor/receiver HLA matching, especially for DQ antigens, rarely taken into account in the allocation process.

This study certainly has some limitations. First of all, it is monocentric and retrospective. The population converted to mTOR inhibitors was not randomized but, rather, was selected on the basis of the absence of previous immunization or rejection episode. This could be regarded as a selection bias, but because conversion concerned the population with the lower immunological risk, our results are all the more striking.

All these findings infer that the brutal withdrawal and replacement of CNI with mTORi is probably a bad immunosuppressive strategy, especially if made during the early stages of transplantation. Our results are probably explained by an overall under-immunosuppression in the mTORi-treated group, but this contradicts with the fact that only 7% of these patients suffered from acute cellular rejection and this proportion did not differ from the CNI group. This immunosuppressive regimen probably alters the balance between humoral and cellular immunity, but explaining the mechanisms behind this process is pure speculation at the time being.

In conclusion, we believe that caution must be taken when converting patients from CNI to mTORi regimen, even those considered at low immunological risk: late conversion is probably more feasible and DQ-mismatched patients should not be considered for this therapeutic strategy.

Disclosure

The results presented in this paper have not been published previously in whole or part, except in abstract format.

Part of this work has been presented as an oral communication at the American Transplant Congress 2012.

Authorship

L-EC: performed study/collected and analyzed data/wrote the paper. RT: designed study. MR: analyzed data. PM: contributed important reagents. BJ: contributed important reagents. TJ: contributed important reagents. NP: analyzed data: DM: analyzed data. J-LQ: analyzed data; FB: contributed important reagents. PZ: contributed important reagents.

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