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Are calcineurin inhibitors still needed in early renal transplantation?

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ABSTRACT

Sirolimus is a potent immunosuppressor that has raised the possibility of renal transplantation without drug-induced nephrotoxicity related to calcineurin inhibitor use.

A retrospective study was conducted on 48 renal transplantation patients (2005-2006) to evaluate the efficacy and safety of calcineurin inhibitor avoidance using Sirolimus under monoclonal antibody induction. An analysis of two groups receiving different immunosuppressive therapy: with calcineurin inhibitor (Tacrolimus group) – Basiliximab, Tacrolimus, Mycophenolate Mofetil plus steroid withdrawal scheme and calcineurin inhibitor free (Sirolimus group) – Basiliximab, Sirolimus, Mycophenolate Mofetil plus steroid was performed. We compared donor and receptor characteristics; efficacy (post-operative graft function and at 12, 24 and 36 months; biopsy proven acute rejection), safety (adverse events, side effects); graft failure and death.

Among the enrolled patients, 31% (n=15) belonged to the Sirolimus group and 69% (n=33) to the Tacrolimus group. No relevant differences in age, gender, pre-existing diabetes mellitus and immunological profile were found. The groups did not differ with respect to primary graft dysfunction (Sirolimus=0%; Tacrolimus=3%) and delayed graft function (Sirolimus=27%; Tacrolimus=15%). There was no statistical difference in mean glomerular filtration rate calculated by Modification of Diet in Renal Disease study formula between the Sirolimus and Tacrolimus groups at 12 months (69.1±23.0 ml/min/1.73m^2 *vs.* 62.8±16.7 ml/min/1.73m^2), 24 months (73.2±23.1 ml/min/1.73m^2 *vs.* 62.2±15.9 ml/min/1.73m^2) and 36 months (75.7±14.0 ml/min/1.73m^2 *vs.* 66.7±20.0 ml/min/1.73m^2). There was a significantly higher rate of biopsy proven acute rejection in the Sirolimus group (Sirolimus=47% *vs.* Tacrolimus=9%; p=0.007) and all episodes occurred in the first 3 months following transplantation. No significant difference was found in frequency of graft loss (Sirolimus=7%; Tacrolimus=3%) and death (n=0) between both groups. Despite a unique safety profile and similar graft function during the first three years, initial immunosuppression with Sirolimus after Basiliximab induction led to an unacceptable risk of acute rejection in comparison to Tacrolimus.

Key-Words:
Acute rejection; adverse effects; calcineurin inhibitor avoidance; graft function; renal transplantation; Sirolimus.

INTRODUCTION

Calcineurin inhibitors (CNI) have been the mainstay of immunosuppressive treatment over the past 20 years. It is widely recognised that these agents

are responsible for the current excellent outcomes in renal transplantation in terms of decreased acute rejection and improved early allograft survival[1]. However, long-term allograft survival has not improved to the extent predicted. CNI intrinsic nephrotoxicity has been considered the Achilles' heel of modern immunosuppression[2], ultimately contributing to the long-term decline in renal allograft function[3]. Moreover, increasing evidence indicates that the toxic effects of CNI contribute not only to chronic allograft nephropathy but also to cardiovascular recipient death, the two major causes of late renal graft loss[4]. With the advent of new non-nephrotoxic drugs, attempts at complete avoidance of CNI have been actively pursued, including the use of Sirolimus regimens.

Sirolimus' (rapamycin) original mechanisms of action (inhibition of a key regulatory kinase in the process of cell division[5]) and toxicity profile make it an effective immunosuppressive agent, with anti-proliferative, antifibrotic and antiangiogenic properties. It has been successfully used with ciclosporin in maintenance immunosuppressive therapy[6-11] and might be considered a good alternative to CNI[12-17].

The aim of this study was to compare the complete avoidance of CNI using a Sirolimus-based immunosuppressive regimen *vs.* a Tacrolimus-based regimen, in terms of efficacy and safety in renal transplantation. Both immunosuppressive regimens included monoclonal antibody induction. We performed a retrospective study based on 48 patients submitted to kidney transplantation at our unit between January 2005 and December 2006. We analysed the data for donor and receptor characteristics, efficacy (post-operative graft function, renal function at 12, 24 and 36 months after transplantation, biopsy proven acute rejection), safety (adverse events, side effects immunosuppressant-related and unrelated), graft failure and death.

PATIENTS AND METHODS

The medical records of the patients submitted to transplantation at the Renal Transplant Unit of Coimbra University Hospital between January 2005 and December 2006 were reviewed, selecting the cases in which induction with interleukin-2 receptor antibody (Basiliximab) was associated with either Sirolimus (Sir) or Tacrolimus (Tac). The choice of immunosuppression was determined by the regimen used at the Unit at the transplant time. The mean post-transplant follow up was 34.1±8.1 months (range 24.4-48.4 months).

Immunosuppressive regimens

All patients received induction therapy with 20 mg of Basiliximab (Simulect®) intravenously before surgery and on day 4, associated with Mycophenolate Mofetil (Cellcept®) 1g before surgery, and after that two times per day. Sir group began Sirolimus (Rapamune®) 6 mg orally within 72 hours (hrs) of surgery and then 4 mg daily. Further doses were concentration controlled to keep 24-hr whole-blood trough levels between 4 and 8 ng/ml. The steroid regimen in this group consisted of 500mg of intravenous Methylprednisolone (IVMP) before surgery, 250g mg by day 2, 125 mg by day 4 and then 20mg oral prednisone. The other group of patients was given Tacrolimus (Prograf®) at 0.2 mg/kg in divided doses, associated with a steroid early withdrawal scheme (500mg of IVMP before surgery, 250g mg by day 2, 125 mg by day 4). Thereafter, Tac doses were concentration controlled to keep 12-hr whole-blood trough levels between 8 and 12 ng/ml.

Diagnosis and treatment of acute rejection

All acute rejection (AR) episodes were proven by ultrasound-guided transplant kidney biopsy and Banff scored[18] prior to the initiation of therapy. The episodes were treated with IVMP at a dose of 500--1000 mg for three days followed by an oral steroids recycle (Sir group) or reinitiation (Tac group). Rejection scored Banff IIA was treated with polyclonal antibody Thymoglobulin (1.5 mg/Kg during 10 days) and manipulation of baseline immunosuppression with conversion to CNI in Sir group.

Renal function measurement

Renal graft function was assessed by serum creatinine (S_{Cr}) and glomerular filtration rate (GFR) estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation[19].

Statistical analysis

Descriptive statistics are presented as mean±SD for the continuous variables and as frequencies and percentages for the categorical variables. Means were compared between the two groups using the Student *t* test or by a non-parametric test if the data were not normally distributed. Categorical variables were compared using the chi-square test. A p-value of 0.05 or less was considered significant.

RESULTS

Forty eight patients were enrolled; 31% (n=15) in Sir group and 69% (n=33) in Tac group.

The demographics and selected clinical characteristics of the study population are shown in Table I.

Table I

Demographic and selected clinical parameters of the study groups' populations[a]

	Sir group (n=15)	Tac group (n=33)
Recipients		
Mean age (range) – (years)	40.6±13.2 (12-62)	43.7±13.5(15-69)
Gender (M:F)	10:5	17:16
Caucasian race	15 (100%)	33 (100%)
Weight (kg)	63.6±17.2	63.2±13.0
Diabetics	2 (13%)	4 (11%)
Time on dialysis (months)	37.9±38.2	48.5±32.2
Panel-reactive antibody	0.22±0.67	5.62±17.8
› 25%	0	1 (3%)
› 50%	0	1 (3%)
2nd transplant	1 (7%)	1 (3%)
Donors		
Mean age (range) – (years)	41.7±15.3 (20-64)	37.2±17.2(4-65)
Age › 50	3 (20%)	8 (33%)
Traumatic death	6 (40%)	15 (45%)
Living donor	1 (7%)	2 (5%)
Transplant		
Cold ischaemia time (hours)	16.9±5.6	16.1±6.1
Cold ischaemia time › 24h	2 (13%)	0
HLA matches		
0 (locus -A, -B, -DR)	0	3 (9%)
› 3 (locus -A, -B, -DR)	10 (66%)	20 (60%)
2 matches in -DR	4 (27%)	12 (37%)
1 matches in -DR	10 (66%)	14 (42%)

[a] There were no significant differences between the groups
HLA, human leucocyte antigen; M, male; F, female

There were no significant differences between the groups regarding donor or recipient age, gender, race, pre-existing diabetes mellitus, living donor kidneys, frequency of retransplantation, cold ischaemia time, sensitisation or number of HLA mismatches.

Considering post-operative renal graft function, the groups did not differ in terms of primary dysfunction [Sir: 0% (n=0); Tac: 3% (n=1)] or delayed graft function [Sir: 27% (n=4); Tac: 15% (n=5)] defined as the need for first-week dialysis (Fig. 1). During the first post-transplant year, no significant differences were found in renal function (Fig. 2).

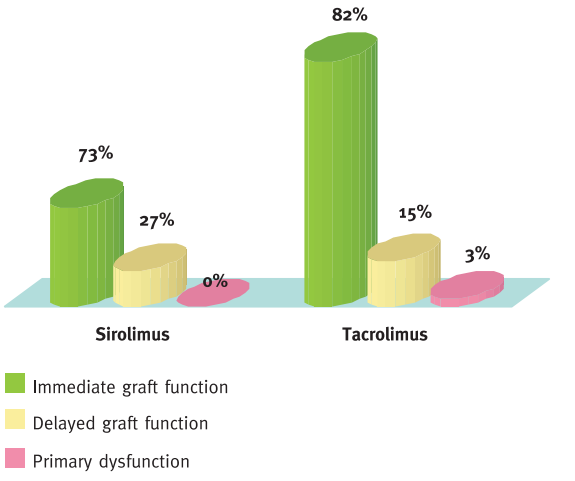


Figure 1

Post-operative renal graft function[a]

[a] There were no significant differences between the groups

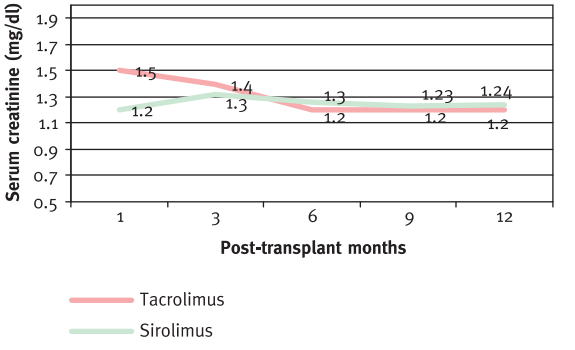


Figure 2

Renal graft function during the first post-transplant year[a]

[a] There were no significant differences between the groups

Table II

Renal function after transplant[a]

	Sir group (n=15)		Tac group (n=33)	
	n	Mean±SD	n	Mean±SD
Serum creatinine (mg/dl)				
Month 12	14	1.2±0.4	31	1.2±0.3
Month 24	11	1.2±0.4	26	1.2±0.3
Month 36	10	1.0±0.2	6	1.1±0.3
MDRD equation GFR (ml/min/1.73m²)				
Month 12	14	69.1±23.0	31	62.8±16.7
Month 24	11	73.3±23.1	26	62.2±15.9
Month 36	10	75.7±14.0	6	66.7±20.0
Δ TGF 12-24 months	11	4.2±7.8	26	0.4±7.9
Δ TGF 24-36 months	10	2.5±10.1	6	3.6±6.9

[a] There were no significant differences between the groups

At 12 months, Sir group presented a serum creatinine of 1.2±0.4 mg/dl and GFR of 69.1±23.0 ml/min/1.73m² compared to Tac group values of 1.2±0.3mg/dl and 62.8±16.7 ml/min/1.73m², respectively. By 24 months (GFR of 73.3±23.1 ml/min/1.73m² *vs.* 62.2±15.9 ml/min/1.73m²) and 36 months (GFR of 75.7±14.0 ml/min/1.73m² *vs.* 66.7±20.0 ml/min/1.73m²), Sir group exhibited a better renal function, but there were still no statistical differences in its measurements and GFR evolution (Table II).

Table III

Acute rejection episodes

	Sir group (n=15)	Tac group (n=33)
Acute rejection (biopsy confirmed)[a]	7 (47%)	3 (9%)
Banff score		
IA	5	3
IB	1	–
IIA	1[b]	–
Treatment		
Intravenous methylprednisolone	7	3
Policlonal antibody	1[b]	–
Immunosuppression manipulation	1[b]	–
Posttransplant	5	3
1st month	1	–
2nd month	1	–
3rd month		

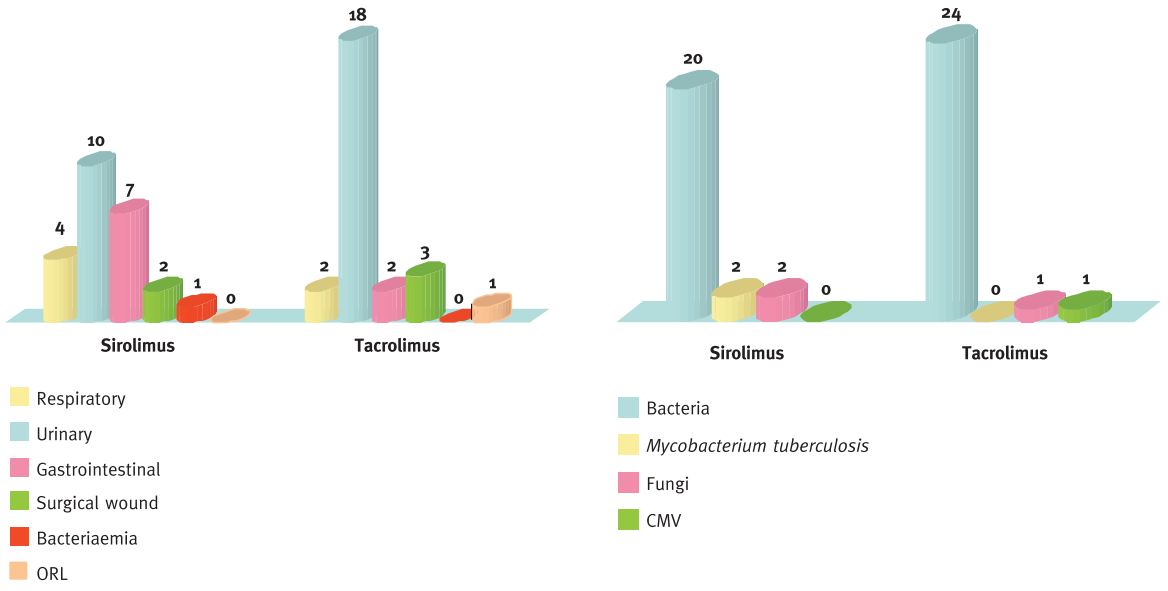
[a] There was statistical difference between the two groups (p=0.007)

[b] Patient with an acute rejection scored Banff IIA, treated with intravenous Methylprednisolone, policlonal antibody Thymoglobulin plus conversion from Sirolimus to Tacrolimus

There was a significantly higher rate of biopsy proven acute rejection (AR) in Sir group (Sir: 47% (n=7) *vs.* Tac=9% (n=3); p=0.007), with the totality of the episodes occurring in the first 3 months after transplantation (Table III). No late AR episodes were diagnosed in either group. All the AR episodes were classified according to the Banff system as acute cellular rejection. Histological severity appeared to be increased in Sir group, but the difference was not statistically significant.

In terms of safety, there were a total of 50 infectious complications during the first year (Sir group: 24 episodes affecting 11 patients (73%), Tac group: 26 episodes involving 17 patients (51%), without significant difference in the total number of events or events per patient between groups. The majority of infections encountered were community-acquired bacterial infections of the urinary tract (Fig. 3). There was a case of CMV disease with gastrointestinal involvement in a Tac group patient (donor and recipient both CMV seropositives) diagnosed at 4 months. In Sir group, two cases of *Mycobacterium tuberculosis* infection were reported (urinary and pulmonary). No cases of malignancy or post-transplant lymphoproliferative disease were found in either group.

The laboratory abnormalities more significantly reported at 12 months with Sir were hyperlipidaemia: cholesterolaemia›200mg/dl in 86% *vs.* 52% with Tac (p=0.04), LDL-cholesterolaemia›100mg/dl in 93% *vs.* 62% with Tac (p=0.04) and triglyceridaemia›150 mg/



a) Location

b) Microbiologic agent

Figure 3

Infectious events[a]

[a] There were no significant differences between the groups

dl in 77% *vs.* 25% with Tac. (p=0.003), with higher mean serum cholesterol and triglycerides levels at 12 months (Table IV), despite the more frequent use of statin in this group (71% *vs.* 24% with Tac. p=0.005). Considering haematological effects, there was no statistical difference in the mean white blood cell count at 1 year, but Sir group had a significantly higher frequency of leucopoenia leading to adjustment of MMF dose (27% *vs.* 4% with Tac p=0.02). Lower haemoglobin levels were also reported at 12 months with Sir than Tac (12.3±1.6 g/dl *vs.* 13.5±1.6 g/dl; p=0.02), although no statistical differences were found in the frequency of anaemia defined by haemoglobin<11 g/dl (13% *vs.* 3% with Tac) and erythropoietin use (7% *vs.* 4%. with Tac). Development of proteinuria>500 mg/24h (31% *vs.* 14% with Tac) and impaired liver tests (13% *vs.* 6% with Tac) occurred in both groups at 12 months, with no statistical difference between them. Other side effects occurring in the post-transplant period are listed in Table IV. Diarrhoea and tremor were exclusively documented in Tac group, at a frequency of 12% and 6%, respectively. Lymphocele (7%) and mouth ulcers (7%) were, on the other hand, adverse events reported in Sir group. At 1 month, the mean trough level of Tacrolimus was 14.5±5.1 ng/ml (range 3.5-23 ng/ml) and of Sirolimus was 8.2±5.4 ng/ml (range 3.5-21 ng/ml). Three patients (20%) in Sir group and one patient (3%) in Tac group discontinued the immunosuppressive medication. Reasons for discontinuation of Sirolimus included abnormal liver function tests – increased AST/ALT (n=1) and acute rejection Banff graded IIA (n=1), while Tac was temporary suspended in one patient with unstable *angina pectoris* and high blood Tac trough levels. Six patients (40%) in Sir group had to decrease or temporarily withdraw MMF co-administration due to leucopoenia (n=4) and active infection (n=2). In Tac group, four patients (12%) had to decrease or temporarily withdraw MMF due to gastrointestinal intolerance (n=2), active infection (n=1) and leucopaenia (n=1).

The frequency of graft loss was 7% in Sir group (1 case of sepsis due to pulmonary tuberculosis at 4th month) and 3% in Tac group (1 case of primary renal graft dysfunction of vascular cause- renal venous thrombosis). At the end of the follow-up period all patients were alive.

Table IV

Adverse events and side effects during the first post-transplant year

	Sir group (n=15)	Tac group (n=33)	*p*
Dyslipidaemia at 12 months			
Mean serum cholesterol › 200mg/dl	86%	52%	0.04
Mean serum cholesterol (mg/dl)	258.6±59.6	191.0±39.6	0.001
Mean serum LDL-cholesterol › 100 mg/dl	93%	62%	0.04
Mean LDL-cholesterol (mg/dl)	163.5±49.6	120.3±33.5	0.02
Mean serum triglycerides › 150 mg/dl	77%	25%	0.003
Mean serum triglycerides (mg/dl)	181.8±85.5	125.4±93.0	0.007
Statin use	71%	24%	0.005
Anaemia at 12 months			
Mean haemoglobin (g/dl)	12.3±1.6	13.5±1.6	0.02
Mean haemoglobin ‹ 11g/dl	14%	3%	ns
Erythropoietin use	7%	4%	ns
Leucopoenia at 12 months			
Mean white blood cell count at 12 months	6.6±2.3	6.2±1.7	ns
Inducing adjustment of MMF dose	27%	3%	0.02
Abnormal liver tests	13%	6%	ns
Proteinuria at 12 months			
Mean proteinuria at 12 months (mg/24h)	716.8±1099.6	239.9±287.7	ns
Proteinuria at 12 months › 500mg/24h	31%	14%	ns
New-onset Diabetes Mellitus[a]	7%	16%	ns
Diarrhoea	–	12%	ns
Mouth ulcers	7%	–	ns
Lymphocele	7%	–	ns
Tremor	–	6%	ns
Ureteral stricture repair	13%	3%	ns
Urine leak	7%	–	ns
Unstable *angina pectoris*	–	3%	ns

[a] Post-transplant diabetes mellitus was defined following the diagnostic criteria of the American Diabetes Association[31] (symptoms of diabetes plus casual glucose concentration ≥ 200 mg/dl or fasting level ≥126 mg/dl or 2 hrs post load glucose ≥200 mg/dl during an oral glucose tolerance test) in patients without glucose metabolism impairment prior to transplant.

DISCUSSION

The optimal immunosuppressive therapy in renal transplantation is not yet established. The two major goals are to avoid acute rejection and to limit the numerous side effects of the immunosuppressive agents.

CNI avoidance is a highly valuble aspiration in renal transplantation. Sirolimus is a potent immunosuppressor that has raised the possibility of renal transplantation with low acute rejection incidence and without CNI-induced nephrotoxicity[12-17].

Previous studies showed that Sirolimus *de novo* scheme with monoclonal antibody induction was associated with low acute rejection incidence, similar to those found with CNI[12]. However in our study, the CNI-free regimen using Sirolimus-MMF-steroids after Basiliximab induction led to a significantly higher biopsy proven acute rejection rate than a regimen of Tacrolimus-MMF-steroid early withdrawal (47% *vs.* 9%; p=0.007). Moreover, histological severity appeared to be increased in Sir group, although the difference was not statistically significant.

The most important aim of CNI avoidance is supposed to be an improvement in renal function and prevention of the almost inevitable long-term renal function decline. Considering post-operative renal function, the current study showed no significant differences between the two regimens. However, delayed graft function rate (DGF) was higher in Sir group (27% *vs.* 15%), as previously reported by other transplant centres[20-23]. It has been suggested that Sir delays recovery from DGF by induction of renal tubular cell

apoptosis in the acute tubular necrosis setting[22] and it has been associated with a unique form of allograft cast nephropathy[23]. In addition, although the Sirolimus group exhibited a sustained higher GFR value than the Tacrolimus group, no statistical difference was found in renal function during the first 3 post-transplant years. A possible explanation for this lack of relevant difference between the two groups could be the significantly higher acute rejection rate exhibited by the patients treated with Sirolimus, since acute rejection has been considered one of the major factors affecting subsequent renal function[24]. Additionally, more severe histological acute rejection episodes presented in the Sirolimus group are more likely to herald chronic allograft dysfunction than less-acute severe rejections in the Tacrolimus group[3]. Another reason for the lack of benefit in terms of renal function of Sirolimus compared to CNI regimens might be the use of Tacrolimus, considered to be less nephrotoxic than Ciclosporin[25]. Larson *et al.* have already reached this conclusion in a large randomised trial of complete avoidance of CNI comparing Sirolimus to Tacrolimus[15].

In terms of safety, our study demonstrated that toxic profiles were different in Sirolimus-based and Tacrolimus-based regimens, each one having unique complications following previously published experience[26]. The most significant adverse effects in the Sirolimus group were hyperlipidaemia (occurring via the inhibition of lipoprotein lipase[27]) with more patients requiring pharmacological treatment than with Tacrolimus and still exhibiting higher mean serum cholesterol and triglycerides levels at 1 year, and leucopoenia requiring MMF dose adjustment. Abnormal liver tests and development of proteinuria were also common with Sirolimus, although no statistical difference was found between groups. Possible mechanisms for Sirolimus particular tubular toxicity have involved reduced tubular protein reabsorption, podocyte dysregulation and over-expression of vascular endothelial growth factor that enhances wall permeability leading to collapsing focal segmental glomerulosclerosis[28-30].

The immunosuppressant-related side effects (infection, malignancy, post-transplant lymphoproliferative disease) were similar in both groups, while the frequency of infectious complications was higher in the Sirolimus group, affecting over 70% of the recipients and leading to one case of graft failure.

Considering transplant outcomes, graft loss frequencies were comparable in both groups and patient survival was registered at 100% at the end of the follow-up time.

Despite the small number of patients and the difference in groups dimension and follow-up time, our data demonstrated that initial immunosuppression with Sirolimus-based regimen was related to a lower efficacy in preventing acute rejection and with similar graft function during the first 3 years in comparison with Tacrolimus-steroid early withdrawal-regimen. Although each regimen had a unique toxicity profile, immunosuppressant-related side effects were statistically comparable in both groups. Sirolimus, however, was associated with a higher frequency and severity of infectious complications. We concluded that Sirolimus *de novo* use with monoclonal antibody induction had an unacceptable acute rejection risk and that CNI are still needed, at least in the early post-transplant period.

Conflict of interest statement. None declared.

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