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ORIGINAL ARTICLE

Evaluation of the efficacy and safety of a slow conversion from calcineurin inhibitor- to sirolimus-based therapies in maintenance renal-transplant patients presenting with moderate renal insufficiency

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Summary

This prospective study assesses over a period of 6 months, the variations in glomerular filtration rate (GFR) and safety parameters within a cohort of 44 cadaveric renal-transplant (RT) patients presenting with moderate renal insufficiency. They were progressively switched from calcineurin inhibitors (CNIs) based- to sirolimus (SRL) based-therapies aiming SRL troughs at levels ~8 ng/ml (range 6–10). All the patients were receiving in addition mycophenolate mofetil. The intent-to-treat (ITT) patient and graft survivals were 100%. Thirty-four patients, i.e. 77.3% completed the study. Overall, there was a significant improvement in the calculated GFR (Nankivell formula) from day 0 to month 6, i.e. from 45.98 (±16.3) to 53.07 (±12.68) ml/mn ($P = 0.03$). However, renal function improved in only 20 cases (group I), and deteriorated in the others (group II). Groups I and II did not significantly differ with respect to time between transplantation and drug switch, GFR, serum creatinine, and proteinuria at baseline. There was only one case of steroid-sensitive acute rejection. Overall, there was a significant increase in proteinuria from 0 (0–3.15) to 0.57 (0–4.85) g/day ($P = 0.002$). Finally, the conversion was associated with a significant increase in lipids, and a significant decrease in hemoglobin levels.

Introduction

In the last decade, the long-term results in organ transplantation, particularly those for renal transplantation, have improved, particularly due to the use of calcineurin inhibitors (CNIs) such as cyclosporine A and tacrolimus. However, these drugs have side effects amongst which is nephrotoxicity. Hence, in solid-organ transplantation, renal insufficiency of the native kidneys is an important issue, which can lead more often to the use of non-nephrotoxic immunosuppressants [1]. Following renal transplantation, the leading cause of late graft loss among surviving recipients is chronic allograft nephropathy (CAN), which is a nonspecific process. Clinically, this process is associated with an inexorable decline in renal function with time, and is associated in renal biopsy with suggesting features [2]. Risk factors that are statistically associated with CAN include both immune and nonimmune mechanisms [3]. Amongst the latter is CNI-related nephrotoxicity. Thus, recently, the longitudinal evolution of CAN over a 10-year period has been studied by Nankivell *et al.* [4]. They observed that, in recipients with kidney–pancreas transplants, the continuous use of CNIs is associated with scarring of the kidney transplants and this occurred in almost all the patients at 10 years with severe lesions at 10 years in 58.4%. Recently, a study has

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shown that the conversion from cyclosporine to azathioprine at 3 months post-transplantation reduced the incidence of CAN; thus, the relative risk of chronic allograft nephropathy was significantly higher in the group that continued cyclosporine [relative risk, 4.3 (95% CI, 1.4–12.9); $P = 0.009$] [5]. The introduction of target rapamycin (TOR) inhibitors, e.g. sirolimus, everolimus, a new class of potent immunosuppressants, has made it possible to develop alternative immunosuppressive combinations [6]. The blockade of mammalian TOR (mTOR) results in the inhibition of IL2-induced lymphocyte proliferation, and of intima proliferation in the vasculature, which is a hallmark of CAN [6]. These properties, associated with the fact that mTOR inhibitors do not appear to be associated with the nephrotoxicity that is a hallmark of the CNIs, has made these drugs a promising alternative to CNI-based immunosuppression in renal-transplant (RT) patients. Recently, it has been demonstrated that either early cyclosporine withdrawal, i.e. month 3 post-transplantation from a sirolimus plus cyclosporine regimen (the RMR study) [7,8], or sirolimus-based therapy without CNIs [9], when given to *de novo* RT patients, resulted in long-term improved renal function, and a diminished prevalence of CAN compared with RT patients who received a CNI-based regimen or cyclosporine A in combination with sirolimus. A recent systematic review of randomized trials has shown that CNI withdrawal at early post-transplant, i.e. before month 3, is associated with an increased risk of acute rejection in the short term with a significant improvement in renal function and a reduction in hypertension [10]. Some reports have demonstrated the safety of CNI withdrawal and the introduction of sirolimus, for various reasons, in chronic RT patients: this has been associated with immediate renal benefits in the majority of reports [11,12,13,14]. Recently, a study reported on the 1-year results of a prospective cohort of RT patients presenting with CAN who switched from CNI to sirolimus with an overlap of 1–2 months [15]. The only independent predictor for positive outcome after conversion from CNI to sirolimus was a proteinuria rate below 800 mg/day. Finally, Stallone *et al.* [16] reported that sirolimus introduction/CNI withdrawal was associated with a reduction in interstitial and vascular alpha-smooth muscle actin expression, slowing down the progression of allograft injury in patients with CAN. The aims of our prospective study, performed in a cohort of RT patients converted from CNI-based immunosuppression to sirolimus-based immunosuppression for chronic allograft dysfunction, were (i) to assess the change in calculated glomerular filtration rate (Nankivell formula) at 6 months postconversion, and (ii) to assess the tolerability of such a conversion.

Patients and methods

This was a noncomparative, open-label, out-patient pilot study conducted at five French kidney-transplant centers. The enrolment period was 18 months and the treatment period was 6 months. Forty-four adult kidney transplant patients were included across the participating centers. All the patients, who received at least one dose of sirolimus (Rapamune® Wyeth Pharmaceuticals Inc., Raritran, NJ, USA), were included in the safety analysis. The study was approved by the ethical committee of the Nancy University hospital. Eligibility criteria to participate in the study included (i) an age between 18 and 70 years old, (ii) recipient of a first or second kidney transplant, (iii) a functioning graft with a stable serum creatinine between 160 and 265 μmol/l, (iv) a renal transplant performed 0.25–8 years ago, and (v) calcineurin-inhibitor-based immunosuppression. Exclusion criteria included (i) an acute rejection episode within the previous 3 months, (ii) patients with grade III chronic allograft nephropathy (according to Banff 1997 classification) because most of these patients often have overt proteinuria, (iii) a malignancy within the 5 years before entering the study, (iv) patients testing positive for human immunodeficiency, hepatitis B or C viruses, and (v) patients with baseline total white blood cell count (WBCC) of $<3000/mm^3$, platelet counts of $<100\ 000/mm^3$, fasting triglycerides of >4 g/l, fasting total cholesterol of >3 g/l, fasting HDL-cholesterol of <300 mg/l, and fasting LDL cholesterol of >2 g/l. A transplant biopsy was not mandatory prior to inclusion in the study.

Conversion protocol

Patients received 6 mg sirolimus as a loading dose on the first day of conversion (D0), then 2 mg sirolimus daily from D1 to D7 of conversion. On D0 of conversion, the daily calcineurin inhibitor (CNI) dose was reduced by 50%. Monitoring of CNI 12 h and SRL 24 h whole-blood trough levels were assessed on D7: if the SRL whole-blood trough levels were greater than 5 ng/ml per day then CNI was reduced by 50%. If the SRL whole-blood trough levels were <5 ng/ml, CNI was continued at the same dose until SRL whole-blood trough levels reached 8 ng/ml. Finally, if the SRL whole-blood trough levels were >8 ng/ml, CNI daily dosage was decreased by 50% and SRL dosage was decreased in order to obtain a trough level of 8 ng/ml at D14. SRL whole-blood trough levels were monitored at D14: if this was >8 ng/ml, CNI was discontinued; if it was <8 ng/ml, CNI was continued at the same dosage until the SRL whole-blood trough levels reached 8 ng/ml. CNI trough levels were also monitored on D14 and D21. To adapt SRL trough levels, we

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used the following formula: new dose (mg) = current dose (mg) × target trough level (ng/ml)/SRL trough level (ng/ml).

Patients withdrawn from the study were not replaced, regardless of the reason for withdrawal. Patients who withdrew or discontinued medication before the end of the protocol-mandated treatment period were given a clinical exam and were assessed for the vital signs of blood pressure, pulse, temperature, hematological, and biochemical parameters, sirolimus whole-blood trough levels, and calculated GFR at 1 week and at 1 month postdiscontinuation.

Concomitant immunosuppression and other treatments, i.e. mycophenolate mofetil, were mandatory at a minimum of 500 mg BID from D0 to month (M) 6. Steroids were administered according to local standard practice, to not exceed a daily dose of 15 mg, but a minimum dosage of 5 mg was required. In cases of acute rejection, an initial treatment with steroids, of IV methylprednisolone pulses, was recommended according to local standards of care. Standard prophylaxis against *Pneumocystis jiroveci* pneumonia was required during the first 6 months postconversion. Scheduled visits were at days 0, 7, 14, 21, and at months 1, 2, 3, and 6. At each visit there was a complete physical exam, a recording of vital signs, an assessment of parameters including hematological (hemoglobin, WBCC, platelet count), biochemistry (serum creatinine), calculated GFR according to the Nankivell formula, i.e. (6.7/plasmatic creatinine in mmol/l) + (weight/4) − (plasmatic urea in mmol/l/2) − (100/height^2 + C (35 for men; 25 for women), and sirolimus trough levels.

Statistical Analysis

Results are expressed as mean ± standard deviation (SD) or median (ranges). Primary end-points, i.e. the mean and median GFR between preconversion and postconversion values at 3 and 6 months, are reported with their associated 95% confidence limits. Analyses of the continuous secondary endpoints were done in a similar way to the analysis of the primary endpoint. All patients who received at least one dose of Rapamune® were evaluated for safety.

Results

The ITT patient and graft survivals were 100%; only one patient experienced acute rejection during the study period. Table 1 summarizes the characteristics of the 44 patients included in the study. Their mean time since transplantation was 3.3 (±1.95) years. All were recipients of a cadaveric transplant. Of the 44 patients, 34 (i.e. 77.3%) completed the study (see Fig. 1). Withdrawal from the study was only due to an adverse event in four cases [one for acnea, one for anemia plus bronchitis; two for acute pyelonephritis (APN)]; for the other withdrawals, this was due to either a protocol deviation or patients voluntarily withdrawing from the study. Most of the patients were male (75%), with initial end-stage renal disease glomerulonephritis in 38.6% of cases, and most patients (77.3%) had no panel reactive antibodies. Their mean age was 44.6 (±12.9) years. Finally, the baseline GFR according to the Nankivell formula was 46 (±16.3) ml/mn.

Table 1. Characteristics of the study population.

	Number of patients	Percentage of patients	Mean ± SD
Gender (M:F)	33:11	75/25	–
Age			44.6 ± 12.9
Etiology of renal failure			
Glomerulonephritis	17		
Interstitial nephropathy	5		
PKD	7		
Others	15		
Peak PRA > 0	10	22.7	
Current PRA > 0	4	9	
HLA mismatches			3.3 ± 1.3
Time since RT (year)			3.3 ± 1.9
Estimated GFR (ml/mn) (Nankivell formula)			45.98 ± 16.3

SD, standard deviation; M, male; F, female; PKD, polycystic kidney disease; PRA, panel reactive alloantibodies; HLA, human leukocyte antigens; RT, renal transplantation; GFR, estimated glomerular filtration rate according to the Nankivell formula.

Table 2 lists the data for the daily doses of sirolimus as well as for SRL whole-blood trough levels throughout the study period. From day 0 to M6, there were significant variations in the daily dosage of sirolimus ($P = 0.0004$) because of the need to maintain sirolimus trough levels within the desired range. Thus, in order to maintain SRL trough levels at around 8 ng/ml, the SRL daily dosage was increased from 2 (±0.2) at D7 to 3.7 (±1.7) mg/day at M6, i.e. to give SRL whole-blood trough levels of 9.9 (±8.9) and 7.8 (±2.9) ng/ml, respectively. With respect to CNI trough levels, for those on cyclosporine A, CsA trough levels were 169 (±138), 86.13 (±111), and 65 (±64) ng/ml at D0, D7, and D14, respectively. For those on tacrolimus, trough levels were 3.7 (±1.8), 2 (±0.9), and 2.1 (±1.2) at D0, D7, and D14, respectively. Elimination of CNIs was achieved, at the latest, by 1 month after introducing sirolimus. The daily dosage of mycophenolate mofetil was decreased from 1.65 (±0.64) to 1.18 (±0.57) g/day from D0 to D7, increased to 1.47 (±0.64) g/day at D14, and remained stable thereafter, i.e. 1.41

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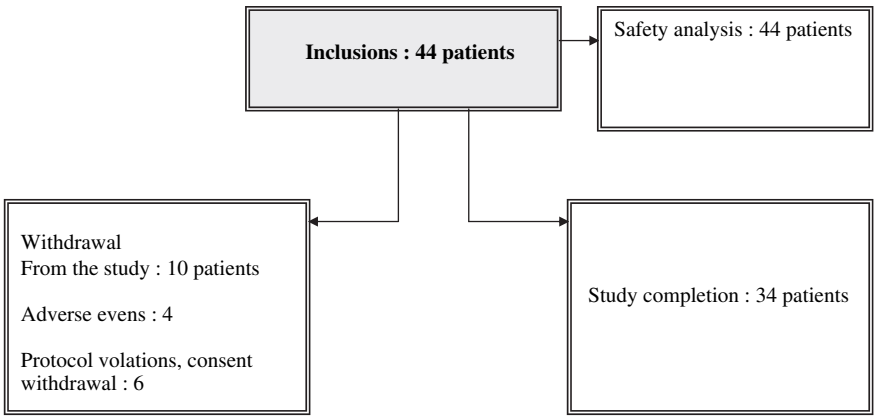

Figure 1 Flow charts of the study population.

Table 2. Data for the daily doses of sirolimus (mg/day) as well as for SRL whole-blood trough levels (ng/ml) throughout the study period.

	Sirolimus daily dosage (mg/day)	Sirolimus trough levels (ng/ml)
D0	6.6 ± 2.4	NA
D7	2 ± 0.2	9.9 ± 8.9
D14	2.3 ± 0.7	7 ± 4.8
D21	2.8 ± 1.4	7.3 ± 2.8
M1	3.2 ± 1.1	8.9 ± 3.2
M2	3.6 ± 1.7	9.2 ± 3.1
M3	3.7 ± 1.6	8.4 ± 2.8
M6	3.7 ± 1.7	9.9 ± 8.9

D, day; M, month; NA, not applicable.

Table 3. Most frequently reported adverse events after the switch from calcineurin- to sirolimus-based therapy.

	Number of patients	Percentage of patients
Hyperlipidemia	16	36.3
Anemia	15	34.1
Acnea, folliculitis, cutaneous eruption	12	27.2
Digestive disorder	10	22.7
Proteinuria	7	15.9
Bronchitis and cough	7	15.9
Edema	5	11.3

(±0.44) g/day at M6 (P = NS). When compared with D0, there was a significant improvement in renal function, i.e. calculated GFR increased from 47.6 (±15.2) to 57.25 (±11.4) ml/mn by M6 ($P = 0.03$) for 20 cases (group I), calculated GFR was stable in one case, but deteriorated in 10 cases (group II) from 50 (±11) to 45.65 (±11.9) ml/mn by M6; values were missing for three patients. Groups I and II did not significantly differ with respect to time between transplantation and switch from CNIs to SRL, calculated GFR, serum creatinine, and proteinuria at baseline.

Safety evaluation

Safety analyses were performed on a total of 44 patients. There was a total of 151 adverse events (AEs) reported during the study. Table 3 shows the most frequently observed AEs. The most frequent incident was hyperlipidemia (36.3%). Hematological AEs, such as anemia, leucopenia, and thrombopenia, were reported in 34.1%, 6.8% and 6.8% of patients, respectively. Pneumopathy was reported in one case (2.2%), bronchitis and cough in 15.9%, and mouth ulcerations in 9%. Serious adverse events (SAEs) were reported in 12 cases, which occurred in 10 patients. Of these, according to the investigator's opinion, ten cases were probably not related to the study drug, whereas two possibly were. These SAEs included acute pyelonephritis ($n = 3$), severe anemia ($n = 2$), gastroenteritis ($n = 1$), peptic esophagitis ($n = 1$), benign intracranial hypertension ($n = 1$), hypoxic pneumonia ($n = 1$), overt *Pneumocystis jiroveci* pneumopathy in a patient who had no prophylaxis ($n = 1$), increase in serum creatinine with proteinuria ($n = 1$), and acute rejection ($n = 1$).

Proteinuria

Data on proteinuria were prospectively collected. At D0 and at M6, proteinuria data were available for 31 (70%) and 23 (52%) patients, respectively. At day 0, 28 out of 31 patients (i.e. 90.3%) had proteinuria of <0.5/g/day; this decreased to 11/23 (47.8%) at M6. Conversely, at D0, only one patient (i.e. 3.2%) had proteinuria of >1 g/day, but this increased to eight patients out of 23, i.e. 34.8% at M6. Overall, for the 17 patients who provided proteinuria data at both D0 and M6, there was a significant increase from 0 (0–3.15) to 0.57 (0–4.85) g/day ($P = 0.002$). Having no proteinuria at baseline (versus having proteinuria at baseline >0) was associated with a significant lower serum creatinine at both baseline [160 (±30)

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Table 4. Outcome of lipid parameters following the switch from CNIs to sirolimus.

	D0	M6	*P* value
Triglycerides (g/l)	1.41 ± 0.71	1.99 ± 1.16	0.0024
Total cholesterol (g/l)	1.92 ± 0.43	2.32 ± 0.57	0.0003
HDL cholesterol (g/l)	0.54 ± 0.15	0.57 ± 0.14	0.08
LDL cholesterol (g/l)	1.12 ± 0.37	1.33 ± 0.53	0.0088

vs. to 200 (±50) μmol/l; $P = 0.009$] and at M6 [150 (±30) vs. to 190 (±40) μmol/l; $P = 0.02$].

Hematological parameters

There was a significant decrease from D0 to M6 in hemoglobin level [12.67 (±1.48) vs. 12.03 (±1.35) g/dl; $P < 0.0001$] and in mean corpuscular volume [90 (±52) vs. 81.5 (±3.7) fl; $P < 0.0001$]. At D0, three patients out of 44 (i.e. 6.82%) were on recombinant erythropoietin (rEpo) therapy. After the switch, 11 patients required rEpo, i.e. at M6, 8 out of 34 patients (23.5%) of patients were receiving rEpo therapy. Conversely, with respect to the WBC and platelet counts, there was no statistical difference from D0 to M6. With respect to lipid profiles after the switch, there was a significant increase in triglycerides, total and LDL cholesterols, whereas the increase in HDL cholesterol did not reach a level of significance (see Table 4). However, the number of patients on lipid-lowering agents was similar at D0 and M6, i.e. 17 patients, although six patients required the onset of this therapy. Finally, the number of patients receiving antihypertensive drugs at D0 and M6 was 31 and 25, respectively, although this treatment was commenced during the study for three cases and discontinued for two others.

Discussion

This single arm pilot study was conducted using the data from 44 RT patients with renal allograft dysfunction and shows that a slow conversion protocol from CNI-based immunosuppression to sirolimus-based immunosuppression is associated with a significant improvement in glomerular filtration rate for the majority of on-therapy patients. Two populations emerged in this analysis: responders (20) and nonresponders (10). This is comparable to what was observed in Weber *et al.*'s study where 66.7% of patients who were switched from CNIs to SRL for various reasons had renal improvement [13]. Very few studies have been carried out in patients with renal allograft dysfunction. However, recently, Dickmann *et al.* [15] performed a study in 59 RT patients with chronic allograft nephropathy as evidenced by a kidney biopsy. The RT patients were progressively switched from CNI to sirolimus. After 1 year, serum creatinine had improved in 54% of patients, from 27.5 (±7.5) to 22.2 (±6.4) mg/L. They identified only one predictive factor for responding to sirolimus conversion: low proteinuria of <800 mg/day at conversion, which was an independent predictor for positive outcome after conversion from CNI to SRL. Another recent study evaluated the predictive factors associated with renal-function improvement after converting 43 RT patients from CNI- to sirolimus-based therapy for chronic allograft dysfunction [17]. After a mean follow-up postconversion of 27 (±1.5) months, they found a significant improvement in renal function, i.e. creatinine clearance (CC) increased from 49.4 (±14.9) to 53 (±16.3) ml/mn at M1 ($P = 0.01$), to 54.7 (±20) ml/mn at M6 ($P = 0.01$), and identified three independent predictive factors for renal response to the switch, i.e. an absence of proteinuria, the presence of antihypertensive therapy at D0, and LDH levels at D30. In that study, renal-function improvement was not translated into renal allograft histology improvement. A recent study showed that after conversion from CNI-based to sirolimus-based immunosuppression in kidney transplant patients with CAN alpha-smooth muscle actin (SMA) expression is dramatically reduced on kidney biopsies 24 months after conversion, whereas in those patients which remained on CNI therapy there was conversely an increase in alpha-SMA expression (16). This finding might result in a slowing down of progression of allograft injury in patients with CAN. There have been other reports of conversion from CNI-based immunosuppression to sirolimus in chronic renal-transplant patients. Dominguez *et al.* [11] studied 20 patients, including 12 with CNI toxicity, with a short follow-up of 6 months. They found a significant improvement in renal function. Citterio *et al.*[12] studied 19 RT patients with progressive allograft dysfunction; their conversion was abrupt, and renal function stabilized or improved in 57% of patients. Finally, Wali *et al.* reported on 107 RT patients with biopsy-proven CAD where, after conversion from CNIs to SRL, creatinine clearance improved among 70% of patients. Interestingly, the most significant benefit was observed among the subgroup with lower baseline creatinine clearance values before conversion [18]. Other reports of conversion to SRL in patients with moderate renal insufficiency or chronic allograft nephropathy revealed similar results: only a low risk of acute rejection episodes (<7%) or graft loss, and a trend towards improved or stable renal function. However, a large fraction of patients, i.e. up to 30%, discontinued the regimen because of adverse effects of SRL [19,20].

We observed, as others have, that sirolimus conversion is associated with a significant increase in proteinuria, from a median of 0 at day 0 to a median of 0.57 g/day at the end of the study period. Proteinuria was reported as an adverse

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event in 16% of patients. An increase in already-present proteinuria or cases of *de novo* proteinuria are a major side effect of conversion from CNIs to SRL. Diekmann *et al.* found that, after 1 year of conversion to SRL, proteinuria was stable in responders, whereas it almost doubled in non-responders [15]). In Bumbea *et al.*'s study, at conversion, almost all patients had no proteinuria, i.e. <150 mg/day, with only a few percent having proteinuria ranging between 0.5 and 1 g/day. At 1 and 2 years after conversion, 19.4% and 20.6% of patients had proteinuria values >1 g/day. In addition to these, five patients developed nephrotic-range proteinuria. In all these cases, the biopsy performed at that time showed lesions of *de novo* focal and segmental hyalinosis superimposed to pre-existing glomerular double contour lesions [17]. These observations, *de novo* focal and segmental hyalinosis lesions, have already been published in a paper describing a large series of *de novo* patients treated with high doses of SRL [18]. In long-term renal transplants it is possible that the withdrawal of CNIs leads to hyperfiltration because these drugs have vasoconstrictive properties on the renal vasculature [21,22].

The conversion to sirolimus is associated with significant increases in triglycerides, total, and LDL cholesterol. Moreover, the first ranking adverse event is hyperlipidemia, i.e. 38%. These side effects are well-known when using mTOR-based immunosuppression and are often manageable.

As far as side effects of sirolimus therapy are concerned, we found that anemia was reported in 34% of patients after conversion, i.e. the second most reported adverse event. Recently, Turkowski-Duhem *et al.* have shown that one of the most powerful independent predicting factor for anemia within the first year post-transplantation is sirolimus therapy and renal function [23]. Augustine *et al.* have also reported a prevalence of anemia of 31% with MMF compared with 57% with sirolimus-based therapy in *de novo* RT patients at 1-year post-transplantation. In a multivariate analysis, the predicting factors for anemia at 1 year post-transplantation were being an older recipient, female gender, older donor age, chronic infection, decreased renal function at 12 months, and sirolimus therapy [24]. Through mTOR inhibition, sirolimus has been shown to block S6 kinase activity and, consequently, to impair cell replication in an erythroid cell line because S6 kinase plays a role in mRNA translation in the cell: the net result is an alteration in erythroid cell development and the resulting anemia [25].

The third commonest reported adverse event is related to cutaneous problems, e.g. acnea, folliculitis, cutaneous eruption in 27% of patients. Cutaneous problems are well-identified side effects of sirolimus-based therapy. Thus, Mahe *et al.* observed, in a cohort of 80 RT patients, cutaneous adverse event in 99% of the patients [26]. There was a serious adverse event in 25% of cases, which led to withdrawal of SRL in 7% of the cohort. Cutaneous lesions included acne-like eruptions (46%), scalp folliculitis (26%), and hidradenitis suppurativa. Despite the high frequency of cutaneous adverse events on SRL therapy, these are usually easily managed, and rarely lead to SRL discontinuation.

Finally, no serious pulmonary side effects were observed, even though bronchitis/cough were reported in 16% of patients. Pneumopathy was observed in only one patient and was not considered SRL-related. This is reassuring because sirolimus has been associated with specific pneumonitis [11,27] as well as with bronchiolitis obliterans organizing pneumonia (BOOP) [28].

We conclude that conversion from CNIs to SRL in RT patients with chronic allograft dysfunction, and taking in addition mycophenolate mofetil is associated with improved renal function in two-thirds of patients; however, 22% of patients dropped out of the study. The most frequent adverse events included hyperlipidemia and anemia. This single arm pilot suggests that (i) successful conversion to a sirolimus-based regimen can be achieved in a subset of patients (to be further defined), (ii) proteinuria is associated with conversion, by a mechanism that remains unclear, and (iii) the AE profile was consistent with previous reports.

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