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Sirolimus for calcineurin inhibitors in organ transplantation: *contra*

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Sirolimus (SRL) is an antiproliferative agent inhibiting the mammalian target of rapamycin (mTOR) proposed as a non-nephrotoxic alternative to calcineurin inhibitors for the prevention of acute rejection in renal transplantation. Despite initial encouraging results, enthusiasm faded with large trials showing an increased risk of acute rejection with this molecule that did not provide superior graft function over cyclosporin or tacrolimus. Recent data showed that SRL, along with an immunosuppressive activity on $CD4^+$ T cells, exerts a paradoxical stimulatory effect on innate immunity, which may explain its incomplete control of alloimmune response. Moreover, SRL therapy is burdened by a concerning safety profile including high risk of delayed graft function and onset of proteinuria. This adds to many other adverse effects, including dyslipidemia, diabetes, myelosuppression, delayed wound healing, infertility, ovarian cysts, and mouth ulcers, that further limit the use of this molecule. Severe cases of interstitial pneumonia have also been reported with this therapy, raising additional concerns. Incomplete control of immune response, along with a poor tolerability, makes SRL far from being the ideal antirejection drug. Progressive restrictions of SRL indication in renal transplantation have, however, been paralleled by evidence showing mTOR abnormalities involved in many pathogenic conditions, thus opening the avenue to new possible applications of this molecule.

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Sirolimus (SRL) and its cognate drug RAD001 (everolimus) are immunosuppressive drugs that act by inhibiting mammalian target of rapamycin (mTOR), an essential regulator of cell cycle able to block lymphocyte proliferation upon cytokine engagement.[1,2] They have been proposed as an alternative antirejection therapy to calcineurin inhibitors for renal transplantation, in light of their immunosuppressive and antiproliferative properties devoid—according to initial reports—of renal toxicity. Most of the promises of mTOR inhibitors, however, have not been fulfilled. Indeed, large trials showed that SRL therapy is associated with an increased risk of acute rejections and worse graft function as compared with cyclosporine (CsA) or tacrolimus (Tac).[3] Moreover, its poor tolerability results in treatment withdrawal in up to 50% of patients due to uncontrolled hyperlipidemia, delayed wound healing, or mouth ulcers.[4,5] Additionally, nephrotoxicity has been reported with increasing incidence and raised further concerns on the safety profile of this molecule.[6] Recent experimental evidence also revealed that final effect of mTOR inhibition *in vivo* is more complex than initially thought. Indeed, the suppression of $CD4^+$ effector T cells with SRL therapy is paralleled by a boost of memory $CD8^+$ T lymphocytes, which on the one hand may account for the poor antirejection activity of this drug and on the other one provides an explanation for the frequently reported signs of immune system activation, such as interstitial pulmonary disease and chronic disease anemia.[7]

Therefore, limited immunosuppressive activity, along with a concerning safety profile, strongly limits the use of this molecule in the transplant arena. Despite these limitations, however, it can be estimated that approximately 5–15,000 patients in the United States and 4–12,000 in Europe, accounting for 5–15% of the overall population of recipients of a kidney transplant over the past 10 years, are exposed to maintenance therapy with SRL-based immunosuppressive regimens.[8–10]

EARLY PROMISES FROM mTOR INHIBITORS HAVE NOT BEEN FULFILLED

Initial trials found that SRL had a superior antirejection effect over placebo[11] or azathioprine[12] in renal transplant patients receiving steroids and full-dose CsA. This, along with the expected renal safety of SRL, prompted face-to-face

comparisons between this molecule and CsA. When added to steroids and azathioprine immunosuppression, the two drugs were associated with a similar rejection rate that was close to 40%.[13] However, when the two drugs were added to a steroid- and mycophenolate mofetil-based immunosuppressive regimen, the rejection rate was remarkably lower (20%) in patients allocated to CsA than in those on SRL (30%). Difference in the antirejection potency between mTOR and calcineurin inhibitors became clearer when induction therapy with anti-CD25 antibody was added to the immunosuppressive armamentarium. The largest prospective, randomized, controlled trial in renal transplant recipients, the Efficacy Limiting Toxicity Elimination-Symphony Study, showed that among renal transplant recipients induced with daclizumab and maintained on chronic immunosuppression with mycophenolate mofetil and steroids, those randomized to SRL had the lowest glomerular filtration rate and highest rate of acute rejections at 1 year compared with those on Tac or CsA. Notably, among subjects on calcineurin inhibitor therapy those on Tac appeared to have the best outcomes (Table 1).[3]

These clinical findings are in line with *in vitro* evidence that SRL has a lower immunosuppressive activity as compared with calcineurin inhibitors on $CD8^+$ memory T cells.[14] Importantly, conversion from CsA to SRL is associated with an expansion of memory T cells in renal transplant patients with Kaposi sarcoma.[15] This is likely associated with an anticancer effect, but increases the risk of acute rejection.

Along the same lines, results from basic immunological research recently showed that, in contrast with what initially expected, the $CD8^+$ response to various viral stimuli was enhanced, rather than suppressed, by SRL therapy in mice and in non-human primates.[7] Notably, SRL titrated to blood levels of 5–20 ng/ml resulted into an expansion of memory $CD8^+$ T cells and SRL-treated lymphocytes exhibited improved functional qualities, such as optimized recall responses and increased protective properties against viral infections.[7,16] During the expansion phase, SRL increased the number of memory precursors, and during the contraction phase (effector to memory transition) accelerated the memory T-cell differentiation program. Conversely, T-memory cell response was blunted when higher doses targeting blood levels of 40–100 ng/ml were administered.[7] Considering that in renal transplant patients SRL target levels normally range from 5 to 15 ng/ml,[17] the data by Araki *et al.*[7] suggest that in clinical practice SRL therapy is expected to enhance rather than reduce the response of T-memory cells. Higher doses targeting levels associated with T-memory cell inhibition cannot be reached in this setting due to the excess risk of serious adverse events.[18] Moreover, if administered 8 days or later after infection in non-human primates, SRL therapy enhanced memory T-cell function and recalled ability independent of achieved serum levels.[7] Thus, in clinical transplantation, SRL therapy is not expected to have specific tolerogenic effects, and the possibility of a reduced antirejection efficacy mediated by memory T-cell activation should be taken into consideration.

Moreover, mTOR has been found to promote proinflammatory cytokine production by monocytes, macrophages, and peripheral dendritic cells following contact with Gram-negative and Gram-positive stimuli. Hence, inhibition of mTOR in these cells results in their immune activation, as confirmed by the upregulation of interleukin-12, interleukin-23, and the tumor necrosis factor *in vitro*. This may explain why introduction of SRL has been associated with an increased frequency of unexplained interstitial pneumonitis in organ transplant patients. Intriguingly, another indirect sign of a proinflammatory effect of SRL is the high incidence of anemia with this drug. Indeed,

Table 1 | Main randomized clinical trials of SRL versus CsA in renal transplant patients on immunosuppressive therapy with steroids plus MMF or AZA

Study	Immunosuppressants in addition to steroids	Study drugs	Patients (no.)	Follow-up (months)	DGF (%)	Acute rejection (%)	Graft survival (%)	Estimated GFR[a] (ml/min)	Study drug withdrawal (%)
Durrbach *et al.*[66]	RATG, MMF	SRL	33	6	45.4	12.1	87.5	44.7	48.5**
		CsA	36		30.6	8.3	97	41.9	16.7
Ekberg *et al.*[3]	Daclizumab, MMF	SRL	399	12	21.1**	40.2**	91.7**	56.7**	6.8
		CsA	399		32.4	27.2	94.3	59	5.1
Büchler *et al.*[28]	RATG, MMF	SRL	71	12	18.6	14.3	90	60	28.2
		CsA	74		12.3	8.6	93	57	14.9
Pescovitz *et al.*[67]	Daclizumab, MMF	SRL	30	6	23.3	40.0	100	82.7	NA
		CsA	15		13.3	13.3	100	77.8	
Flechner *et al.*[68]	Basiliximab, MMF	SRL	31	60	NA	12.9	96.4*	66.7**	NA
		CsA	30			23.3	76.7	50.7	
Kreis *et al.*[69]	MMF	SRL	40	12	25	27.5	92.5	NA	43
		CsA	38		24	18.4	89.5		26
Groth *et al.*[13]	AZA	SRL	41	12	NA	41	98	69.5	58.5
		CsA	42			38	90	58.7	45.2
Weighted average		SRL	645	13.7	22.6	33.9	92.4	51.0	17.9
		CsA	634		28.6	23.6	93.0	58.0	11.2

Abbreviations: AZA, azathioprine; CsA, cyclosporine; DGF, delayed graft function; GFR, glomerular filtration rate; MMF, mycophenolate mofetil; NA, not available; RATG, rabbit anti-human thymoglobulin; SRL, sirolimus.
[a]Mean values at last available follow-up visit. *$P<0.05$, **$P<0.001$ vs CsA. Average has been weighted by sample size.

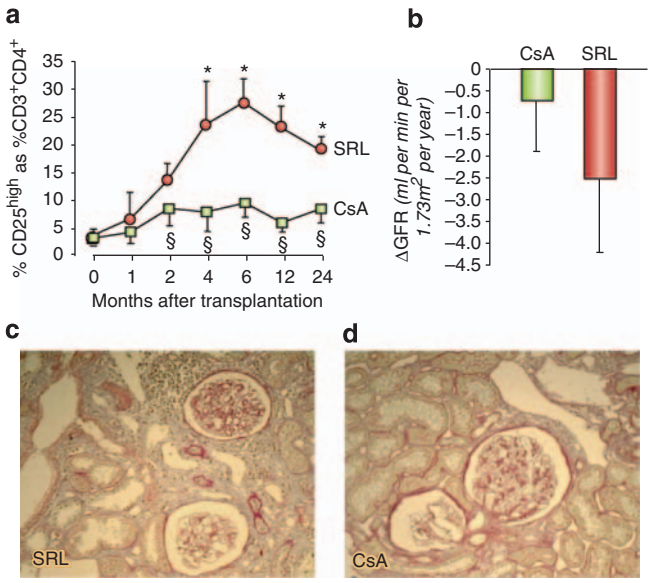

Figure 1 | Impact of SRL and CsA therapy on regulatory T cells and kidney graft outcomes. Time course of circulating $CD4^+CD25^+$ regulatory T cells (**a**) and rate of measured glomerular filtration rate (GFR) decline from month 6 to month 30 after renal transplantation (**b**) in two cohorts of patients randomized to sirolimus (SRL) or cyclosporine (CsA) therapy in combination with alemtuzumab induction and mycophenolate mofetil maintenance immunosuppression. (**c**, **d**) Show two representative photomicrographs of per-protocol renal biopsies at 2 years after transplant in patients on SRL (**c**) or CsA (**d**) therapy. All samples from SRL patients showed mild-to-moderate tubular atrophy, interstitial fibrosis with focal interstitial inflammation, and arteriosclerosis. $^*P<0.05$ vs baseline, $^{\S}P<0.05$ vs SRL at the same time point. Adapted from Ruggenenti *et al.*[23]

hemoglobin reduction is paralleled by increased expression of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α and defective IL10-dependent inflammatory autoregulation.[19]

The aforementioned clinical and experimental results concur to demonstrate that immune response during mTOR inhibition is mediated by a suppression of effector $CD4^+$ T cells, which is however counterbalanced by an activation of the innate immune response. This eventually results into a poor control of alloreactivity, which leads to an increased risk of acute rejection when SRL is used as immunosuppressive agent.[20,21]

In this context, initial enthusiasm on a stimulatory effect of SRL on regulatory T cells waned in more recent years. Indeed, although these cells may control alloreactive response and promote increased allograft survival in rodent models of transplantation,[22] a randomized controlled study found that the enhanced number of circulating regulatory T cells observed in renal transplant recipients allocated to SRL therapy compared with those on CsA was not associated with any protective effect against renal allograft injury (Figure 1).[23]

IS SRL LESS NEPHROTOXIC THAN CsA?

Early studies in animals fuelled enthusiasm on mTOR inhibitors as antirejection drugs devoid of irritating nephrotoxic effects of calcineurin inhibitors.[23] An initial small trial found that renal transplant patients on SRL therapy had significantly lower serum creatinine than controls on CsA.[13] However, this finding was challenged by data from a subsequent randomized, controlled study in 719 renal transplant patients showing that, on the top of CsA and steroid immunosuppression, SRL, compared with azathioprine, was associated with a lower graft function at 12 months after transplant, despite reduced incidence of acute rejections.[12] This was initially interpreted as the result of a poorly understood interaction between SRL and CsA that intensified the nephrotoxic effect of CsA. More recently, however, evidence came out of a specific nephrotoxic effect of SRL.

The Sirolimus Renal Conversion Trial found that, among 87 renal transplant patients with a baseline glomerular filtration rate higher than 40 ml/min, conversion to SRL approximately 3 years after transplantation was associated with increased proteinuria and no glomerular filtration rate improvement, compared with maintenance of calcineurin inhibitor therapy.[24] Even more concerning was that the Drug Safety Monitoring Board halted the entry of patients with glomerular filtration rate between 20 and 40 when the primary safety end point of acute rejection, graft loss, or death was reached by 8 of 48 patients after SRL conversion and none of the 25 in the calcineurin inhibitor continuation arm. These findings were in apparent contrast with those of the Rapamune Maintenance Regimen study showing that in 525 renal transplant recipients on SRL and steroids maintenance therapy, complete CsA withdrawal 3 months after transplantation was associated with improved allograft survival as compared with calcineurin inhibitor continuation. These findings, however, were biased by the fact that about one-fifth of patients initially enrolled in the study were not considered in the analyses because of primary non-function, patient death, or renal vascular thrombosis within 3 months since transplantation. In this group, patient and graft survival at 1 year were 82 and 55%, respectively. Moreover, at 4 years after transplant, roughly a half of the included patients withdrew the study,[5] a drop out rate remarkably higher than that observed in trials of CsA- or Tac-based immunosuppressive regimens.[25] Thus, despite the possibility to use SRL as alternative to CsA is intriguing, available data raise concern about the risk/benefit profile of this approach. Consistently, the Early Conversion from Cyclosporine to Sirolimus After Renal Transplantation study[24] showed that conversion from CsA to SRL at 3 months after transplant was associated with fast improvement of renal function compared with continued CsA therapy, but was burdened by a numerically higher incidence of acute rejections, and more frequent adverse effects, such as mouth ulcers, diarrhea, acne, and high triglyceride levels. Notably, as elegantly highlighted by Servais *et al.*,[26] graft function improvement reflected changes in glomerular hemodynamics after removal of the vasoconstrictory effects of CsA,[27] but this did not translate into any kidney structural amelioration.

The disappointing effects of SRL therapy on renal graft outcomes have been initially explained by the poor immunosuppressive effect of this drug, but they also raised concerns on a direct nephrotoxic effect of mTOR inhibitors. This possibility was consistent with evidence that in the Efficacy Limiting Toxicity Elimination-Symphony Study 5.3% of patients on SRL therapy developed proteinuria compared with 2.0% of those on CsA.[3] Along the same line, in the Sirolimus versus CsA in Kidney Recipients Receiving Thymoglobulin trial,[28] 38.8% of patients on SRL developed clinical proteinuria compared with 5.6% of those on CsA ($P<0.001$). Possible mechanisms underlying the harmful renal effects of SRL were clarified by studies showing that prolonged exposure of podocytes to mTOR inhibitor decreased the expression level of the slit-diaphragm proteins nephrin and the cytoskeletal adaptor protein Nck. SRL also reduced cell adhesion and cell motility, which was accompanied by an enhanced formation of dot-like actin-rich structures.[29] Consistently, in animal models of kidney disease, such as puromycin aminonucleoside toxicity[30] and protein overload,[31] SRL prevented podocyte regeneration and aggravated renal injury. These experimental data support a direct toxic effect of SRL on podocyte function and structure that may explain why proteinuria levels increase when renal transplant patients are shifted from CsA to SRL.[32] Moreover, detrimental effect of SRL on podocyte survival might predispose to *de novo* focal segmental glomerulosclerosis lesions reported in renal transplant patients receiving high doses of SRL.[33] mTOR blockade may also promote apoptosis of tubular epithelial cells and impair their regeneration, which has been associated with tubular dysfunction[34] and delayed recovery of renal function in some patients after transplant.[35]

On the other hand, data showing that SRL reduced tubulointerstitial inflammation, interstitial fibrosis, and compensatory renal hypertrophy in the accelerated experimental model of membranous nephropathy[36] were not eventually confirmed in humans. Indeed, SRL failed to reduce urinary proteins in nine patients with idiopathic membranous nephropathy, and in the majority of them treatment had to be prematurely withdrawn because of severe adverse events, including worsening proteinuria, acute kidney failure, or infections.[37]

Thus, experimental and clinical data converge to indicate that SRL has inherent nephrotoxicity that, however, appears to differ from patient to patient. Different susceptibility to SRL toxicity may rely on patients' genetic background, preexisting renal damage, and drug levels.[33]

REASONS FOR FURTHER CONCERN

In addition to poor immunosuppressive potency and renal toxicity, there are additional drawbacks from SRL therapy, such as dyslipidemia, diabetes, myelosuppression, mouth ulcers, and retarded wound healing, infertility, that further strongly limit SRL prescription (Table 2). Of even more concern are the cases of life-threatening interstitial pneumonitis reported in patients receiving SRL. This poor safety profile further limits the room for mTOR inhibitor use in organ transplantation.

Dyslipidemia

SRL therapy is associated with an increased incidence of hypercholesterolemia largely mediated by the reduced fractional catabolic rate of very low-density lipoprotein associated with mTOR inhibition.[38] Finding that approximately 60% of patients receiving mTOR inhibitors in clinical trials

Table 2 | Percentages of patients with major side effects other than proteinuria reported in randomized clinical trials of SRL vs CsA in renal transplant patients on immunosuppressive therapy with steroids plus MMF or AZA

Study	Study drugs	New-onset Diabetes	Hypertension	Lymphocele	Delayed wound healing	Anemia	Infections	Cancer	Hypertriglyceridemia
Durrbach *et al.*[66]	SRL	NA	No difference	24.2*	9.1	No difference	NA	3.0	NA
	CsA			2.0	2.8			2.8	
Ekberg *et al.*[3]	SRL	7.8	11.8	15.8	16.6	25.0	20.3	2.1	5.0
	CsA	4.7	11.5	6.8	11.0	17.4	22.8	0.7	2.9
Büchler *et al.*[28]	SRL	9	NA	8	NA	11.8	6*[a]	NA	No difference
	CsA	3		4		6.4	23		
Pescovitz *et al.*[67]	SRL	13.3	36.7	NA	20.0	53.3	17	NA	14
	CsA	20.0	53.3		0	6.7	7		6
Flechner *et al.*[68]	SRL	NA	No difference	19.4	6.5	NA	45.2	9.7	NA
	CsA			13.3	0		53.3	20	
Kreis *et al.*[69]	SRL	15	40	NA	NA	43	5*[a]	0	73
	CsA	16	47			29	21	0	50
Groth *et al.*[13]	SRL	20	17	NA	NA	37	14[a]	0	51**
	CsA	7	33			24	12	5	12
Weighted average	SRL	8.6	12.6	12.8	12.0	24.3	17.4	1.9	11.5
	CsA	5.2	13.5	5.5	7.1	15.2	21.8	1.9	5.8

Abbreviations: AZA, azathioprine; CsA, cyclosporine; MMF, mycophenolate mofetil; NA, not available; SRL, sirolimus.
Numbers are percentages or mean values (± s.d.) at last available follow-up visit (g per 24 h).
[a]Cytomegalovirus infection. *$P<0.05$, **$P<0.001$ vs CsA. Average has been weighted by sample size.

required lipid-lowering therapy, which is roughly twice the number of those receiving lipid-lowering therapy in comparator groups,[39,40] raises further concerns about the safety profile and cost-effectiveness of SRL therapy in the transplant population. Although the long-term consequences of mTOR inhibitor-induced dyslipidemia in kidney transplant recipients are unknown, it is reasonable to expect that subjects on SRL are at increased cardiovascular risk and in most cases might need concomitant treatment with statins or other lipid-lowering medications.

Diabetes

Another concerning metabolic effect of mTOR inhibition is the increased risk of post-transplant diabetes. In an analysis of more than 20,000 kidney transplant recipients from the US Renal Data System database, Johnston *et al.*[41] found that SRL-treated patients had a 25% increased risk of new-onset diabetes as compared with those receiving other immuosuppressive drugs.

Impaired insulin receptor substrate signaling could explain SRL-induced new-onset diabetes.[42] Other mechanisms include ectopic triglyceride deposition with SRL leading to insulin resistance,[43] impairment of insulin-mediated suppression of hepatic glucose production,[44] or a direct toxic effect on pancreatic β-cells.[45]

Myelosuppression

The myelosuppressive effect of SRL is the direct consequence of the antiproliferative activity of this compound and is exacerbated by mycophenolate mofetil co-medication.[46] This frequently results in thrombocytopenia and leucopenia. Anemia is a less frequent complication of SRL therapy and, as observed in the anemia of chronic renal insufficiency, is often associated with low levels of serum iron, high ferritin concentrations, and refractoriness to erythropoietin treatment. These changes are believed to reflect a status of chronic inflammation that in patients on SRL therapy might be sustained by a stimulatory effect on innate immunity.[20,47]

Mouth ulcers

Although not serious, this is the most frequent cause of SRL discontinuation,[48] in particular in patients on concomitant mycophenolate mofetil therapy.[49] The development of mouth ulcers is dose-related: they usually appear after the loading dose and often improve after a dose reduction.[50] Of note, topic application of clobetasol, a high-potency topical steroid, promote a prompt resolution of the mouth ulcers without the need of empiric SRL dose changes, which may expose to an increased risk of acute rejection.[50]

Impaired wound healing

Initial reports on SRL use showed an impaired wound healing in patients treated with SRL, probably as a consequence of its antiproliferative activity. Subsequent analyses suggested that this phenomenon was particularly relevant in obese patients and accentuated by the concomitant use of steroids.[51] However, a systematic program of wound care in kidney transplant recipients given SRL has been shown to reduce wound healing complications to the same rates reported with other antirejection agents. Thus, a special attention to wound care is needed in transplant patients on SRL therapy.[52]

Infertility

Different reports showed that SRL is associated with altered sex hormone levels and impaired sperm quality.[53] Renal transplant patients on chronic SRL therapy have significantly reduced total sperm count and a decreased proportion of motile spermatozoa compared with patients who did not receive SRL. Of even higher concern, the fathered pregnancy rate among patients on SRL was 20-fold lower than the one observed in patients free of SRL. In only a half of patients who interrupted SRL there was a significant improvement in sperm parameters.[53] This is a frequently underestimated toxicity of SRL that however should be taken into serious consideration.

Ovarian toxicity has also been reported in patients receiving SRL, presenting with a high prevalence of ovarian cysts of benign nature.[54,55] This suggests that evaluation of female patients on SRL therapy should include menstrual history and pelvic ultrasound, to assess the presence and monitor the progression of such alterations.

Pulmonary disease

SRL-induced pulmonary toxicity is a rare but serious entity that must be considered in the differential diagnosis of a transplant patient presenting with respiratory compromise.[49] In most cases, patients present with a constellation of symptoms and signs consisting of fever, dyspnea, fatigue, dry or productive cough, and occasionally hemoptysis. The outcome of patients with SRL-associated pulmonary disease varies and may be fatal in around 5% of cases. However, most patients resolved their clinical and radiographic findings with discontinuation or dose-reduction of the drug. High-dose intravenous steroids have been shown to accelerate recovery.[56]

The pathophysiology of SRL-associated pulmonary toxicity is largely unknown. It has been suggested that SRL may promote exposure of cryptic pulmonary antigens, resulting in lymphocytic alveolitis and interstitial pneumonitis.[57] Alternatively, a direct drug toxicity effect may be responsible for the syndrome of alveolar hemorrhage without lymphocytic alveolitis.[58] SRL-induced activation of innate immunity could represent an additional mechanism.[20]

CONCLUSIONS AND PERSPECTIVES

mTOR inhibitors have been introduced into the clinic as a potential non-nephrotoxic alternative to calcineurin inhibitors for organ transplantation, but their limited immunosuppressive effect, along with poor safety profile, dramatically limited their use in this clinical setting. In renal transplant

patients, *de novo* therapy with SRL has been associated with increased incidence of delayed graft function and acute rejections, along with reduced renal graft function compared with calcineurin inhibitor-based immunosuppressive regimens. This, along with the evidence of a direct nephrotoxic effect, made of SRL a poorly attracting alternative to CsA or Tac. Metabolic complications, together with other serious adverse effects, further limited its use in the transplant arena.[59]

On the other hand, uncontrolled activation of mTOR pathways has a central role in the development of different tumors, and mTOR inhibition has been associated with antitumor effects.[60] On the basis of this evidence, temsirolimus has been recently approved by European Medicine Agency and Food and Drug Administration for treatment of advanced renal cell carcinoma.[61] As SRL has been also associated with a reduced incidence of skin and solid organ cancer compared with calcineurin inhibitors in transplant patients, conversion to SRL appears to be a reasonable approach in those patients who develop a malignancy after kidney transplantation.

Recent findings that SRL promotes expansion of memory $CD8^+$ T cells might open the perspective of a new indication for mTOR inhibitors to stimulate the immune response to vaccines. Boosting memory T-cell response by mTOR inhibitor therapy might help inducing long-lasting protective immune memory against bacterial or viral pathogens strong enough to prevent their replication,[62] especially in transplant recipients and other immunosuppressed patients with autoimmune disorders. Consistently, SRL therapy seems to be associated with reduced incidence of BK virus infection compared with calcineurin inhibitors. Thus, conversion to mTOR inhibitors may represent a valuable option in those cases with persistent infection resistant to antiviral therapy.[63,64] Even more intriguing is the evidence that SRL can directly inhibit human immunodeficiency virus replication.[65] Altogether, the above data can be taken to suggest that no renal transplant patient should receive *de novo* SRL therapy and that the use of SRL should be restricted to very selected patients, such as those with post-transplant malignancies or, probably, treatment-resistant viral infection. In such patients, the risk/benefit profile of SRL therapy should be carefully considered on a case-by-case basis. On the other hand, in subjects with stable kidney function and no evidence of treatment-related side effects, there is no reason to stop mTOR inhibitor therapy.

Further research should aim at exploring new specific clinical indications for the immunostimulatory properties of the drug.

DISCLOSURE

All the authors declared no competing interests.

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