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Sirolimus use in de «novo renal» transplantation

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INTRODUCTION

The clinical development of sirolimus started in 1992 with the first Phase I addition pharmacokinetic studies in stable renal transplant patients maintained with cyclosporine and steroids[1]. Therefore, sirolimus was born at a time when two paradigms in post-transplant immunosuppression seemed unquestionable: irreplaceable calcineurin inhibitors as base therapy and the acute rejection percentage as the primary efficacy variable. During the last decade and as far as short-term results have steadily improved in a manner that is not parallel manner to long-term results[2], a slow shift towards an immunosuppression paradigm placing more attention on the effects on early renal function as a surrogate variable for long-term graft survival is being experienced[3]. In the future a subsequent change may be experienced placing early histology as a surrogate marker of long-term failure, which would presumably enable a reduction in sample size and follow-up time in the design of future clinical trials[4]. It is important to be aware of this paradigm change in order to understand sirolimus development and the different «de novo» regimens tested.

Table 1 lists the main characteristics of the randomized trials with sirolimus in «de novo» renal transplant.

SIROLIMUS IN COMBINATION WITH STANDARD DOSES OF CYCLOSPORINE: THE PATH TO U.S. REGISTRATION

One of the first trials consisted of an addition Phase I for adding a short 14 day treatment with sirolimus in renal recipients being treated with cyclosporine and steroids that showed that short-term toxicity was limited to a slight leukothrombopenia together with moderate hypercholesterolemia, but respected the renal glomerular filtration[5]. Previous studies in rats had likewise shown that sirolimus preserved renal glomerular filtration and renal plasma flow, although a certain degree of tubulopathy and cyclosporine-associated nephrotoxicity enhancement was observed[6,7].

Phase I/II trials (studies 123 and 203) tested the use of different «de novo» sirolimus doses with standard or reduced cyclosporine and steroid doses. The primary efficacy variable was acute rejection and both studies showed that sirolimus addiction reduced the occurrence thereof. In the one-year follow-up sirolimus apparently did not significantly exacerbate the nephrotoxic effect of cyclosporine[8,9].

Phase II studies 207 and 210 started in 1996, testing sirolimus as a base therapy against cyclosporine together with steroids and an antimetabolite. These studies showed a progressive difference in renal function favoring sirolimus[10]. However, the acute rejection incidence in both studies was the primary efficacy variable and reached 41% of the patients treated with sirolimus and azathioprine and 27% of those treated with sirolimus and mycophenolate, figures which already then seemed fairly high[11,12].

Thus, trials 301 and 302, registration phase III with 1269 patients were performed with the combination of sirolimus together with cyclosporine and steroids. Efficacy was measured in both studies by means of a compound variable including acute rejection incidence confirmed by biopsy plus patient or graft loss, and this was statistically better in the arms with sirolimus than in the comparing arm with a placebo or azathioprine[13,14]. Thus, in September, 1999, the FDA approved the continued combination of cyclosporine, sirolimus and corticoids for acute rejection prophylaxis in renal transplant. However, these studies showed a poorer glomerular filtration rate in groups with sirolimus than in control groups. Subsequent studies in rats demonstrated that maintaining

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Table I. Randomized studies with sirolimus in «de novo» renal transplant

Nº of study	First author, publication and year	N Rand.	Experimental arm with sirolimus	Control arm	Months follow-up	Experimental group findings
Combinations with cyclosporine without induction						
203	Kahan *Transplantation* 1999[9]	149	CsA (full or reduced doses) +SRL (1 or 3 mg/m^2/day) +	CsA (full or reduced doses) + Placebo +Ster	12	With SRL less acute rejections, without apparent CsA nephrotoxicity enhancement
301	Kahan *Lancet* 2000[13]	719 719	CsA+ SRL (2 mg versus 5 mg) + Ster	CsA+ Aza +Ster	12	With SRL showed less acute rejections but worse renal function.
302	MacDonald *Transplantation* 2001[14]	576	CsA+SRL (2 mg versus 5 mg)+Ster	CsA+ Placebo + Ster	12	With SRL showed less acute rejections but worse renal function.
301 and 301	Mathew, *Clin Transplant* 2004[152]	1295	CsA+SRL (2 mg versus 5 mg) +Ster	CsA+ (Aza or Placebo) +Ster	24	SRL shows less skin cancers than the control group.
309	Mathew, *J Clin Pharmacol* 2006[164]	477	SRL tablet + CsA + Ster	SRL solution + CsA + Ster	12	Slower absorption of tablet formulation (Tmax 2.1 h versus 3.4 h, p = 0.05) with no other pharmacokinetic differences. No differences in efficacy and safety. Acne reported more frequently with the oral solution (28% versus 18%, p=0.02)
154	Vincenti *Transplantation* 2002[165]	308	SRL + mCsA + Ster	SRL + CsA + Ster	6	No differences in acute rejection nor in renal function
4351	Muehlbacher *Am J Transpl* 2003[19]	420	SRL + mCsA + Ster	SRL + CsA + Ster	12	Similar acute rejection rate and better renal function when minimizing CsA
154 and 4351	Cohen *Am J Transplant* 2004[166]	631	SRL + mCsA + Ster	SRL + CsA + Ster	12	Similar acute rejection rate and better renal function n when minimizing CsA
146	Ferreira *Clin transplant* 2005[20]	70	SRL + mCsA + Ster	mSRL + mCsA + Ster	12	In black patients, in the presence of a low exposure to CsA, there is a trend towards less rejections with SRL levels > 15 ng/ml, but at the expense of worse renal function
542	Ciancio *Transplantation* 2004[40,49]	150	(SRL + TAC) or (SRL + CsA) + TAC + MMF +	DAC + Ster DAC + Ster	12	More rejections (14%), more hyperlipidemia, and worse renal function in the CsA + SRL group than in the others
Combinations with tacrolimus without induction						
193	Paczeq *Am J Transplant* 2003[59]	128	SRL +mTAC + Ster	mSRL + TAC + Ster	6	Trend towards more rejections when minimizing TAC (17% versus 7%) with the need for amendment to increase dosage. Better renal function when minimizing tacrolimus
777	Russ *Transplant Proc* 2003[38]	61	SRL +mTAC + Ster	mSRL + TAC + Ster	6	No differences in acute rejection nor in renal function
539	Daloze *Transplantation* 2002[60]	171	SRL +mTAC + Ster	mSRL + TAC + Ster	6	No differences in acute rejection. Better renal function when minimizing tacrolimus.
193, 777 and 539	Whelchel *Am J Transplant* 2003[61]	361	SRL +mTAC + Ster	mSRL + TAC + Ster	5	A trend towards more rejections when minimizing TAC (17% versus 10%). Better renal function when minimizing tacrolimus.
	Van Hooff *Transplantation* 2003[37]	104	SRL (0.5 mg or 1 mg or 2 mg) + TAC + Ster	TAC + Ster	6	Less rejections and more hypercholesterolemia with SRL.
	Gonwa *Transplantation* 2003[36]	361	SRL + TAC + Est	MMF + TAC +Est	6	Similar rate of acute rejections, worse renal function and lower rate of acute tubular necrosis

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542	Ciancio *Transplantation* 2004[40, 49]	150	(SRL + TAC) or (SRL + CsA) + DAC	TAC + MMF + DAC + Ster	12	More rejections (14%), more hyperlipidemia, and worse renal function in the CsA + SRL group than in the others
TERRA	Wlodarczyk *Transplant Proc* 2005[62] Vitko *Am J Transplant* 2006[44]	977	(SRL 0.5 mg + TAC) or (SRL 2 mg + TAC) + Ster	TAC+MMF+Ster	6	The group with greatest exposure to SRL showed less acute rejection, but orse renal function and hyperlipidemia
			Calcineurin inhibitor following induction combinations			
622	Lo *Clin Transplant* 2004[86]	39	SRL+ Thy + mTAC + Ster	mSRL+Thy+TAC + Ster	6[c]	40% histological nephrotoxicity due to tacrolimus inthe control group
	Burke *Am J Transplant* 2005[90]	101	SRL + Thy + DAC + TAC + Ster	MMF+Thy+DAC + TAC + Ster	24[d]	Less acute rejections
			Calcineurin inhibitor withdrawal combinations			
479[a]	Baboolal *Transplantation* 2003[22]	133	SRL + CsA (withdrawal at 3rd month) + Ster	SRL+mCsA+Ster	6	Similar acute rejection rate and better renal function when eliminating CsA
	Jardine *Am J Transplant* 2004[23]	279			12	Similar acute rejection rate and better renal function when eliminating CsA
310 [a]	Johnson *Transplantation* 2001[21]	430	SRL+ CsA (withdrawal at 3rd month) + Ster	SRL+CsA+Ster	12	After CsA withdrawal, slight increase in acute rejections in the SRL group with no significant differences. Better renal function in the group discontinuing CsA
	Oberbauer *Transplantation* 2003[26]				24	Better renal function in the group discontinuing CsA
	Oberbauer *Transplantation* 2003[167]				24	Better quality of life parameters in the KTQ fatigue and appearance questionnaire, and in the SF-36 vitality questionnaire, when cyclosporine is eliminated
	Kreis JASN 2004[27]				36	Better renal function in the group discontinuing CsA Better graft survival in the group eliminating cyclosporine
	Mathew *Clin Transplant*[152]				24	Lower neoplasia rate when CsA is eliminated
	Mota *Am J Transplant* 2004[29]				24	Biopsies show less development of chronic graft nephropathy when eliminating la CsA
	Oberbauer *Transplant Int* 2005[28]				48	Better graft survival, better renal function and better blood pressure
	Russ *Transplantation* 2005[17]				48	CsA withdrawal results in better renal function regardless baseline renal function, but the benefits are more marked in patients with baseline GFR < 45 ml/min
	Campistol *J Am Soc Nephrol* 2006[33]				60	Lower rate of skin and non-skin malignancies after withdrawing CsA
	Legendre *Transplant Int* 2005[31]				60	CsA withdrawal statistically improved renal function in the following subgroups of poor-risk prognosis for long-term renal function: cadaver donor, donor older than 50 years, more than 3 HLA mismatches, ischemia time > 24 hours, acute rejection, baseline GFR < 45 ml/min, or proteinuria reported by the investigators. Differences were not significant in the second transplantas and in patients with DGF.

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212	Gonwa *Transplantation* 2002[24]	197	SRL + m CsA and withdrawal + Ster	SRL + CsA +Ster	12	Cyclosporine elimination achieves better renal function
520	Grinyo, *Am J Transplant* 2004[39]	87	High SRL + Low TAC (withdrawal 3rd) month + Est	Low SRL + High TAC + Ster	12	A trend toward better renal function and diastolic blood pressure when eliminating tacrolimus
	Morales *Am J Transplant* 2005				24	A trend towards better renal function and diaastolic blood pressure when eliminating tacrolimus, with similar proteinuria
Calcineurin inhibitor-free combinations						
207	Groth, *Transplantation* 1999[12]	83	SRL + Aza + Ster	CsA+Aza+Ster	12	High acute rrejection rates (approx 40%) in both arms. Serum creatinine was better in the SRL group
210	Kreis, *Transplantation* 2000[11]	78	SRL + MMF + Ster	CsA+MMF+Ster	12	High acute rejection rates in both arms (27% with SRL and 18% with CsA). Serum creatinine was better in the SRL group
207 y 210	Campistol *Transpl Int* 2005[68]	115	SRL+ (Aza o MMF) + Ster	CsA + (Aza o MMF) + Ster	12	Lower urinary telopeptides excretion and lower serum osteocalcin concentration.
	Morales, *Am J Transplant* 2002[10]	161	SRL + (Aza o MMF) + Ster	CsA + (Aza o MMF) + Ster	24	Better renal function in the SRL arm than in the CsA arm
	Mathew, *Clin Transplant* 2004[152]					No tumors with SRL versus 5% with CsA
171	Flechner, *Transplantation* 2002[70]	61	BAS + SRL + MMF + Ster	BAS+ CsA + MMF + Ster	12	Excellent 6% acute rejections in the sirolimus group
	Flechner, *Am J Transplant* 2004[71]				24	Better renal function in the SRL group Better renal function, proteinuria and histology in the SRL group
	Dean *Transplantation* 2004[84] Larson *Am J Transplant* 2006[85]	123	SRL + Thy + MMF + Ster	TAC + Thy + MMF + Ster	12[b]	A need for excluding patients with BMI > 32 32 kg/m^2 and reducing SRL levels to 15 ng/ml due to a high rate for surgical complications (55%) with sirolimus Better renal function after one month, but the same after 12 months. Less chronic vasculopathy
	Glotz *Am J Transplant* 2005[89]	141	SRL + Thy + MMF + Ster	TAC + Thy + MMF + Ster	6	Greater glomerular filtration rate, healing anomalies, hyperlipidemia and anemia. No differences in DGF nor in proteinuria
969	Thervet *Am J Transplant* 2004[157]	72	SRL + Ac + MMF + Ster	CsA+Ac+MMF + Ster	6	More withdrawals due to adverse effects. Greater duration of DGF
	Hamdy *Am J Transplant* 2005[73]	132	SRL + BAS + MMF + Ster	SRL+BAS+TAC + Ster	24	Better renal function, lower drop out rate and diarrhea, but higher cholesterol, more intimal vascular proliferation and more herpes zoster. Similar proteinuria
Combinations with reduced exposure to steroids						
184	Kandaswamy *Am J Transplant* 2005[95].	239	(SRL + mTAC) o (mSRL + TAC) + Thy	CsA+MMF+Thy +Ster (withdrawal 5th day)	24[e]	Overall, 83% steroid-free More complications in surgical wound.
	Reinsmoen *Am J Transplant* 2005[102]	42	+ Ster (withdrawal 5th day)		3	No differences in acute rejection between treatment arms. The presence of donor-specific anti HLA antibodies is a risk factor for acute rejection
SW01	Benfield *Am J Transplant* 2005[106]	132[f]	SRL + BAS + ICN + Ster (withdrawal 6th month)	SRL+BAS+ICN + Ster	24	No differences in acute rejection. Study discontinued due to high PTLS incidence in EBV-negative patients

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Nº of study	First author, publication and year	N Rand.	Experimental arm with sirolimus	Control arm	Months follow-up	Experimental group findings
	Kumar *Transplantation* 2005[56]	150	SRL + BAS + TAC Ster-free	MMF + BAS + TAC Ster-free	24	Lower incidence of subclinical acute rejection and a trend to lower moderate/severe CAN. Similar rates of DGF, NODM (4% in each group) and surgical complications
Calcineurin inhibitor-free combinations with reduced exposure to steroids						
101132	Lebranchu *Am J Transplant* 2005[88]	150	SRL + ATG + MMF + Ster (withdrawal 6th month)	CsA + ATG + MMF + Ster (withdrawal 6th month)	12	A trend towards better GF, more proteinuria and lymphoceles. Overall 88% eliminated steroids
	Joannides *Am J Transplant* 2005[111]	29	SRL + ATG + MMF + Ster (withdrawal 6th month)	CsA +ATG + MMF + Ster (withdrawal 6th month)	7	No differences in GFR. Lower systolic blood pressure and greater radial artery endothelia-dependent vasodilation (induced by post-ischemic hyperemia)
	Gelens *Am J Transplant* 2005[112]	54	(SRL + DAC + MMF) or (SRL+ TAC) (only 2 days steroids)	TAC + MMF (only 2 days steroids)	6	CNI-free group had 65% acute rejection. The study was halted

Abbreviations: Ac: Polyclonal antibodies; ATG: Antithymocyte globulin; Aza (azathioprine); BAS: basiliximab; CsA (cyclosporine); DAC: daclizumab; Ster (Steroids); CAN: chronic allograft nephropathy, CNI: calcineurin inhibitor; mCsA (cyclosporine minimization); mSRL (reduced-dose sirolimus); mTAC (tacrolimus minimization); MMF (mycophenolate mofetil); DGF: Delayed graft function; SRL (sirolimus); Thy: thymoglobulin, EBV: Epstein-Barr virus.
a: Randomization at 3rd month.
b: Mean follow-up is 21 months (extreme 6-31). Actuarial data is provided at 12 months.
c: Mean follow-up of 7.9 and 6.9 months (all at least 6 months). Actuarial data is provided at 6 months.
d: No complete follow-up data.
e: Mean follow-up of 16 months. Data is provided. Actuarial data is provided at 24 months.
f: Randomization at 6th month

this combination enhanced cyclosporine nephrotoxicity probably due to an increase in the renal concentration of cyclosporine[15] or by means of the increased expression of TGF-β[16]. This toxicity enhancement is probably not only limited to nephrotoxicity. Thus, this toxicity synergy has also been observed in hypercholesterolemia, in the decrease in bone marrow cellularity[15], in the trend to induce more anemia[17], and in toxicity on endothelial cells which would eventually predispose the development of hemolytic uremic syndrome[18].

SIROLIMUS WITH WITHDRAWAL OR REDUCED DOSES OF CYCLOSPORINE: THE PATH TO EUROPEAN REGISTRATION

Nephrotoxicity exacerbation due to cyclosporine led to the design of several trials testing reduced doses of cyclosporine [19,20] or the withdrawal thereof[21-25].

Muehlbacher *et al*. tested the combination of sirolimus plus steroids with standard doses against reduced doses of cyclosporine (135 versus 85 ng/ml of cyclosporine at 1 year, $p<0.001$), achieving similar acute rejection rates with better renal function[19]. Baboolal *et al*. compared elimination against minimization of cyclosporine (50 to 100 ng/ml). Their results at 6 months suggested that these small doses of cyclosporine contributed nothing in terms of antirejection safety, but worsened renal function. Results of this trial at 12 months showed better renal function in the elimination group at the expense of an increase in acute rejection[23].

The cyclosporine withdrawal trial with the longest follow-up (study 310), recruited 525 patients initially treated with cyclosporine, sirolimus and steroids and randomized after 3 months to stay with the triple therapy or to discontinue cyclosporine and continue maintenance with sirolimus and steroids. The primary efficacy variable was equivalence in graft survival between both groups shown at the first year[21]. With this data, in December 2000 the EMEA proceeded to authorize use of sirolimus in renal transplant in initial combination with cyclosporine and followed by withdrawal thereof and requested an extension of the study to 5 years. As soon as randomization occurred, significant diffe-

rences in renal function started to become evident, which were maintained over time up to the 5 years[21,26-28], accompanied by better histological parameters in the cyclosporine discontinuation arm[29,30]. The improvement in renal function was observed independently from basal renal function[17] and in the presence of adverse factors for long-term graft survival such as a cadaveric donor, donor over 50 years of age, high immunological disparity, ischemia time exceeding 24 hours, previous acute rejection or post-transplant proteinuria[31]. At 4 years of follow-up, graft survival was statistically greater in the cyclosporine discontinuation arm, so the trial was amended to close that arm, and in April 2003 the FDA included cyclosporine discontinuation in the U.S. drug registry[28]. The continue combination of cyclosporine and sirolimus seems to achieve worse graft survival than the combination of cyclosporine with mofetil mycophenolate, as the American registry suggested, despite the lack of dosing data of each drugs[32].Furthermore, cyclosporine withdrawal entailed a reduced risk of cutaneous and non-cutaneous neoplasias at five years[33], a reduced figure for mean blood pressure and the need for hypertensive drugs, and a better hemoglobin figure[28]. In contrast, cyclosporine withdrawal was followed by a greater percentage of acute rejection on biopsy at the first year after withdrawal (4.2% versus 9.8%, p=0.03)[21], although these differences disappeared past the first year (6.5% vs. 10.2%, p = 0.223 at 4th year)[28]. It has been put forward that the control arm was not the most indicated or that another maintenance arm only with cyclosporine and steroids should have been included, and that that would partly invalidate the conclusions of this study. However, it must be considered that the control arm reflected the usage scheme that had been approved by the FDA for over 3 years by virtue of its better anti-rejection control, and that it was further amended at mid-trial to reduce the target levels of cyclosporine from 75 to 200 ng/ml before the amendment, to 50 to 150 ng/ml afterwards, given which it constituted a minimization arm in the long term.

SIROLIMUS IN COMBINATION WITH TACROLIMUS

It was initially thought that these two structurally similar drugs would be antagonistic due to competitive interaction with the same immunophilin, FKBP-12. Initial experiences in Halifax showed that the combination was clinically possible and that tacrolimus, unlike with cyclosporine, did not show pharmacokinetic interaction with sirolimus, which allowed simultaneous administration of both drugs[34,35]. These and subsequent clinical experiences showed that the combination of sirolimus with tacrolimus offered acute rejection rates that were similar to the combination with cyclosporine and even lower than 10% when the desired levels of both drugs were obtained [36-43,44]. Some preclinical data in rats suggests that the combination of sirolimus with tacrolimus can be less nephrotoxic than with cyclosporine[45]. Some similar clinical findings have been suggested in hepatic transplant[46,47] or renal transplant[48,49], although other authors have not found this pattern[50]. Likewise, it has been suggested that the combination with tacrolimus would be less hypercholesterolemic than with cyclosporine[49,51]. As regards whether the combination of sirolimus with tacrolimus is more nephrotoxic than the more standard combination of tacrolimus with mycophenolate there are more studies suggesting so[36,52-56] than there are suggesting the contrary[57]. A randomized American trial with 316 patients compared sirolimus against mycophenolate with a short term follow-up of 6 months. The acute rejection rate was similar in the two groups. The group of sirolimus showed a higher serum creatinine and a lower rate of acute tubular necrosis[36]. A retrospective study of the American transplant registry recently analyzed transplant results with respect to immunosuppression at the time of release, finding that graft survival was better with the tacrolimus plus mycophenolate scheme than with the tacrolimus plus sirolimus scheme, although the database did not contain information on the dose of each drug[58]. The acute rejection rate was very similar between both groups, which, with the limitations of this kind of studies, suggests a possible underlying nephrotoxic effect.

The importance of sirolimus and tacrolimus doses in joint administration of both drugs has been analyzed in three randomized studies with very similar results. The Australian group (study 777), the European group (study 193) and the North American group (study 539) communicated their 6-month results of the randomized trials that compared standard tacrolimus doses with reduced sirolimus doses versus reduced tacrolimus doses with standard sirolimus doses, without antibody induction[38,59,60]. A joint analysis of the 3 trials at 6 months[61] suitably summarizes the findings: the final acute rejection rate was fairly greater in the arm with lower exposure to tacrolimus (17% versus 10%, p = 0.04) once an amendment was performed to increase the doses of both drugs, and renal function was significantly better in the arm with lower exposure to tacroli-

mus. Van Hooff *et al.* researched the safety and efficacy of tacrolimus and steroids together with 3 different fixed doses of sirolimus in a randomized short-term trial at 6 months which used tacrolimus plus steroids as a control group. There were no differences found regarding patient or graft survival. The groups with sirolimus presented a statistically lower acute rejection rate and more hypercholesterolemia and no data on renal function was provided[37]. The TERRA trial compared two combinations of tacrolimus with fixed doses of sirolimus of 0.5 mg/d or 2 mg/d with a control group with tacrolimus and mycophenolate. The group of 2 mg of SRL showed better rejection control at 6 months, but worse renal function[44,62].

Similarly to what occurs with cyclosporine, the best combination with tacrolimus would probably be one which, after a combined start with both drugs, proceeded to withdraw the calcineurin inhibitor. Until now, only one prospective randomized trial has dealt with tacrolimus withdrawal from an initial sirolimus plus tacrolimus regimen. The results of this trial after one year showed a trend towards a better renal function and diastolic blood pressure in the tacrolimus withdrawal arm[39], and after two years the same trend was observed without proteinuria being observed[63]. A recent systematic review has jointly analyzed the randomized trials in which withdrawal of the calcineurin inhibitor from an initial sirolimus regimen was performed, finding that it is associated with an improvement of renal function and blood pressure at the expense of a 6% increase in acute rejections[64].

CALCINEURIN INHIBITOR-FREE SIROLIMUS EXPERIENCES WITHOUT INDUCTION

The combination of sirolimus together with mycophenolate mofetil, two antifibrotic agents, could achieve better prevention of chronic graft nephropathy, as has thus been demonstrated in murine models[65,66].

The first clinical trials 207 and 210 mentioned above with the combination of sirolimus with antimetabolites did not use induction with antibodies. Thus in a multicenter trial, Kreis *et al.* compared an immunosuppressant regimen based on sirolimus at very high initial doses versus a regimen with cyclosporine in 78 patients[11]. All the subjects received mycophenolate at an initial dose of 2 grams per day for 6 months; afterwards these were discontinued and replaced with azathioprine. At 12 months after the transplant, the subjects randomized to the CsA/MMF group presented an insignificantly lower incidence of acute rejection episodes than the SRL/MMF group. In contrast, the mean value of estimated creatinine clearance was greater in subjects treated with SRL/MMF at 12 months after the transplant and was uniformly higher from month 1 onwards. Subjects treated with SRL/MMF had thrombocytopenia and diarrhea with a significantly higher frequency than the subjects treated with CsA/MMF. The SRL/MMF group had an incidence of cytomegalovirus (CMV) viremia, of hyperuricemia, of trembling and increase in serum levels of creatinine significantly lower than the CsA-MMF cohort at 12 months after the transplant.

It is interesting to point out the lack of interactions between SRL and MMF, which does occur when administering MMF simultaneously with CsA. Holt *et al.* published the pharmacokinetic profiles obtained in 32 subjects treated with SRL and in 31 subjects treated with CsA in weeks 1, 4, and 12[67]. The overall mean values of the concentration-time area under the curve ($AUC_{0\text{-}6h}$) of MPA normalized according to the MMF dose were significantly greater in the cohort with SRL.

Morales *et al.* published the results of the combined analysis after 2 years of the study mentioned above and of an additional phase 2 clinical trial with azathioprine, with a similar design, in which an immunosuppressant regimen based on SRL versus one based on CsA were compared (10, 12). From week 10 to year 2, the calculated glomerular filtration rate (GFR) was significantly greater in subjects treated with SRL than in subjects treated with CsA (69.3 *vs*. 56.8 ml/min, at 2 years, $P = 0.004$). Likewise, Campistol *et al*. reported pooled results of bone metabolism markers from both trials: urinary telopeptides and serum osteocalcin were lower in sirolimus-based group than in the cyclosporine one[68].

The 311 trial was an extension study that included patients on sirolimus treated concomitantly with or without cyclosporine. Sirolimus-based therapies used combinations with MMF or azathioprine. Although it was not a randomize trial, the study, the CNI-free group showed higher renal function and hemoglobin at 4-year than the group treated with sirolimus plus ciclosporina[69].

SIROLIMUS IN ASSOCIATION WITH ANTIBODIES

Monoclonal antibodies against the IL-2 receptor

Excepting the aforementioned trial 207, the following experiences in the combination of siroli-

mus with mycophenolate have been carried out using antibodies in the induction. Flechner *et al.* published the results of a single-center and randomized prospective trial in which an immunosuppressant regimen based on SRL was compared with a regimen based on CsA in 61 patients[70]. All the patients were treated with basiliximab, mycophenolate and steroids. Acute rejection control with sirolimus was very satisfactory, and renal function was significantly greater in the group from month 3 onwards[70]. After two years, the sirolimus group still showed a better renal function and histological evolution, with a trend towards lower proteinuria[71]. The same Cleveland group has continued its experience reducing the mycophenolate mofetil dose from 2 gr/day to 1 gr/day, thus reducing the incidence of digestive adverse effects[72].

Hamdy et al. recently reported the results of a randomized trial with basiliximab, sirolimus and steroids, that compared tacrolimus against mofetil mycophenolate in 132 patients with living donor. The CNI-free group exhibited at 2-years a higher renal function, lower discontinuation rate and diarrhea, but higher cholesterol, higher intimal vascular proliferation, and more herpes zoster Proteinuria was similar in the two groups, although there was a trend to be higher in the MMF group[73].

Other non-randomized studies have used different combinations of sirolimus with daclizumab or basiliximab in renal transplants[74-83]. Most of these experiences have had a short follow-up and have included a limited number of patients with heterogeneous characteristics, frequently with marginal donors or different graft delay risks. For all these reasons, precautions must be maximized when reaching conclusions from these experiences. Vincenti *et al.* found that the combination of an antibody against the IL-2 receptor plus sirolimus, mycophenolate and steroids would not be useful in the Afro-American population[75]. Similarly, the Texas group experience suggests that the combination of antibodies against the CD25 receptor plus sirolimus could be insufficient for the high-risk population (Afro-American or retransplant population)[80,81].

Thymoglobulin

The Mayo Clinic group has published the results of a randomized study of thymoglobulin induction and maintenance with mycophenolate and steroids in 123 patients in which sirolimus was compared to tacrolimus. Due to a 55% surgical wound complication rate in the sirolimus group, the trial was amended to exclude patients with a body mass index exceeding 32 kg/m^2 and to reduce sirolimus target levels to 15 ng/ml. After this amendment, the complication rate decreased to 35%[84]. A later communication from this group stated that though the renal function achieved was significantly better one month after the transplant, it tended to equalize at one year after transplant[85], at which time the sirolimus group showed less chronic vascular disorders in the protocol biopsy.

Lo *et al.* from the Memphis group have communicated the results of another trial with thymoglobulin in 39 patients which randomized the patients to receive high doses of sirolimus with tacrolimus minimization versus low doses of sirolimus together with standard doses of tacrolimus[86] This last group presented histological nephrotoxicity due to tacrolimus in almost 40% of the patients, which caused the discontinuation of recruitment in that arm. The tacrolimus minimization group was then compared with a calcineurin inhibitor-free regimen by thymoglobulin, sirolimus, mycophenolate and steroids. The calcineurin inhibitor-free group statistically showed better creatinine clearance at one year and less interstitial fibrosis in the biopsy performed at 3 months[87].

The preliminary results of three randomized trials with thymoglobulin and sirolimus88-90 have been reported. Glotz *et al.* have reported the results at 6 months of a French-Belgian study with thymoglobulin induction and mycophenolate and steroid maintenance and which randomized the patients between sirolimus and tacrolimus. Renal glomerular filtration, the wound healing disorder rate, hyperlipidemia, anemia and thrombopenia were significantly greater in the sirolimus group without any differences being found in delayed graft function or in 24 hour proteinuria[89]. The University of Miami group is carrying out a randomized trial in kidney and pancreas transplant using induction with thymoglobulin plus daclizumab followed by tacrolimus and maintenance with steroids, and comparing sirolimus against mycophenolate mofetil[90]. After two years of follow-up statistically less acute rejection episodes in the sirolimus group were observed in the 101 recruited patients.

There have been other uncontrolled experiences with thymoglobulin and sirolimus[74,78,81,82,91-94]. The Texas University group has retrospectively analyzed their cohorts treated with antilymphocyte antibodies together with sirolimus and delayed cyclosporine introduction, finding that their surgical complication rate was greater when using thymoglobulin than when using basiliximab[78].

T lymphoid depletion facilitates post-transplant immunosuppression reduction and its pro-tolerogenic role has been suggested. Swanson *et al.* used a combination of high doses of antithymocyte globulin with sirolimus with tolerogenic intention. At one year, ten of the twelve patients were in monotherapy with sirolimus and with creatinine at 1.2 mg/dl. 3 rejections occurred in patients with sirolimus levels under 5 ng/ml[92].

Other experiences with sirolimus after induction with antithymocyte globulins have been designed to make regimens with low exposure to steroids possible and will be discussed below[83,88,95,96].

Anti-CD52 (Alemtuzumab)

Campath-1H is a monoclonal antibody against antigen CD52 present in lymphocytes, monocytes and dendritic cells. Knechtle *et al.* from the University of Wisconsin reported on their non-randomized pilot experience of induction with Campath –1H followed by monotherapy with sirolimus in 29 renal transplant recipients. After 3 years, acute rejection had been observed in 44% of the patients, half of which were positive for C4d[97,98], and graft survival reached 96%. As a result of the occurrence of this humoral component, thymoglobulin was also added to the last five patients. Almost half the patients were in monotherapy with sirolimus without steroids after 3 years, showing a satisfactory cardiovascular profile in terms of blood pressure and lipids[99]. No biopsy showed data for chronic graft nephropathy, and after 6 and 12 months they showed less expression of fibrosis mediators such as Smad3 and TGF-b, and less VEGF expression than a historic control group treated with calcineurin inhibitors with mycophenolate[100].

Sirolimus in steroid withdrawal regimens

The Minnesota group has recently published the results of a randomized study with thymoglobulin in induction and steroid discontinuation 5 days after the transplant. The 239 patients were randomized to receive maintenance based on cyclosporine plus mycophenolate or high doses of tacrolimus with low doses of sirolimus or low doses of tacrolimus with high doses of sirolimus. With a mean follow-up of 16 months, 83% of the patients remained without receiving steroids. Patient and graft survival, acute rejection rate, and renal function were similar among the three groups. Wound healing complication rates were greater in the groups with sirolimus[95]. At 5 years, 86% of all 589 patients included in their rapid steroid withdrawal cohorts was steroid-free, 92% of grafts survived free of acute rejection, and showed lower cataracts, diabetes, avascular necrosis and fractures compared with a historic control of maintenance with steroids[101]. A recent communication from this group has monitored the immunological risk by means of the serial determination over time of intracellular ATP concentrations in CD4 lymphocytes, the quantification of _ interferon-producing T lymphocytes measured by ELISPOT and donor-specific anti HLA antibodies. The intracellular ATP concentrations decreased more effectively in the schemes with sirolimus. The presence of pre-transplant donor-specific antibodies was a risk factor for acute rejection, not so in the treatment arm[102].

The University of Cincinnati team has tested in 77 low immunological risk patients a steroid withdrawal at 4 days in a multicenter immunosuppression study based on sirolimus plus tacrolimus after induction with basiliximab[103]. After one year, 57% were still in the treatment they were assigned to. The acute rejection rate shown on biopsy was of 13%, and the mean weight gain after one year was 3 kg. The same Cincinnati group has suggested by means of a retrospective analysis that a steroid-free regimen consisting of thymoglobulin, sirolimus, mycophenolate and low doses of cyclosporine would show lower doses of wound complications and lymphoceles than their historic cohort with cyclosporine, mycophenolate and corticoids[104]. For the high immunological risk population they use a regimen of thymoglobulin with daclizumab, tacrolimus, sirolimus and mycophenolate[83], with an acute rejection rate of 27%, although the short follow-up and number of patients requires caution when drawing any type of conclusions.

Anil Kumar *et al.* from Drexel University in Philadelpia have published the results of a study with 150 patients treated with basiliximab, tacrolimus and two days of steroids, randomized to receive sirolimus or mycophenolate and surveyed by protocol biopsies. The study provides data at two years, although only a little bit more than the half of the patients has completed this follow-up. At 2 years, the cumulative incidence of subclinical rejection was higher in the group of MMF, without differences with regard to renal function, mild/moderate chronic allograft nephropathy, delayed graft function or new onset diabetes mellitus (approximately 4%)[56]. All patients remain steroid-free at the end of follow-up, but 33% of them in MMF group and 20% in SRL group have received steroids because of acute or subclini-

cal rejection at some moment during follow-up. A sub-analysis from this study showed that these regimens were also successful in the more risky Afro-American population[105].

A double-blind cooperative study in pediatric transplant randomized the patients showing a rejection-free biopsy after 6 months to slowly withdraw the steroids in 6 months or to maintain them, after an initial regimen including basiliximab, calcineurin inhibitor, sirolimus and steroids. 132 patients were randomized. Two years after the transplant there were no differences regarding acute rejection rates between both groups (16% in the maintenance group and 8% in the discontinuation group, although the percentage of steroid-free patients after 2 years was not provided)[106]. Although the results regarding immunosuppression effectiveness were satisfactory, the trial was prematurely suspended due to an increased incidence of post-transplant lymphoproliferative syndrome, especially in the group of younger Epstein-Barr virus seronegative patients[107].

Hricik et al. reported the results of a non-controlled experience of sirolimus plus tacrolimus with steroid withdrawal from the third month onwards in afroamerican population. After withdrawing, 27% of patients developed acute rejection, often associated with a bad therapeutic compliance. However, steroid withdrawal was associated with renal function impairment[108,109]. A positive ELISPOT test of donor-specific interferon g producing T cells in the pre-transplant period, predicted the development of acute rejection and renal function at 12 months[110].

Calcineurin inhibitor-free sirolimus in steroid withdrawal regimens

Very preliminary results have been communicated of some trials seeking a long term steroid-free and calcineurin inhibitor-free maintenance by using different combinations of immunosuppressants[88,111,112]. The French group using induction with thymoglobulin, a steroid withdrawal in the 6th month and maintenance with sirolimus and MMF make it possible for 88% of the patients to be steroid-free after one year with an acute rejection rate of 13%. The group with sirolimus achieves a better renal function and lower CMV infection rate than that of cyclosporine, but with more proteinuria and lymphoceles[88]. A subanalysis of this trial has performed radial artery vasodilation measurements, finding that endothelial function is better preserved with sirolimus than with cyclosporine[111]. Gelens et al. found, in a series including numerous non heart-beating donors, an unacceptably high acute rejection rate with a regimen including induction with daclizumab and only two days of steroids followed by maintenance with sirolimus and MMF[112].

Delayed introduction of sirolimus in «de novo» transplant

Sirolimus use starting at the time of transplant has been associated with several adverse effects such as delayed graft function (DGF)[113-117], lymphocele development (118-120), and delayed wound healing (84, 121, 122). There have therefore been some attempts to reduce the adverse effects by delaying the introduction of sirolimus[93,123-125-127] or avoiding the load doses[76,128].

Sirolimus in pediatric population

In addition to the aforementioned randomized trial of steroid withdrawal, others non-controlled experiences with sirolimus in «de novo» pediatric renal transplantation have been reported[129-134]. Most significant information from these studies limits to:

a) Pharmacokinetics of the combination of sirolimus plus cyclosporine in patients older than 12 years is quite similar to adults[129]. Thus, FDA approves the use of sirolimus in this population with the same dosing scheme as in adults[135]. Clearance is higher in younger population, and therefore, administration schemes with higher doses or in a twice daily basis, have been proposed[136], although further studies are needed.
b) El-Sabrout *et al*. have reported their experience with the combination of sirolimus, tacrolimus and steroids after induction with anti-IL2R in 20 pediatric patients, and they have not observed any acute rejection event, with a serum creatinine of 1,2 mg/dl at first year[132,133].
c) In CNI-free regimens based on induction, sirolimus administered twice daily, mycophenolate and steroids, sirolimus half-life is lower than 10 hours, so higher doses administration are suggested[134,137] (the median of administered sirolimus doses were 9 mg/m^2/d at 3 months). Only one patient out of 13 has experienced a subclinical acute rejection episode in a short follow-up period of 3 months. However, a similar trial sponsored by NIH was tested in 34

patients and found a 24% of acute rejection with a glomerular filtration of 83 ml/min at 6 months[130].

Trials underway and future possible developments for sirolimus

Two large randomized studies currently underway, the ORION study and study PROTECT-318, will try to establish whether sirolimus-based therapies and calcineurin inhibitor-free therapies are better than the traditional ones based on cyclosporine or tacrolimus together with mycophenolate. The ORION study will do so by means of induction with daclizumab, and study PROECT by means of basiliximab. The ORION study will use tacrolimus as a control group and study PROTECT will use cyclosporine. The ORION study has further included a group using tacrolimus during the first three months and subsequent withdrawal.

DISCUSSION

What does sirolimus contribute in immediate transplant?

Those present at the meeting maintained that the results of standard therapies based on a calcineurin inhibitor and an antimetabolite (mainly mycophenolate mofetil) are satisfactory in the short term regarding rejection control and safety profile, but that the current immunosuppression challenge would be in the mid-term, increasing mean graft life. In this sense, although it must be demonstrated in clinical trials and long term follow-up, sirolimus could contribute the following:

1. A low acute rejection incidence, both in immediate post-transplant, such as in long term conversions. In this sense, some participants in the meeting considered that it could be almost equipotent with cyclosporine[11,12,70].
2. A reduction in the incidence of CMV infections, such as has been suggested in several experiences in renal[88,138-140], hepatic[141], cardiac[54,142], or medullary transplant[143,144].
3. A better control of blood pressure and of renal function when calcineurin inhibitors are eliminated at the expense of a slight increase in acute rejection risk, such as suggested in a recent meta-analysis[64].
4. The antifibrotic effect preclinically observed alone[145-147] or in combination with mycophenolate mofetil[65,66] could result in obtaining better histological parameters, such as has been clinically observed after cyclosporine withdrawal[25,29,30] or in calcineurin inhibitor-free regimens[71,87], although more follow-up is required to know whether this translates into a longer mean graft life.
5. The increasing preclinical and clinical evidence of the antitumor role of sirolimus[33,148,149-153,154], together with the absence of other alternatives suggests that sirolimus should be present in the immunosuppressant regimen of transplant recipients with a history of pre-transplant neoplasia, as well as in relapsing skin non-melanocytic tumors after transplant[155],although prospective studies in this patient population will be necessary[156].
6. Although most participants consider that sirolimus could play a role in conventional standard transplant, most referred to experiences especially in the marginal donor population, due to age or different risks in graft delay including non heart-beating donors. In this sense the existence of both negative[74,112,157] and positive[124,158,159] experiences must be noted.
7. In the familiar non-epidemic hemolytic uremic syndrome, the use of sirolimus-based regimens may help to avoid calcineurin inhibitors[160], although two cases of patients who relapsed under sirolimus treatment have been reported[161].

In the opinion of the participants these positive contributions must be counterbalanced with

1. An increase in lymphocele rate[118,119], which is especially delicate in double transplants. This must be confronted from a surgical point of view such as the Texas group did by reducing its lymphocele rates by means of a greater use of drainages and interrupted suture[162]. Other useful approaches could include the delay in the start of sirolimus or fast steroid discontinuation regimens if its effectiveness and safety were demonstrated.
2. An anemia-producing effect similar to mycophenolate as regards intensity, but which characteristically seems to be microcytic with normal iron levels, which suggests an iron metabolism disorder[163].
3. Uncertain delayed graft function, which could be resolved with the delayed introduction of SRL[76,93,124].
4. A greater number of initial discontinuations due to adverse effects in some recent studies. To this

effect it must be pointed out that though in trial 310 there were more discontinuations during the first year in the calcineurin inhibitor-free group (27% versus 17%, p = 0.02[21]), this rate was reversed in the 3rd year (37% versus 47%, p=0.04[27]).

5. The increase in cyclosporine nephrotoxicity[7,13-15], and probably also in tacrolimus[45], makes the design of «de novo» regimens with sirolimus more difficult.

Which are the best combinations with SRL?

1. The currently approved indication of combined use with CsA during the first three months and subsequent withdrawal of CsA is not supported by any of the participants, because though they all consider that SRL allows early withdrawal of the CNI (in the 3rd month) resulting in an improvement in renal function, without an excessive immunological cost, none of them feels comfortable with the combined use with CsA due to the increase in the nephrotoxic effect of CsA.
2. The philosophy must be the use of non-nephrotoxic drugs and in the event of using CNI preferably with tacrolimus, adjusting them downwards or during a short period.
3. The combination of SRL with tacrolimus in immediate post-transplant allows adequate immunosuppression control, easy handling, does not require induction, and allows tacrolimus withdrawal in a significant number of patients, without the risk of acute rejection and with a very adequate safety profile. This combination preceded by induction could even serve in high immunological risk patients. In those patients in whom tacrolimus withdrawal is not possible, the combined use with similar SRL and tacrolimus levels (4-5 ng/ml) could be possible, allowing steroid withdrawal.
4. Sequential regimen: this sequential regimen has the advantages of resolving the problems of the adverse effects associated to sirolimus in immediate transplant (delayed graft function, delayed healing, lymphocele, etc.). Alternatives are discussed in this sense, which some call «early conversion» and others «delayed de novo use», which show a preference for the earliest possible use, without it being possible to establish the optimal starting point yet. In relation to this the need of maintaining a proactive attitude in the face of early renal function impairment and the logistic and organization difficulties that this attitude would generate is noted.
5. Some propose «de novo delayed» SRL introduction between the 5th and the 15th day in order to prevent immediate post-transplant problems (lymphocele, delayed healing), and others propose a more delayed introduction once delayed graft function has been overcome.

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