行政院國家科學委員會專題研究計畫　成果報告

無毒性之腎移植免疫抑制方案-動物實驗模式

計畫類別：個別型計畫
計畫編號：NSC91-2314-B-002-382-
執行期間：91 年 08 月 01 日至 92 年 07 月 31 日
執行單位：國立臺灣大學醫學院泌尿科

計畫主持人：闕士傑

報告類型：精簡報告

處理方式：本計畫可公開查詢

中　華　民　國 92 年 12 月 22 日

Non-nephrotoxic immunotherapy

Shih-Chieh J. Chueh

Department of Urology, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan.; supported by a grant from National Science Council, Taiwan (NSC-91-2314-B-002-382)

List of Abbreviations

AUC: area under the concentration-time curve
Aza: azathioprin
C0: trough concentration
C2: concentration at 2-hour post-dose
Cmax: maximal concentration
CAD: coronary artery disease
CsA: cyclosporine A
CNI: calcineurin inhibitor
Cr: creatinine
DGF: delayed graft function
EBV: Epstein-Barr virus
GFR: glomerular filtration rate
HLA: human leukocyte antigen
HRQOL: health-related quality of life
LDL: low-density lipoprotein
MMF: mycophenolate mofetil
mTOR: mammalian target of rapamycin
P K: pharmacokinetic
Pred: prednisolone
PTDM: post-transplantation diabetes mellitus
PTLD: post-transplant lymphoproliferative disorders
RATG: rabbit antithymocyte globulin
RMR: rapamycin maintenance regimen
SRL: sirolimus, rapamycin, rapamune®
ST: steroids
Tac: tacrolimus

Abstract

This review covers briefly the long-term results of pre-launching Phase I/II through Phase III clinical trials of sirolimus (SRL), an update strategy of 10 years' experience from a single center, and focuses on the recent results of many new studies of renal transplantation which included a diversity of different regimens containing SRL and other immunosuppressants, or SRL-based regimens aiming to spare other drugs with known toxicities. SRL, as a base therapy, is evolving into another cornerstone of immunosuppression in kidney transplantation. Its optimal target concentrations need to be specifically and meticulously tailored when used in combination with other immunosuppressants, the concentrations or doses of which also require delicate therapeutic monitoring, to achieve excellent outcomes with fewer adverse effects.

Introduction

Sirolimus (rapamycin, SRL, Rapamune®), a macrocyclic lactone, is a new potent immunosuppressant with a distinctive mechanism, different from those of calcineurin inhibitor (CNI) or antimetabolites, to inhibit mammalian target of rapamycin (mTOR) and act during both co-stimulatory activation and cytokine-driven pathways [95]. Since the approval of this novel drug by the Food and Drug Administration of the United States in 1999 and by the European Agency in 2000, it has raised great interest in the field of transplantation, and more new or long-term data of its clinical applications are accruing rather fast and even exponentially lately.

The mechanism of action, preclinical findings, clinical pharmacology, results of Phase I through Phase III clinical trials, general safety and toxicity of SRL, especially in combination with cyclosporine (CsA), had already been soundly reviewed [41;44;74;96]. This review covers briefly the long-term results of pre-launching phase II and III clinical trials of SRL, and mainly focuses on the results of many recently published studies which contained a diversity of regimens for renal transplantation consisting of a combination of SRL and other immunosuppressants, or regimens aiming to spare other immunosuppressant drugs with known toxicities, and this review also includes many relevant reports presented in American Transplant Congress during May 30- June 4, 2003 at Washington, D.C..

Brief Summary and new data of SRL in combination with CsA

A Phase I/II dose-escalation trial of SRL using limited courses of steroids (ST) and a concentration-controlled CsA maintenance in mismatched living-donor renal recipients revealed a dramatically reduced incidence of acute allograft rejection episodes to 7.5% over 3 years (as compared to 32% from a control cohort of CsA/ST-treated patients) [53]. Then a randomized, controlled, multicenter Phase II trial showed the incidence of biopsy-proven acute rejection episodes within the first 6 months after transplant was reduced to 8.5% in patients receiving ST, SRL (1 or 3 mg/m2/day) and full-dose CsA (p=0.018). Similar low rates of acute rejection episodes were observed among non−African American, but not African American recipients, treated with SRL and reduced-dose CsA (target level at 50% of full-dose range) [45].

Two large-scale Phase III prospective, randomized, double-blind trials including nearly 1300 renal transplant patients compared the efficacy and safety of two dose levels of SRL versus azathioprine (Aza, US) or placebo (Global) comparators administered with a CsA-ST baseline regimen. At 6 months, the rate of efficacy failure (a composite of the occurrence of acute rejection, graft loss, or death), was lower among the two SRL groups (2 mg 18.7%, 5 mg 16.8% for the US; 24.7% and 25.6%, respectively, for the Global trial) than among the Aza and placebo

comparators group (32.3% and 47.7%, respectively; all $p \leq 0.002$). The frequency of biopsy-confirmed acute rejection episodes at 6 months was also lower among the SRL groups (2 mg 16.9%, 5 mg 12.0% for the US; 30.0% and 19.2% for the Global trial) than among their respective comparator group (29.8% and 41.5%, all $p \leq 0.003$). Patients on SRL showed a delay in the time to first acute rejection episode and decreased frequency of moderate and severe histological grades of rejection episodes and antilymphocyte antibody treatment compared with the control groups. At 12 months, graft and patient survival was similar among all groups in the 2 trials. Analysis of 24-month data of the Phase III trials revealed that patients in the 5 mg/d SRL groups experienced a significant delay in the onset and reduction in the incidence of acute rejection episodes compared with Aza or placebo groups (P =.02/P =.001). Graft and patient survival rates and also the occurrence of transplant-related infections, lymphoproliferative disorders (PTLD), or malignancies were similar among all treatment arms. Between 12 and 24 months, patients treated with 2 mg/d SRL displayed relatively stable mean serum creatinine (Cr) values (mean around 1.8 mg/dL), yet which remained higher than those of the comparators. Both 5 mg/d groups showed an increase in mean serum Cr during this interval, which was significantly higher than the value in both comparators at 24 months. Both SRL groups showed persistently elevated triglyceride levels compared with Aza-treated

patients at month 24; whereas the difference was less-pronounced in the Global trial. Data from both trials demonstrated that the addition of SRL to a CsA-ST regimen yielded a durable immunosuppressive effect associated with a progressive resolution of adverse effects over time except for hyperlipidemia, which required continued countermeasure therapy. A post-hoc analysis which studied the relation between outcomes and drug concentrations documented that the SRL-CsA combination displays pharmacodynamic synergy in man [39;43;71].

Other lessons learned from these trials revealed that adverse effects attributable to CsA, including nephrotoxicity, hypertension proclivities, and new onset post-transplant diabetes mellitus (PTDM), tend to be exacerbated by SRL, which increases CsA exposure per milligram administered dose. SRL and CsA share the same cytochrome P4503A4 metabolic pathways, and both drugs are substrates for the p-glycoprotein countertransport mechanism. The exacerbation of renal dysfunction seemed to be due to a pharmacokinetic interaction of SRL to greatly increased CsA concentrations in whole blood and, particularly, in kidney tissue. In contrast, the pharmacodynamic effects of CsA to potentiate SRL-induced myelosuppression and hyperlipidemia occurred independently of pharmacokinetic interactions [88]. Neither the patients' ethnicities nor their pretransplant CMV serological status were associated with the occurrence of hematological complications in SRL-treated recipients.

Thrombocytopenia is usually observed during the first 4 weeks of SRL treatment. The occurrence, but not the severity or the persistence, of both thrombocytopenia and leukopenia correlate significantly with high SRL trough concentrations (≥16 ng/mL). In 89% of patients, the first episode of either type of cytopenia resolved spontaneously. Among the remaining 11%, 7% responded to SRL dose reduction, 4% to temporary drug suspension, and no patient required permanent cessation of SRL therapy [31].

A new tablet formulation of SRL offers more convenience than the original liquid formulation, and showed similar area under the concentration-time curve (AUC) and trough concentrations (C0) of SRL at 2, 4, and 8 weeks after a milliliter-to-milligram conversion, without any episode of acute rejection nor with changes in other laboratory values. The only significant difference was the lower dose-corrected maximal concentration (Cmax) values of the tablets ($p<0.05$). AUC values of CsA were not appreciably different [56].One striking finding of long-term SRL use is its low incidence of post-transplant malignancy. In a single-center experience of 1008 renal recipients treated with SRL-CsA containing regimen, with a 1-10 year (mean 60.3 months) follow-up period, only 30 cases of malignancy were encountered, resulting in a fairly low incidence of post-transplant malignancy, much lower than the incidence from a regimen containing tacrolimus (Tac)/ mycophenolate mofetil (MMF) [51]. In vitro and animal studies have also shown that SRL inhibited the proliferation

of Epstein-Barr virus (EBV)-infected B cell lines from patients with PTLD, and that of murine renal cancer cells [2;70].

Based on the experience from the clinical trials, the present strategy of immunosuppression for immediate functioning renal grafts at University of Texas, Health Science Center at Houston is the de novo use of SRL with CsA minimization: The initial CsA target concentration at 2-hour post-dose (C2) is 200-400 ng/ml: the bottom of the range is employed for low-risk, and the top, for high-risk recipients. The SRL regimen begins with a pre-transplant loading dose of 15 mg followed on Day 1 with 10 mg once or twice, then 5-10 mg/day, depending on the recipient's risk group and targeting at a C0 value of 10±3 ng/ml within 5 days. Then between 1 week and 3 months the dose adjustments of CsA are tailored according to the renal function; aiming at a serum Cr value < 1.2mg/ml, and a Cr clearance above 65 ml/min. For the majority of patients, whose SRL C0 value can be kept around 10 ng/ml, the target CsA C2 level is about 200 ng/ml by 3 months; for those with some SRL toxicity demanding reduction of SRL C0 to 5 ng/ml the target CsA C2 level is around 600 ng/ml [50].

This concept of de novo low CsA exposure from the beginning was further supported by Formica et al. who reported their experience using SRL (target C0 value, 10-15 ng/mL) with low dose CsA (target C0 value, 50-100 ng/mL), seeking to determine

whether it might provide effective immunosuppression while reducing associated nephrotoxicity. Among 121 renal transplant recipients, 62 received the SRL based regimen and 59 received MMF with all patients receiving CsA and ST. Unlike observations from the Phase III SRL studies, renal function was not adversely affected. However, similar to earlier clinical experiences, hematopoeitic abnormalities and hyperlipidemia were observed among patients who received SRL, and those abnormalities were readily controlled [17].

Other applications of SRL-CsA combination besides the previous-mentioned de novo usage are as follows:

Refractory Rejection

In a case of ongoing acute rejection in spite of repeated antilymphocyte antibody treatments SRL successfully reversed the markedly decreased renal perfusion, acute rejection, and allograft function [103]. Extension of this experience into a non-randomized trial of 36 renal recipients with either Banff grade IIB or III ongoing rejection episodes despite prior treatment with pulse or oral recycling of ST and at least one course of antilymphocyte treatment examined the efficacy of SRL (n=24) or MMF (n=12) added to a baseline regimen of CsA-ST to reverse these refractory rejections. Rescue therapy reversed the renal dysfunction in 96% of patients in the SRL group versus 67% in the MMF group (P=0.03) despite the fact that a greater

fraction of patients in the SRL (17 of 24) than the MMF group (6 of 12) had experienced two or more episodes of acute rejection before study entry and the fact that the recurrent bouts of acute rejection occurred within the first 6 months posttransplant in 94% of patients in the SRL group compared with 50% (P=0.005) in the MMF group. Among the patients who were reversed successfully, the rates of rebound acute rejection were similar (4% vs. 8%). The mean serum Cr values were slightly, although not significantly, lower among SRL than MMF patients at 1, 3, 6, and 12 months. The 1-year patient and graft survival rates were similar: namely, 88% vs. 92% and 83% vs. 67% for the SRL versus MMF groups [33].

Steroid withdrawal or sparing regimen

In Phase I/II and Phase II studies, steroids were successfully withdrawn in 67-93 % of renal allograft recipients in 1 week to 3 months after transplantation [46;52]. A further single-center open-labeled observation of 156 renal transplant recipients treated with SRL-CsA-ST triple therapy tempted steroid withdrawal at 1 week to more than 2 years post-transplant when the exposure of CsA Cav/ SRL C0 were over 200 ng/ml and 10 ng/ml, respectively. With a mean follow-up time of 379 days after withdrawal there was a 75.4% successful rate of steroid withdrawal, with 7.7% of graft loss [73]. In 30 long-term stable renal recipients treated with CsA-steroid immunosuppression who requested steroid withdrawal for a variety of steroid-induced

side effects, SRL successfully substituted for steroids in the majority (87%, 26/30) of patients, with the benefit of better quality of life assessments in many aspects, especially improved physical activity in all patients, and no significant adverse effects on blood pressure, serum cholesterol, triglyceride, and creatinine levels. SRL was targeted to 10 ng/ml while the CsA exposure was reduced by > 50% of the pre-enrollment levels for this withdrawal. Two grafts were lost 7 and 11 months after steroid withdrawal due to chronic rejection [38].

Delayed Graft Function (DGF)

Avoidance of CNIs, which were the cornerstone of immunosuppression in the past 20 years, for a prolonged period de novo after cadaveric renal transplantation may facilitate recovery from DGF when the nephrotoxic properties of CNI may exacerbate the ischemia-reperfusion injury. This can be successfully achieved by the use of chimeric (c-) anti-interleukin-2 receptor (IL-2R) monoclonal antibodies (mAb) in combination with SRL. In a pioneer series of 6 consecutive patients at risk for DGF treated with SRL (2-12 mg/day), c-IL-2R mAb (basiliximab), and ST, the inception of CsA therapy was withheld until serum Cr levels recovered. During the first 2 months posttransplant, none of the 6 patients displayed any evidence of acute rejection episodes, cytokine release syndrome, or hypersensitivity reactions. None of the patients received empiric bolus or high-dose steroid therapy for a presumed rejection

episode. All patients recovered renal function within 8 weeks posttransplant and maintained stable allograft function [30]. An extension of the observation onto 3 contemporaneous but nonrandomized cohorts were compared for acute rejection episodes, patient and graft survival rates, renal function, and adverse reaction profiles for 12 months. Patients with DGF were treated with either SRL/c-IL-2R mAb/ST with inception of CsA once the serum creatinine value was ≤2.5 mg/dl (n=43; group 1) or anti-lymphocyte preparations/ST/delayed CsA for 7 to 14 days (n=18; group 3). A third cohort displayed immediate function and was treated de novo with CsA/c-IL-2R mAb/ST (n=21; group 2). The incidence of acute rejection episodes was significantly lower among group 1 (16%) compared with groups 2 (52%, P=0.004) or 3 (39%, P=0.05). Among the seven rejection episodes in group 1, six of seven occurred among African-American or retransplant recipients, and a separate cluster of six of seven occurred among patients with lower SRL concentrations (≤ 9 ng/ml). Furthermore, Fewer patients in group 1 required additional antilymphocyte antibody treatment to reverse either steroid-resistant or Banff grades II or III acute rejection episodes. Patient and graft survival rates, as well as mean serum creatinine values, were similar at 12 months among the three groups. However, group 1 patients displayed higher serum cholesterol and triglyceride values, as well as lower hemoglobin, platelet, and leukocyte values compared with the other two groups. This study suggested that a

SRL/c-IL-2R mAb/ST induction regimen with delayed CsA inception provides excellent acute rejection prophylaxis [32]. Further modification of the protocol for high-risk recipients (African-American or retransplants) by substitution of thymoglobulin for c-IL-2R mAb significantly decreased the incidence of acute rejection episodes from 33% to 3%, although also with higher incidence of infectious complications [49].

The observation of Shaffer et al. echoed the use of SRL without CNI in DGF patients. There was no episode of acute rejection in 16 renal recipients with DGF or marginal donor kidneys who were administered thymoglobulin, SRL, MMF and steroids. The graft and patient survival were both 100% at a mean follow-up of 243 day [97].

A similar experience was reported by another group [7]. In their retrospective review of 14 consecutive kidney transplant recipients with DGF, followed up for 0.5-5.2 months, daclizumab induction (2 mg/kg), SRL (5-15 mg loading, then 2-5 mg/day maintenance), steroids, and MMF (1.5-3 g/day) were given. Nine patients required hemodialysis after transplantation. The mean time to initiation of CNIs was 21$\pm$13 d. Average serum creatinine levels at the initiation of SRL and at 1 month after transplantation were 8.4$\pm$2.7 and 2.1$\pm$1.2 mg/dL, respectively. Two patients (14%) experienced acute rejection within the first month after transplantation, and both had

initially undetectable serum SRL levels. No grafts were lost during the period of follow-up.

Contrary to the above reports, other authors from the same center of the last report recently suggested a different opinion, because they noticed prolongation of DGF coincident with their use of sirolimus. To investigate possible causes of prolonged DGF, extensive donor, recipient, transplant, and post-transplant data were retrospectively reviewed on 132 consecutive DGF cases between 1/1/97 and 6/30/01. Cox proportional hazards analysis of time to graft function was used in univariate and multivariate models to identify factors that prolong DGF. SRL had a large and highly significant effect on time to graft function (hazard ratio 0.48, $p = 0.0007$). This hazard ratio indicates that a recipient on SRL is half as likely to resolve DGF or twice as likely to remain on dialysis as compared to a recipient without SRL. SRL retained its profound negative association with time to graft function in all multivariate models. The authors initially concluded that SRL may not be the optimal immunosuppressive choice in the DGF setting [78]. However, they further found out that this prolongation of DGF by SRL does not adversely affect allograft function at 3 and 12 months, and graft or patient survival; yet the incidence of acute rejection episodes in these SRL-treated patients was higher than those treated with a regimen containing lymphocyte-depleting antibody without SRL [77].

Smith et al. also observed a higher risk of developing DGF in patients receiving SRL on the day of transplant compared to those not receiving SRL (p=0.02), and the development of DGF was significantly associated with an increasing dose of SRL (OR=1.13 per additional mg of SRL, p= 0.004) [104]. Stallone et al. reported that SRL did prolong DGF in recipients of suboptimal cadaveric donors (25 vs. 15 days, p= 0.02) as compared to the other group of recipients receiving CsA-based immunosuppressants, but interestingly these SRL-treated patients had better allograft renal function (mean serum creatinine of 1.4 vs. 1.9 mg/dl, p= 0.04) at 1 year post-transplant [105].

Elimination of CsA from SRL-CsA combination

In order to evaluate whether CsA could be eliminated from a SRL-CsA-ST regimen at 3 months, Johnson et al. conducted an open-label RMR (Rapamycin Maintenance Regimen) Study. Upon enrollment, 525 renal allograft recipients received 2 mg of SRL (C0>5 ng/ml), CsA, and steroids. At 3 months$\pm$2 weeks, 430 (82%) eligible patients were randomized (1:1) to remain on SRL-CsA-ST or to have CsA withdrawn and therapy continued with SRL (C0= 20-30 ng/ml)-ST. In the randomized patients, there was no difference in graft survival (95.8% vs. 97.2%, SRL-CsA-ST vs. SRL-ST) or patient survival (97.2% vs. 98.1%, respectively). The

incidence of biopsy-confirmed primary acute rejection was 13.1% during the pre-randomization period. After randomization, the acute rejection rates were 4.2% and 9.8% for SRL-CsA-ST and SRL-ST, respectively; which is slightly higher in the SRL-ST arm (P=0.035), but without an increase in graft loss within one year. Renal function (calculated glomerular filtration rate [GFR], 57 vs. 63 ml/min, P<0.001) and blood pressure significantly improved when CsA was withdrawn. Hypertension, CsA nephrotoxicity, hyperuricemia, and Herpes zoster occurred statistically more frequently in patients remaining on CsA, whereas thrombocytopenia, abnormal liver function tests, and hypokalemia were more common for SRL-ST therapy [37]. A protocol biopsy (at transplantation and at 1 year) analysis of a subgroup of patients in RMR study showed progression of a chronicity score in 64% of SRL-CsA-ST treated patients versus 47.4% of SRL-ST patients, although this difference was not yet statistically significant [92].

Long-term follow-up of the patients in the RMR study up to 36 months revealed that the discontinuation rate was significantly higher for SRL-CsA-ST group (48% vs. 38%, p=0.041) [48]. Graft survival (81.4% vs. 89.8%, or 85.6% vs. 92.6%, if loss to follow-up excluded), mean renal function (GFR, 47.3 vs. 59.0 mL/min), and blood pressure (including systolic, diastolic, and mean) were significantly better after CsA withdrawal [42,71]. The patients with their GFR in the lowest 3 quartiles at the

baseline (GFR≤ 67 mL/min; i.e. who with moderately impaired function) [48], and the patients with the presence of risk factors of reduced renal function (e.g.: CAD donor, DGF, donor age> 50 years, or HLA mismatch≥ 4) [64] undergoing CsA withdrawal had markedly and significantly better renal function outcomes. At 3 years, there were no significant differences in the incidence of death (7.4% vs. 4.2%), biopsy-proven acute rejection (6.0% vs. 10.2%), or the levels of serum lipids (including total cholesterol, triglyceride, LDL-C) after randomization [42,71]. The assessment of health-related quality of life (HRQOL) at months 12, 24 and 36, comparing with that at months 3, showed significantly better HRQOL in the SRL-ST patients regarding appearance, fatigue, vitality and social functioning scales (all p≤ 0.05) [61,62]. Based on the actual GFR values, the slope of GFR (-3.02 vs 0.77 mL/min per year, p<0.001), and graft loss rate, a predictive model of graft survival estimated a dramatic 20% difference in outcome between these 2 groups of patients over 10 years [4] [6;59;68;81;82;84;93]. The conclusion drawn from 36-month long-term observation of the RMR study is that SRL, CsA, and steroids for 3 months posttransplant, followed by elimination of CsA, is a safe and effective alternative to continuous therapy with SRL-CsA-ST that can result in better renal function, graft survival, HRQOL and lower blood pressure.

Gonwa et al. (Sirolimus Renal Function Study Group) conducted a similar

open-label, controlled, randomized study comparing the renal function in 97 patients receiving SRL (2mg/day, fixed dose)+ CsA (full dose)+ST (group A), versus concentration-controlled SRL (10-20 ng/ml)+ CsA (reduced dose)+ ST with subsequent elimination of CsA after months 2 (group B, 100 patients). The results showed better renal function (both serum Cr and GFR, $p < 0.01$) in group B patients at 12 months, with similar rates of biopsy-confirmed acute rejection, graft survival, and patient survival. Seventy-six of the 100 recipients completed the CsA withdrawal. However, patients in group B had a significantly greater incidence of abnormal liver function tests, diarrhea, hypokalemia, and thrombocytopenia. A subgroup analysis of black recipients in group B also revealed better renal function than black patients in group A [23].

Another randomized study comparing the efficacy and renal function in patients receiving concentration-controlled SRL (C0= 4-12 ng/ml)+ CsA (C0= 125-250 ng/ml)+ ST for 3 months with subsequent elimination (eCsA) or minimization (mCsA, C0= 50-100 ng/ml) of CsA, and increased SRL maintenance concentrations (C0= 8-16 ng/ml) also demonstrated better renal function (both serum Cr and GFR, $p < 0.005$) in eCsA patients at 12 months, with 4/58 (mCsA) and 8/59 patients (eCsA) experienced acute rejection episodes after randomization, while the other adverse events in the 2 groups were similar [36].

Combinations of SRL with other immunosuppressants

SRL in combination with Tacrolimus

Results of clinical trials

Although both SRL and tacrolimus (Tac) bind to FK-binding proteins (FKBP) in the lymphocytes to exert their immunosuppressive activities, the amount of FKBP are still excessive even when occupied by highest therapeutic concentrations of both drugs in combination without definite antagonistic effects. Since McAlister et al. reported that a pilot series of 32 recipients of liver, kidney, or pancreas transplants treated with SRL and low-dose Tac experienced a low rate of acute rejection episodes and good graft function with some mild drug-related toxic effects [75], great enthusiasm had emerged in using this SRL-Tac combination for primary immunosuppression. Several groups reported preliminary (small patient number), retrospective, nonrandomized, or single-arm treatment results [3;14;22;28;57;62;66;91;100;110;114], with different concentration ranges of these two drugs or by adding other immunosuppressants in the regimen (detailed on Table 1); however, only very few large-scale, randomized, prospective studies [4;13;18;21;24;27;65;69;83;89;99;109;113] were carried out, and they yielded different, intricate or equivocal results. All these made a scientific non-biased

evaluation of the efficacy and safety of this SRL-Tac combination quite difficult.

Gonwa et al.[20] reported the first randomized, multicenter, clinical trial comparing the combination of SRL or mycophenolate mofetil (MMF) with Tac +steroid-based immunosuppression in kidney transplantation. By 6 months of follow-up, the incidence of biopsy-confirmed acute rejection, patient and graft survival and the incidence of posttransplant diabetes mellitus were similar in both treatment groups. There was a significantly higher incidence of study drug discontinuation in patients receiving SRL (P=0.008), and renal function was significantly better in the MMF group (P=0.018). Hyperlipidemia and high diastolic blood pressure was significantly more prevalent in the SRL group. There were significantly more leukopenia and gastrointestinal adverse events in the MMF group. They concluded that tacrolimus is equally effective in renal transplantation when combined with SRL or MMF. The Tac-MMF combination may be superior in terms of improved renal function and improved cardiovascular risk factors including hyperlipidemia and hypertension [79]

Pharmacologic interactions between SRL and Tac

Since the clinical development of SRL started with its combination with CsA, the pharmacologic interactions between SRL and Tac are far less studied and understood than those between SRL and CsA, which has been reviewed extensively

elsewhere [40;42;74].

In a pharmacokinetic (PK) study of 10 stable renal transplant recipients, lymphocyte proliferative response to PHA, Con A and Anti-CD3 were all significantly decreased in patients who received both Tac and SRL compared to Tac alone. The mRNA expression of proinflammatory cytokines TNF-alpha, cyclins G and E (all $p< 0.05$) were decreased, and of TGF-beta and p21 (both $p< 0.05$) were increased in patients treated with SRL+Tac. Circulating levels of IFN-gamma, IL-4, and IL-2 (all $p < 0.05$) were significantly inhibited and elevation of TGF-beta ($p < 0.04$) was observed in patients treated with Tac and SRL combination [58]. Although these in vitro findings demonstrate that the addition of SRL to Tac therapy enhances immunomodulation and causes increased immunosuppression, there was no enough solid data to show whether the interaction is synergistic or merely addictive.

In contrast to the fact that simultaneous dosing of SRL with CsA increases the exposure of SRL than a 4-hour-apart dosing strategy [55], neither pharmacokinetic (PK) profiles of SRL nor those of Tac were altered by simultaneous administration when compared with a 4-hour dosing protocol. These data were from completed full PK studies of 25 liver and kidney- pancreas transplant recipients treated with a combination of SRL [C0 range = _6-12 ng/mL] and low-dose Tac [C0 range = _3-7 ng/mL]. The correlation between C0 levels and AUC drug exposure was excellent in

this study (Tac: r2 = 0.82; SRL: r2 = 0.83), indicating that trough level monitoring is adequate to control therapy for both drugs [76].

Contrary to the well-defined increased dose-corrected drug exposure of both CsA and SRL when they are co-administered as compared to when either one is used alone, the available data of the influence on their respective dose-corrected exposure of co-administration of Tac and SRL compared to separate dosing is not that clear and somewhat confusing. In a review of pharmacokinetics of Tac-based study, Undre reported that co-administration of Tac and SRL, while having no effect on exposure to SRL, results in reduced exposure to Tac at SRL doses of 2 mg/day and above, and he suggested that the concentrations of Tac should be monitored when SRL is co-administered at doses more than 2 mg/day [107]. Another report focusing on recipients on a low dose of SRL combining with a standard dose of Tac concluded that it require dose increments of SRL over time in order to maintain constant SRL exposure [63]. Interestingly, Sindhi et al. showed that in pediatric patients the exposure of Tac was not affected significantly after SRL was added [101]. Other important PK interactions of SRL with Tac in pediatric patients included shorter half-life (13-19 hours) of SRL in children, which might necessitate twice daily dosing in children. Liver and small intestine recipients may require larger doses to achieve target drug exposure [94;102].

The combination of SRL and Tac is not always safe and without sequela. There was a report of severe acute oliguric renal failure after exposure to SRL-Tac regimen in two living donor kidney recipients who required temporary dialysis therapy and cessation of SRL-Tac therapy [67]. Another consideration is that exposing patients simultaneously under two highly potent immunosuppressants, though resulting in a quite low incidence of short-term acute rejection episodes, as shown on the Table, might easily lead to over-immunosuppression and unwanted long-term adverse effects, like post-transplant diabetes mellitus, BK virus infection, and PTLD, which might be more evident in years [48].

SRL in combination with antimetabolites

Totally CNI-Free SRL-base Studies

The clinical development of SRL in Europe, besides joining the Phase III Global pivotal trial, started earlier in two Phase II studies [26;61] in which SRL was tested as a cornerstone of the immunosuppressant regimen to subtitute CNI, which has been the mainstay of immunosuppressant for the past 20 years.

These two randomized open-label, concentration-controlled study in renal transplantation comparing SRL to CsA in a triple-drug therapy regimen with one trial

using Aza-ST and the other using MMF (2 g/day)-ST supplement. At 12 months, graft survival, patient survival, and the incidence of biopsy-proven acute rejection episodes (41% SRL vs. 38% CsA [25]; 27.5% SRL vs. 18.4% CsA [60]) were similar between both arms of each trial. In both studies, there is a trend for better renal function in SRL-treated patients.

The profiles of the adverse events, which indicate the likelihood of SRL toxicities at a higher concentration-exposure, in these 2 studies were also similar. The most frequently reported side effects were thrombocytopenia (37- 45%), leukopenia (39%), hypertriglyceridemia (51%), hypercholesterolemia (44%) and diarrhea (38%). Other abnormalities also significantly more often associated with SRL included higher incidences of herpes simplex (24%) and pneumonia (17%), increased liver enzymes and hypokalemia. These abnormalities improved 2 months after transplantation when the SRL target C0 level was lowered from 30 to 15 ng/ml.

The pooled 2-year data analysis of renal function parameters from these two studies showed that from week 10 through year 2, calculated GFR was significantly higher in SRL- than in CsA-treated patients (69.3 vs. 56.8 mL/min, at 2 years, $p = 0.004$). Serum uric acid was significantly higher and magnesium was significantly lower in the CsA-treated patients; these parameters were more likely to be within normal limits in the SRL group. Mean serum potassium and phosphorus were lower in

SRL-treated patients [80].

Flechner et al. [16] conducted another similar randomized, prospective CNI-free study in 61 adult primary kidney transplant recipients by adding IL-2R mAb and lowering the target SRL concentration in the immunosuppressive regimen. Each patient received induction therapy with 20 mg basiliximab on days 0 and 4, and maintenance therapy with MMF 2 g per day and steroids. Thirty-one patients received SRL, 5 mg daily after a 15-mg loading dose. Doses were then concentration-controlled to keep SRL C0 levels at 10- 12 ng/mL for 6 months and 5-10 ng/mL thereafter. Thirty patients began CsA at 6- 8 mg/kg/day and were then concentration-controlled to keep 12-hr C0 of 200- 250 ng/mL. Mean follow-up is 18.1 months (range, 12- 26 months). The percentages of 1-year patient survival, graft survival, and biopsy-confirmed acute rejection rates (SRL 6.4% vs. CsA 16.6%), were not significantly different between the SRL-treated and the CsA-treated patients. At 6 and 12 months, respectively, the SRL-treated patients enjoyed significantly better (P=0.008 and P=0.004) mean serum Cr levels (1.29 and 1.32 mg/dL) and calculated Cr clearances (77.8 and 81.1 mL/min) than CsA-treated patients (1.74 and 1.78 mg/dL, and 64.1 and 61.1 mL/min, respectively). SRL-treated recipients have significantly (P=0.001) higher 1-year C0 levels of mycophenolic acid (4.16 ng/mL) than CsA-treated patients (1.93 ng/mL). SRL also delays the repopulation of

basiliximab-depleted CD25 T cells compared with CsA.

The overall results of these studies suggest that SRL, if well concentration-controlled, can be used as primary base therapy in the prophylaxis of acute renal transplant rejection, and has a safety profile that differs from CsA, with a more favorable outcome in renal function.

Conversion to SRL for CNI- free Immunosuppression

The first important formal report of conversion to SRL immunosuppression was carried out initially without drug monitoring to adjust SRL doses. In 20 patients 0 to 204 months posttransplant with chronic CsA or Tac nephrotoxicity (12), acute CsA or Tac toxicity (3), severe facial dysmorphism (2), PTLD in remission (2), and hepatotoxicity (1), CNI was switched to fixed dose (5 mg/day) of SRL. After a follow-up of 7 to 24 months, in the 12 patients switched because of chronic nephrotoxicity, there was a significant decrease in serum Cr (2.6 to 2.3 mg/dl at 6 months, $P<0.05$). Facial dysmorphism improved in both two patients. No relapse of PTLD was observed. SRL was discontinued in four of the 20 patients because of adverse effects. Five patients developed pneumonia and two had bronchiolitis obliterans. There were no deaths. The authors concluded that SRL conversion provides adequate immunosuppression to enable CsA withdrawal, and SRL drug

levels should be monitored to avoid over-immunosuppression [11].

Wyzgal et al. [111] converted 13 renal transplant recipients with biopsy proven CNI nephrotoxicity to SRL therapy, targeting SRL C0 levels of 12-20 ng/ml. Although the renal function (including serum Cr and GFR) significantly improved up to 6 months, the severity of proteinuria continued to deteriorate ($p= 0.04$). One of the 13 patients experienced an episode of acute rejection after conversion, and two were taken off SRL because of pneumonia.

Diekmann et al. converted initially 20, further increased to 59, renal transplant recipients with biopsy proven CNI nephrotoxicity to SRL, targeting a lower SRL C0 levels of 8-12 ng/ml. After one year of follow-up, graft survival was 90%, and about 55% of patients had better or stable graft function (mean serum Cr from 2.76 to 2.22 mg/dl, $p< 0.01$), whereas the others' renal function and severity of proteinuria continued to deteriorated significantly (mean serum Cr from 3.23 to 4.43 mg/dl, $p< 0.01$). Important adverse effects in their series included anemia, necessitating erythropoietin therapy in 65% of patients, and dyslipidemia. SRL was discontinued in 14% of patients because of side effects or graft failure. They also identified that those who with low proteinuria or serum Cr below 3 mg/dl are more likely benefit from SRL conversion [9;10].

The experience from University of Maryland, Baltimore in converting 107 renal

recipients with biopsy proven chronic allograft nephropathy showed a different scenario. Although improvement of Cr clearance (CrCl) was noted in 70% of their patients, yet most significant improvement was observed in the group with lowest mean pre-conversion baseline CrCl (28.4$\pm$19.4 ml/min) [108].

Other reports of conversion to SRL because of moderate renal insufficiency or chronic allograft nephropathy yielded similar results with low risk of acute rejection (3.3-7%) and graft loss, and a trend towards improved or stable renal function. However a substantial part (7-30%) of patients discontinued because of the adverse effects of SRL [1;8;83;85].

The present strategy of chronic immunosuppressive maintenance at University of Texas, Health Science Center at Houston still stands on the basis of SRL-CsA combination with steroid elimination first. For each individual patient, the relative severity of adverse effects associated with CsA or with SRL determines the drug dose ratio during chronic therapy. Generally, CsA exposure is gradually reduced over time. Virtually all patients receive $\leq$ 50 mg CsA microemulsion twice daily at 6 months, thereafter taper to 50 mg once daily by 2 years. For 140 patients treated with this low-exposure CsA plus SRL regimen, there was a significant reduction in the incidence of chronic allograft nephropathy. In the presence of a serum Cr$\geq$ 2.0 mg/dl, CsA is further reduced to an alternate or every third day regimen with SRL C0 level

kept at 10 ng/ml, at which level there is a lowest incidence of chronic allograft nephropathy, as found by a receiver operating characteristic analysis. Only for the patient whose serum Cr fails to improve with the above maneuver is CsA discontinued, and in a few high-risk patients CsA is substituted with MMF [47].

Chronic SRL Monotherapy

In order to change the fact that transplant recipients need life-long multidrug treatment which usually includes CNIs and steroids, and often with undesirable chronic side effects, Swanson et al. [106] carried out an open-label pilot study containing aggressive T-cell depletion (high dose of rabbit antithymocyte globulin, RATG, for 8-10 days) combined with SRL (targeting at C0 of 10-15 ng/ml) monotherapy in 12 patients. Only 3 doses of 125-500 mg methylprednisolone were given as a pre-medication for RATG. This approach was tolerated well, all patients achieved good renal function at 12 months, and most of them (10/12) did not need chronic steroid or CNI treatment. Under protocol biopsies, 3 rejection episodes (1 Banff 1A, 1 Banff 1B, 1 subclinical 1A) were encountered, which correlated with low SRL concentrations, indicating continued dependence on maintenance immunosuppression of these renal recipients. Adverse events included 8 admissions in 6 patients, 8 mouth ulcers, 2 arthralgia and 10 patients requiring anti-hyperlipidemic drugs. No severe infectious events, malignant disease, or PTLD

were encountered. Further investigation of the intragraft RNA transcriptional analysis of the allograft specimen at various time points of protocol biopsies, and compared to specimen from grafts of standard triple immnunotherapy showed that there were less intragraft inflammation (CD3, CD28, CD154, IL2, IL12) in the RATG treated grafts at 1 month post-transplant and at the time of acute rejection [54].

This observation of successful SRL monotherapy was echoed by a similar study from Donati et al., who described a protocol of lymphocyte depletion induction with thymoglobulin (7 mg/kg cumulatively) followed by SRL maintenance (C0= 10-15 ng/ml during 1st 3 months then 5-10 ng/ml) and short-term therapy with MMF (for 5 months) and steroid (for 3 months), but without any CNI. Graft and patient survival were both 96% in 23 patients enrolled during a follow-up of 80-350 days, and mean serum Cr level in the remaining 21 grafts was 1.27mg/dl, with only one episode of acute rejection encountered. But adverse events, like thrombocytopenia, leucopenia, bacterial and fungal infection, hematoma, lymphocele, and delayed wound healing were of serious concern with this approach [12].

Application of SRL in Special Patient Population

African-Americans renal transplant recipients or recipients of black ethnicity have long been known as a group of high-risk patients. Accumulated data from

various centers revealed that the addition of SRL to the immunosuppressive armaments can mitigate the greater proclivity to acute rejection episodes and graft loss of the African-Americans.

African-American renal transplant recipients treated with either CsA-ST (n = 90) or SRL-CsA-ST (n = 47) regimen were compared with 120 Caucasian patients treated with SRL-CsA-ST for 2-year rates of patient and graft survival as well as acute rejection episodes by using Kaplan-Meier and log-rank tests. Addition of SRL to the CsA-ST regimen reduced the incidence of acute rejection episodes in African-Americans from 43.3% to 19.2% (P = 0.004), a value similar to that in Caucasian patients. The 97.9% 2-year graft survival rate among 47 African-American patients treated with SRL-CsA-ST was significantly higher than the 85.6% rate shown among the 90 CsA-ST treated African-American transplant recipients (P = 0.0479) and similar to that in Caucasians. The 95.7% patient survival rate among the African-American SRL-CsA-ST group was similar to the 97.8% rate in the African-American CsA-ST cohort [87]. An extended cohort recruiting more African-American renal recipients (n= 122) treated with SRL-CsA-ST onto 3 years still showed decreased cumulative incidence of acute rejection episodes from 60% to 22%, with similar graft and patient survival rate, in spite of reduced CsA doses by over 50% compared to the CsA-ST cohort. Interestingly, African-Americans treated with

SRL-CsA-ST experienced significantly fewer SRL-related side effects than the Caucasians treated with the same regimen [86]. The addition of sirolimus to a CsA-based regimen reduced acute rejection episodes and graft loss experienced by African-American renal transplant recipients.

Hricik et al. reported a 2-year study comparing 56 African-Americans treated with steroids, SRL (target C0 at 10-20 ng/ml), and low-dose Tac (target C0 at 5-8 ng/ml), without the use of induction antibody therapy versus 65 Caucasian renal recipients treated with steroids, MMF, and high-dose Tac (target C0 at 8-12 ng/ml). The incidence of acute rejection in the first 3 post-transplant months was 7.1% in African Americans and 16.9% in whites (P=NS). Actuarial 2-year patient, graft, and rejection-free graft survival rates were equivalent in the two groups. lower trough levels of tacrolimus, compared with of white patients. [Jeff: What does this mean? Please delete the above sentence] Post-transplantation diabetes mellitus (PTDM, 36% in African-Americans vs. 15% in Caucasian Americans, P=0.024) [Jeff: What are you comparing? See text added above] remains a problem for African-Americans receiving this combination of immunosuppressants, despite similar doses of corticosteroids and lower tacrolimus blood levels [35]. An amendment of the protocol tried to withdraw steroid after 3 months in 30 African-Americans treated with corticosteroids, SRL, and low-dose Tac in order to reduce the incidence of PTDM.

Although the incidence of acute rejection (13%), graft and patient survival were acceptable, and 80% recipients completed steroid withdrawal, there was significant deterioration of long-term graft renal function (mean serum Cr increased from 1.4 mg/dl before tapering steroid, to 1.65 [those without rejection], or 2.2 mg/dl [all recipients], both $p< 0.05$) [34].

In a study of 70 kidney recipients of black ethnicity randomized after day 7 to median (target C0 at 8-12 ng/ml, n=34) or high (target C0 at 15-20 ng/ml, n=36) levels of SRL, combining with reduced exposure of CsA (C0 at 1 m= 170, at 6 m=70 ng/ml) and steroid, the incidences of biopsy proved acute rejection at 6 months were both quite low (11.7% and 8.3%, respectively), and only 3 graft loss occurred in all these 70 patients. Except from lower hemoglobin levels in the high SRL group patients, renal function, lipid profiles, and episodes of other adverse events were similar in both groups [72].

Conclusions

Sirolimus (SRL), originally designed to be an adjunct immunosuppressant to the traditional immunosuppressant armaments, developed over the past 10 years into capable of playing a diversity of roles in organ transplantation depending on how the immunosuppressive regimen is constructed. Some of these regimens have been time-tested to yield excellent long-term outcomes in renal transplantation; whereas the

others, though seem feasible with the immediate outcome, still await the results or adverse effects of longer follow-up to be proven as practical for routine applications. SRL, as a base therapy, is evolving into another cornerstone of immunosuppression in kidney transplantation because of its high immunosuppressive potency. Its optimal target concentrations need to be specifically and meticulously tailored when used in combination with other immunosuppressants, the concentrations or doses of which also require delicate therapeutic monitoring, to achieve excellent outcomes with fewer adverse effects.

Table [2]: Study Designs and Results of Various SRL-Tac Combined Immunosuppression in Kidney Transplantation

	Study Type	**Comparator**	**Other IS**	**N**	**[SRL]**	**[Tac]**	**F/U (mons)**	**GS/PS (% / %)**	**AR (%)**	**sCr (mg/dl)**	**Specific AE Remark**	**Discontinuation (%)**
Gonwa et al. [19;79]	p/r/c	SRL	ST	185	4-12	5-15 (8.5)	6	93/97.3	13	1.77	hyperCHO hyperLDL	21.1
		MMF		176	1.5g/d MMF	(8.7)		95.5/97.7	11.4	1.44*	More MMF dose changes	10.8*
Lawen et al [64]	p/nr/c	SRL+Tac	Bax/ATG	25	5 mg/d	3-5	9	96/92	16	1.4	ND	ND
		MMF+CsA	ST	38	2g/d MMF	CsA0-4AUC 4400-5500		100/97.3	8.9	1.54	ND	ND

Youseff	np/nr/c	High risk	ST	48	5-15	5-15	12	93.8/97.9	8.3	ND	3/48lymphocele	3/48
, Small		recipients									2/48 pneumonia	
[112]		AZA+CsA		103	AZA2-3	CsA-ND		89.3/99	38.8*	ND	ND	ND
					mg/kg/d							
Keough-	p/nr/c		ST	24	8-12 then	3-6	12	ND	16.7	GFR=	ND	ND
Ryan et					5-10					75.9		
al [57]										ml/min		
		MMF+CsA		75	MMF 2g/d	C2 CsA		ND	32	GFR=	ND	ND
						1700-2100 then				73.8		
						800-1000				ml/min		

Burke et al [5]	p/r/c	SRL+Tac (A)	Dac ST	50	8 (bid)	10/<3m 6-8/3-12m 6/>12m	12	96/ND	ND	ND	Higher SRL dose to C0 of 8 than (C)	ND
		MMF+Tac (B)		50	MMF 2g/d	10		95/ND	ND	ND		ND
		SRL+CsA (C)		50	8 (bid)	C0 CsA 200-250 /<3m 175-225/3-12m 150-200/>12m		92/ND	ND	ND	More hyperlipid	ND

Lo et al [69;109]	p/r/c	SRL+Tac	ATG ST	41	10.9	4.4	12	85/98	Protocol bx@3m 10	GFR=68	1/41HUS slightly more PTDM, wound complications	ND
		SRL+MMF		27	14.2	MMF 2g/d		93/100	19 (3/5 SCAR)	GFR=81 *	ND	ND
Whelchel et al [83;109]	p/r/c	Low Tac	ST	184	9.5	3-7 (5.9)	6	94.6/96.2	14.9	1.38 GFR=70 .2	Anemia Hyperlipid	29.3

]		High Tac		177	8.2*	8-12 (9.2*)		96.6/98.3	10.1	1.65* GFR=58 .9*	Anemia Hyperlipid diarrhea	29.9
Grinyo et al [24]	p/r/c	Taper Tac off	ST	42	8-16	3-8/<3m then taper	6	Similar GS/PS	11.1 (22.7)	1.3	Off Tac in 70% Higher CHO* 27% low plt	ND
		High Tac		44	4-8	8-12/<3m 5-10/>3m			10.7 (9.5)	1.5*	4% low plt*	ND
					Difficult to achieve target trough in both groups							

Kumar et at.[62]	p/r/c		Bax Tac ST (2 d	20	10	10-15	12	95/95	5 15SCAR 20CAN	1.8	Protocol bx No PTDM	ND
		MMF	taper off)	29	MMF2g/d	10-15		95/100	14 14SCAR 25CAN	1.7	3% PTDM	ND
Woodle et al [110]	p/nr/nc	-	Bax ST (5 d taper off)	66	8-15	6-9/<1m 4-8/>1m	6	100/100	6	1.38	80% off ST improved BP control, renal function improving over	12/66

											time	
Hartwig et al [29]	np/nr/ nc	-	ST	11	6-8	5-7	13.8	100/100	0	1.6	hyperlipidemia	ND
Shapiro et al [98]	np/nr/ nc	-	ST	30	6-10/<3m 5-7 />3m	8-10/<3m 5-7/>3m	7.7	93/97	16, 12 (SCAR)	1.8	PTDM 10% Protocol bx	30
Rashid et al [90]	np/nr/ nc	-	ST, 65% Bax/Dac	74	13.9/<1m 7.5/>1m	10/<1m 5-10/>1m	19	100/ND	13.5/ 1 yr	ND	PTDM 8%	3/74

El-Sabr	np/nr/	-	Bax	20	10-15	10-15/<2m	13	100/100	5	1.2	pediatric pts	ND
out et al	nc		ST			5-10/>2m					15%lymphocele	
[15]											5%PTLD	

Study Type: p= prospective, np=not prospective (retrospective), r= randomized, nr=not randomized, c= comparative, nc=single treatment arm

IS= immunosuppressant(s)

N= patient number in that specific group

[SRL]: the concentration ranges of SRL or the dose or concentration ranges of the comparator in that specific group

[Tac]: the concentration ranges of Tac or the dose or concentration ranges of the comparator in that specific group

F/U: duration of follow-up

GS/PS: graft survival rate/ patient survival rate

AR: incidence of acute rejection episodes

AE: adverse events

*= statistically significant difference as compared between the study group and its comparator

ND= not determined/ not mentioned

SCAR= subclinical acute rejection

Bax= basiliximab, ATG= antithymocyte globulin, Dac= daclizumab

Reference List

1. Amm JM, Ramamurthy G, Degala A, Patel A, Goggins M, Karthikeyan V, Fisher K, Parasuraman R, Venkat KK (2003) Rapamycin substitution for calcineurin inhibitors in renal tranplant recipients with chronic allograft nephropathy: a report of 57 cases. Am J Transplantation 3:Abstract 235

2. Balbtoni CE, Nepomuceno RR, Krams SM, Martinez OM (2003) Sirolimus inhibits cell growth and the expression of cyclin proteins in EBV-associated B cell lymphomas derived from patients with PTLD. Am J Transplantation 3:Abstract 684

3. Burke GW, Ciancio C, Blomberg BB, Rosen A, Suzart K, Roth D, Kupin W, Esquenazi V, Miller J (2002) Randomized trial of three different immunosuppressive regimens to prevent chronic renal allograft rejection. Transplant.Proc. 34:1610-1611

4. Burke GW, Ciancio C, Blomberg BB, Rosen A, Suzart K, Roth D, Kupin W, Esquenazi V, Miller J (2002) Randomized trial of three different immunosuppressive regimens to prevent chronic renal allograft rejection. Transplant.Proc. 34:1610-1611

5. Burke GW, Ciancio C, Blomberg BB, Rosen A, Suzart K, Roth D, Kupin W, Esquenazi V, Miller J (2002) Randomized trial of three different immunosuppressive regimens to prevent chronic renal allograft rejection. Transplant.Proc. 34:1610-1611

6. Campistol JM, Oberbauer R, Kreis H, Brault Y, Burke JT (2003) Predicting 10-year graft survival with sirolimus used either as base therapy or in association with cyclosporine. Am J Transplantation 3:Abstract 1258

7. Chang GJ, Mahanty HD, Vincenti F, Freise CE, Roberts JP, Ascher NL, Stock PG, Hirose R (2000) A calcineurin inhibitor-sparing regimen with sirolimus, mycophenolate mofetil, and anti-CD25 mAb provides effective immunosuppression in kidney transplant recipients with delayed or impaired graft function. Clin.Transplant. 14:550-554

8. Crowley KL, Hardinger KL, Koch M, Miller B, Mindel G, Brennan D (2003) A single-center experience with sirolimus conversion therapy in renal allograft recipients. Am J Transplantation 3:Abstract 786

9. Diekmann F, Budde K, Torregrossa JV, Oppenheimer F, Fritsche L, Neumayer HH, Campistol JM (2003) Improvement of renal transplant function in patients with chronic calcinurin-inhibitor nephrotoxicity and low proteinuria one year after conversion to sirolimus. Am J Transplantation 3:Abstract 181

10. Diekmann F, Waiser J, Fritsche L, Dragun D, Neumayer HH, Budde K (2001) Conversion to rapamycin in renal allograft recipients with biopsy-proven calcineurin inhibitor-induced nephrotoxicity. Transplant.Proc. 33:3234-3235

11. Dominguez J, Mahalati K, Kiberd B, McAlister VC, MacDonald AS (2000) Conversion to rapamycin immunosuppression in renal transplant recipients: report of an initial experience. Transplantation 70:1244-1247

12. Donati D, Ambrosini A, Marconi AM (2003) Pilot study of lymphocyte depletion induction with thymoglobulin followed by sirolimus and mycophenolate mofetil: a calcineurin-inhibitors free, steroid sparing and likely tolerogenic protocol for kidney transplantation. Am J Transplantation 3:Abstract 1120

13. El Sabrout R, Weiss R, Butt F, Delaney V, Qadir M, Hanson P, Butt K (2002) Rejection-free protocol using sirolimus-tacrolimus combination for pediatric renal transplant recipients. Transplant.Proc. 34:1942-1943

14. El Sabrout R, Weiss R, Butt F, Delaney V, Qadir M, Hanson P, Butt K (2002) Rejection-free protocol using sirolimus-tacrolimus combination for pediatric renal transplant recipients. Transplant.Proc. 34:1942-1943

15. El Sabrout R, Weiss R, Butt F, Delaney V, Qadir M, Hanson P, Butt K (2002) Rejection-free protocol using sirolimus-tacrolimus combination for pediatric renal transplant recipients. Transplant.Proc. 34:1942-1943

16. Flechner SM, Goldfarb D, Modlin C, Feng J, Krishnamurthi V, Mastroianni B, Savas K, Cook DJ, Novick AC (2002) Kidney transplantation without calcineurin inhibitor drugs: a prospective, randomized trial of sirolimus versus cyclosporine. Transplantation 74:1070-1076

17. Formica RN, Lorber KM, Friedman AL, Bia MJ, Lakkis F, Smith JD, Lorber MI (2003) Sirolimus-based immunosuppression with reduce dose cyclosporine or tacrolimus after renal transplantation. Transplant.Proc. 35:S95-S98

18. Gaber LW, Lo A, Egidi MF, Gaber AO (2003) Renal protocol biopsy findings

in patients receiving rapamycin bases immunosuppression with or without low dose calcineurin inhibitor. Am J Transplantation 3:Abstract 843

19. Gonwa T, Mendez R, Yang HC, Weinstein S, Jensik S, Steinberg S (2003) Randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 6 months. Transplantation 75:1213-1220

20. Gonwa T, Mendez R, Yang HC, Weinstein S, Jensik S, Steinberg S (2003) Randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 6 months. Transplantation 75:1213-1220

21. Gonwa T, Mendez R, Yang HC, Weinstein S, Jensik S, Steinberg S (2003) Randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 6 months. Transplantation 75:1213-1220

22. Gonwa T, Mendez R, Yang HC, Weinstein S, Jensik S, Steinberg S (2003) Randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 6 months. Transplantation 75:1213-1220

23. Gonwa TA, Hricik DE, Brinker K, Grinyo JM, Schena FP (2002) Improved renal function in sirolimus-treated renal transplant patients after early cyclosporine elimination. Transplantation 74:1560-1567

24. Grinyo JM, Campistol JM, Garcia J, Paul J, Morales JM, Arias M, Prats D (2003) Sirolimus and tacrolimus in renal transplant: results of a randomized trial of a maintenance therapy based in sirolimus versus the combination of sirolimus and tacrolimus. Am J Transplantation 3:Abstract 1256

25. Groth CG, Backman L, Morales JM, Calne R, Kreis H, Lang P, Touraine JL, Claesson K, Campistol JM, Durand D, Wramner L, Brattstrom C, Charpentier B (1999) Sirolimus (rapamycin)-based therapy in human renal transplantation: similar efficacy and different toxicity compared with cyclosporine. Sirolimus European Renal Transplant Study Group. Transplantation 67:1036-1042

26. Groth CG, Backman L, Morales JM, Calne R, Kreis H, Lang P, Touraine JL, Claesson K, Campistol JM, Durand D, Wramner L, Brattstrom C, Charpentier B (1999) Sirolimus (rapamycin)-based therapy in human renal transplantation:

similar efficacy and different toxicity compared with cyclosporine. Sirolimus European Renal Transplant Study Group. Transplantation 67:1036-1042

27. Hartwig T, Pridohl O, Witzigmann H, Lamesch P, Fangmann J, Hauss J, Kohlhaw K (2001) Low-dose sirolimus and tacrolimus in kidney transplantation: first results of a single-center experience. Transplant.Proc. 33:3226-3228

28. Hartwig T, Pridohl O, Witzigmann H, Lamesch P, Fangmann J, Hauss J, Kohlhaw K (2001) Low-dose sirolimus and tacrolimus in kidney transplantation: first results of a single-center experience. Transplant.Proc. 33:3226-3228

29. Hartwig T, Pridohl O, Witzigmann H, Lamesch P, Fangmann J, Hauss J, Kohlhaw K (2001) Low-dose sirolimus and tacrolimus in kidney transplantation: first results of a single-center experience. Transplant.Proc. 33:3226-3228

30. Hong JC, Kahan BD (1999) Use of anti-CD25 monoclonal antibody in combination with rapamycin to eliminate cyclosporine treatment during the induction phase of immunosuppression. Transplantation 68:701-704

31. Hong JC, Kahan BD (2000) Sirolimus-induced thrombocytopenia and leukopenia in renal transplant recipients: risk factors, incidence, progression, and management. Transplantation 69:2085-2090

32. Hong JC, Kahan BD (2001) A calcineurin antagonist-free induction immunosuppression strategy for delayed graft function in renal transplantation. Transplant.Proc. 33:1271-1272

33. Hong JC, Kahan BD (2001) Sirolimus rescue therapy for refractory rejection in renal transplantation. Transplantation 71:1579-1584

34. Hricik DE, Knauss TC, Bodziak KA, Weigel K, Siegel C, Valente J, Schulak JA (2003) Steroid withdrawal in african american kidney transplant recipients receiving sirolimus and tacrolimus: analysis of renal function beyond one year. Am J Transplantation 3:Abstract 96

35. Hricik DE, Anton HA, Knauss TC, Rodriguez V, Seaman D, Siegel C, Valente J, Schulak JA (2002) Outcomes of African American kidney transplant recipients treated with sirolimus, tacrolimus, and corticosteroids.

Transplantation 74:189-193

36. Jardine AG (2003) 12 month results of a phase III prospective, randomised study to evaluate concentration controlled rapamune with cyclosporine dose minimization or elimination in *de novo* renal allograft recipients. Am J Transplantation 3:Abstract 1206

37. Johnson RW, Kreis H, Oberbauer R, Brattstrom C, Claesson K, Eris J (2001) Sirolimus allows early cyclosporine withdrawal in renal transplantation resulting in improved renal function and lower blood pressure. Transplantation 72:777-786

38. Kahan BD, Podbielski J, Dejian L, VanBuren C (2003) Substitution of sirolimus for steroids in long-term renal transplant recipients treated with cyclosporine. Am J Transplantation 3:Abstract 779

39. Kahan BD (2000) Efficacy of sirolimus compared with azathioprine for reduction of acute renal allograft rejection: a randomised multicentre study. The Rapamune US Study Group. Lancet 356:194-202

40. Kahan BD (2001) Sirolimus: a comprehensive review. Expert.Opin.Pharmacother. 2:1903-1917

41. Kahan BD (2001) Sirolimus: a comprehensive review. Expert.Opin.Pharmacother. 2:1903-1917

42. Kahan BD (2002) Update on pharmacokinetic/pharmacodynamic studies with FTY720 and sirolimus. Ther.Drug Monit. 24:47-52

43. Kahan BD (2003) Two-year results of multicenter phase III trials on the effect of the addition of sirolimus to Cyclosporine-based immunosuppressive regimens in renal transplantation. Transplant.Proc. 35:S37-S51

44. Kahan BD, Camardo JS (2001) Rapamycin: clinical results and future opportunities. Transplantation 72:1181-1193

45. Kahan BD, Julian BA, Pescovitz MD, Vanrenterghem Y, Neylan J (1999) Sirolimus reduces the incidence of acute rejection episodes despite lower cyclosporine doses in caucasian recipients of mismatched primary renal allografts: a phase II trial. Rapamune Study Group. Transplantation 68:1526-1532

46. Kahan BD, Julian BA, Pescovitz MD, Vanrenterghem Y, Neylan J (1999) Sirolimus reduces the incidence of acute rejection episodes despite lower cyclosporine doses in caucasian recipients of mismatched primary renal allografts: a phase II trial. Rapamune Study Group. Transplantation 68:1526-1532

47. Kahan BD, Knight R, Schoenberg L, Pobielski J, Kerman RH, Mahalati K, Yakupoglu Y, Aki FT, Katz S, Van Buren CT (2003) Ten years of sirolimus therapy for human renal transplantation: the University of Texas at Houston experience. Transplant.Proc. 35:S25-S34

48. Kahan BD, Knight R, Schoenberg L, Pobielski J, Kerman RH, Mahalati K, Yakupoglu Y, Aki FT, Katz S, Van Buren CT (2003) Ten years of sirolimus therapy for human renal transplantation: the University of Texas at Houston experience. Transplant.Proc. 35:S25-S34

49. Kahan BD, Knight R, Schoenberg L, Pobielski J, Kerman RH, Mahalati K, Yakupoglu Y, Aki FT, Katz S, Van Buren CT (2003) Ten years of sirolimus therapy for human renal transplantation: the University of Texas at Houston experience. Transplant.Proc. 35:S25-S34

50. Kahan BD, Knight R, Schoenberg L, Pobielski J, Kerman RH, Mahalati K, Yakupoglu Y, Aki FT, Katz S, Van Buren CT (2003) Ten years of sirolimus therapy for human renal transplantation: the University of Texas at Houston experience. Transplant.Proc. 35:S25-S34

51. Kahan BD, Knight R, Schoenberg L, Pobielski J, Kerman RH, Mahalati K, Yakupoglu Y, Aki FT, Katz S, Van Buren CT (2003) Ten years of sirolimus therapy for human renal transplantation: the University of Texas at Houston experience. Transplant.Proc. 35:S25-S34

52. Kahan BD, Podbielski J, Napoli KL, Katz SM, Meier-Kriesche HU, Van Buren CT (1998) Immunosuppressive effects and safety of a sirolimus/cyclosporine combination regimen for renal transplantation. Transplantation 66:1040-1046

53. Kahan BD, Podbielski J, Napoli KL, Katz SM, Meier-Kriesche HU, Van Buren CT (1998) Immunosuppressive effects and safety of a sirolimus/cyclosporine combination regimen for renal transplantation. Transplantation 66:1040-1046

54. Kampen RL, Hoffmann SC, Hale DA, Mannon RB, Cendales LC, Swanson SJ, Kirk AD (2003) Intragraft renal allograft transcriptional analysis during rabbit anti-thymocyte globulin induction and sirolimus monotherapy compared to standard of care triple immunosuppression. Am J Transplantation 3:Abstract 619

55. Kaplan B, Meier-Kriesche HU, Napoli KL, Kahan BD (1998) The effects of relative timing of sirolimus and cyclosporine microemulsion formulation coadministration on the pharmacokinetics of each agent. Clin.Pharmacol.Ther. 63:48-53

56. Kelly PA, Napoli K, Kahan BD (1999) Conversion from liquid to solid rapamycin formulations in stable renal allograft transplant recipients. Biopharm.Drug Dispos. 20:249-253

57. Keough-Ryan TM, Weerasinghe, Kirkland SA, Lawen JG, Kiberd BA (2003) Comparison of sirolimus vs. cyclosporine based immunosuppressive therapy in renal transplant recipients. Am J Transplantation 3:Abstract 252

58. Khanna A, Plummer M, Bromberek K, Woodliff J, Hariharan S (2002) Immunomodulation in stable renal transplant recipients with concomitant tacrolimus and sirolimus therapy. Med.Immunol. 1:3

59. Kreis H, Oberbauer R, Mota A, Claesson K, Riad H, Campistol JM, Wilczek H, Arias M, Henriques AC, Paczek L, Chapman J, Burke JT (2003) Sirolimus-based therapy following early cyclosporine withdrawal results in superior renal allograft survival compared with a continuous combination of sirolimus and cyclosporine. Am J Transplantation 3:Abstract 1203

60. Kreis H, Cisterne JM, Land W, Wramner L, Squifflet JP, Abramowicz D, Campistol JM, Morales JM, Grinyo JM, Mourad G, Berthoux FC, Brattstrom C, Lebranchu Y, Vialtel P (2000) Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. Transplantation 69:1252-1260

61. Kreis H, Cisterne JM, Land W, Wramner L, Squifflet JP, Abramowicz D, Campistol JM, Morales JM, Grinyo JM, Mourad G, Berthoux FC, Brattstrom C, Lebranchu Y, Vialtel P (2000) Sirolimus in association with mycophenolate mofetil induction for the prevention of acute graft rejection in renal allograft recipients. Transplantation 69:1252-1260

62. Kumar A, Lee D, Xiao SG, Moritz MJ, Fyfe B, Heifets M, Sierka D, AnilKumar MS (2003) Comparison of tacrolimus and sirolimus combination with FK506 and mycophenolate mofetil in kidney transplant recipients with steroid avoidance. Am J Transplantation 3:Abstract 771

63. Kuypers DRJ, Claes K, Evenepoel P, Maes B, Vanrenterghem Y (2003) Twelve-month pharmacokinetic study of the novel combination of tacrolimus and rapamycin in *de novo* renal allograft recipients. Am J Transplantation 3:Abstract 1257

64. Lawen J, Keough-Ryan T, Clase C, Kiberd B (2001) Sirolimus and low-dose tacrolimus with antibody induction in kidney transplantation: preliminary results of a pilot study. Transplant.Proc. 33:3223-3225

65. Lawen J, Keough-Ryan T, Clase C, Kiberd B (2001) Sirolimus and low-dose tacrolimus with antibody induction in kidney transplantation: preliminary results of a pilot study. Transplant.Proc. 33:3223-3225

66. Lawen J, Keough-Ryan T, Clase C, Kiberd B (2001) Sirolimus and low-dose tacrolimus with antibody induction in kidney transplantation: preliminary results of a pilot study. Transplant.Proc. 33:3223-3225

67. Lawsin L, Light JA (2003) Severe acute renal failure after exposure to sirolimus-tacrolimus in two living donor kidney recipients. Transplantation 75:157-160

68. Legendre C, Mota A, Friend P, Segoloni G, Grinyo JM, Hutchison B, Morales JM, Lawen J, Martinez J, Hartmann A, Doyen K (2003) Superior renal funtion after early cyclosporine withdrawal and sirolimus maintenance therapy, regardless of baseline renal function: intent-to-treat results at 3 years. Am J Transplantation 3:Abstract 1225

69. Lo A, Egidi MF, Gaber LW, Amiri HS, Vera S, Nezakatgoo N, Christenson A, Kelley M, Gaber AO (2003) Comparison of two different rapamycin based immunosuppressive regimens in cadaveric renal transplantation. Am J Transplantation 3:Abstract 1205

70. Luan FL, Hojo M, Maluccio M, Yamaji K, Suthanthiran M (2002) Rapamycin blocks tumor progression: unlinking immunosuppression from antitumor efficacy. Transplantation 73:1565-1572

71. MacDonald AS (2001) A worldwide, phase III, randomized, controlled, safety and efficacy study of a sirolimus/cyclosporine regimen for prevention of acute rejection in recipients of primary mismatched renal allografts. Transplantation 71:271-280

72. Machado PG, Felipe CR, Park SI, Garcia R, Franco M, Alfieri F, Casarini DE, Tedesco-Silva H, Medina-Pestana JO (2003) Concentration-controlled use of sipolimus associated with reduced exposure of cyclosporine in black patients. Am J Transplantation 3:Abstract 777

73. Mahalati K, Kahan BD (2001) A pilot study of steroid withdrawal from kidney transplant recipients on sirolimus-cyclosporine a combination therapy. Transplant.Proc. 33:3232-3233

74. Mahalati K, Kahan BD (2001) Clinical pharmacokinetics of sirolimus. Clin.Pharmacokinet. 40:573-585

75. McAlister VC, Gao Z, Peltekian K, Domingues J, Mahalati K, MacDonald AS (2000) Sirolimus-tacrolimus combination immunosuppression. Lancet 355:376-377

76. McAlister VC, Mahalati K, Peltekian KM, Fraser A, MacDonald AS (2002) A clinical pharmacokinetic study of tacrolimus and sirolimus combination immunosuppression comparing simultaneous to separated administration. Ther.Drug Monit. 24:346-350

77. McTaggart R, Bostrom A, Bacchetti P, Roberts J, Tomlanovitch S, Feng S (2003) Prolongation of delayed graft function by sirolimus does not adversely affect transplant outcomes. Am J Transplantation 3:Abstract 1602

78. McTaggart RA, Gottlieb D, Brooks J, Bacchetti P, Roberts JP, Tomlanovich S, Feng S (2003) Sirolimus prolongs recovery from delayed graft function after cadaveric renal transplantation. Am.J.Transplant. 3:416-423

79. Mendez R (2003) Six-month results of the first prospective, randomized, multi-center kidney transplant study comparing tacrolimus+rapamune vs. tacrolimus+MMF combination therapy. Am J Transplantation 3:Abstract 1552

80. Morales JM, Wramner L, Kreis H, Durand D, Campistol JM, Andres A, Arenas J, Negre E, Burke JT, Groth CG (2002) Sirolimus does not exhibit nephrotoxicity compared to cyclosporine in renal transplant recipients.

Am.J.Transplant. 2:436-442

81. Oberbauer R, Hutchison B, Eris J, Riad H, Claesson K, Lawen J, Mota A, Castagneto M, Morales JM, Kreis H, Wang F, Zhang H (2003) Three-year assessment of health-related quality of life in sirolimus-treated kidney transplantatients after cyclosporine elimination. Am J Transplantation 3:Abstract 249

82. Oberbauer R, Hutchison B, Eris J, Arias M, Claesson K, Mota A, Kreis H, Kleinman L, Wang F, Chen J, Revicki DA (2003) Health-related quality-of-life outcomes of sirolimus-treated kidney transplant patients after elimination of cyclosporine A: results of a 2-year randomized clinical trial. Transplantation 75:1277-1285

83. Paczek L, Dedochova J, Matl I, Pohanka E (2003) An open non comparative pilot study of renal function after conversion form cyclosporine to sirolimus in stable renal allograft recipients with mild to moderate renal insufficiency. Am J Transplantation 3:Abstract 258

84. Paczek L, Mota A, Schena FP, Johnson RWG, Prats D, Mathew T, Morales JM, Daloze P, Bourbigot B, Gioud-Paquet M (2003) Renal function benefit from sirolimus maintenance therapy after early cyclosporine withdrawal in the presence of risk factors. Am J Transplantation 3:Abstract 180

85. Peddi VR, Cohen DJ, First MR (2003) An open-label pilot study evaluating the safety and efficacy of converting from calcineurin inhibitors to sirolimus in renal allograft recipients on maintenance therapy with moderate renal insufficiency. Am J Transplantation 3:Abstract 234

86. Podder H, Dejian L, Schoenberg L, Knight R, Kats S, VanBuren C, Kahan B (2003) Improved outcomes of renal transplantation in 122 african-americans treated with a sirolimus-cyclosporine regimen: comparison to a cyclosporine-prednisone regimen and to caucasians. Am J Transplantation 3:Abstract 795

87. Podder H, Podbielski J, Hussein I, Katz S, Van Buren C, Kahan BD (2001) Sirolimus improves the two-year outcome of renal allografts in African-American patients. Transpl.Int. 14:135-142

88. Podder H, Stepkowski SM, Napoli KL, Clark J, Verani RR, Chou TC, Kahan BD (2001) Pharmacokinetic interactions augment toxicities of

sirolimus/cyclosporine combinations. J.Am.Soc.Nephrol. 12:1059-1071

89. Rashid I, El Sabrout R, Butt F, Delaney V, Qadir M, Hanson P, Butt K (2002) Medium-term outcome using sirolimus-tacrolimus combination in adult renal transplant recipients. Transplant.Proc. 34:1649-1650

90. Rashid I, El Sabrout R, Butt F, Delaney V, Qadir M, Hanson P, Butt K (2002) Medium-term outcome using sirolimus-tacrolimus combination in adult renal transplant recipients. Transplant.Proc. 34:1649-1650

91. Rashid I, El Sabrout R, Butt F, Delaney V, Qadir M, Hanson P, Butt K (2002) Medium-term outcome using sirolimus-tacrolimus combination in adult renal transplant recipients. Transplant.Proc. 34:1649-1650

92. Ruiz JC, Campistol JM, Mota A, Prats D, Gutierrez A, Castro A, Pinto JR, Garcia J, Morales JM, Grinyo JM, Arias M (2002) Early cyclosporine a withdrawal in kidney transplant recipients under a sirolimus-based immunosuppressive regimen: pathological study of graft biopsies at 1-year posttransplant. Transplant.Proc. 34:92-93

93. Schena FP, Jamieson N, Colon J, Shoker A, Pena J, Martinez J, Walker R, Arns W, Johnson R, Gioud-Paquet M (2003) Favorable cardiovascular risk profile when sirolimus is used without cyclosporine compared to combination therapy: 3-year results of the rapamune maintenance regimen trial. Am J Transplantation 3:Abstract 1275

94. Schubert M, Shaw L, Holt D, Venkataramanan R, Sindhi R (2003) Pharmacokinetics of sirolimus in pediatric transplant recipients receiving tacrolimus. Am J Transplantation 3:Abstract 7

95. Sehgal SN (1998) Rapamune (RAPA, rapamycin, sirolimus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. Clin.Biochem. 31:335-340

96. Sehgal SN (1998) Rapamune (RAPA, rapamycin, sirolimus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. Clin.Biochem. 31:335-340

97. Shaffer D, Nylander WA, Kizilisik, Helderman JH, Langone A (2003) A pilot study of a calcineurin-inhibitor free protocol for kidney transplant recipients with delayed graft function or marginal donor kidney. Am J Transplantation

3:Abstract 787

98. Shapiro R, Scantlebury VP, Jordan ML, Vivas CA, Jain A, Hakala TR, McCauley J, Johnston J, Randhawa P, Fedorek S, Gray E, Chesky A, Dvorchik I, Donaldson J, Fung JJ, Starzl TE (2002) A pilot trial of tacrolimus, sirolimus, and steroids in renal transplant recipients. Transplant.Proc. 34:1651-1652

99. Shapiro R, Scantlebury VP, Jordan ML, Vivas CA, Jain A, Hakala TR, McCauley J, Johnston J, Randhawa P, Fedorek S, Gray E, Chesky A, Dvorchik I, Donaldson J, Fung JJ, Starzl TE (2002) A pilot trial of tacrolimus, sirolimus, and steroids in renal transplant recipients. Transplant.Proc. 34:1651-1652

100. Shapiro R, Scantlebury VP, Jordan ML, Vivas CA, Jain A, Hakala TR, McCauley J, Johnston J, Randhawa P, Fedorek S, Gray E, Chesky A, Dvorchik I, Donaldson J, Fung JJ, Starzl TE (2002) A pilot trial of tacrolimus, sirolimus, and steroids in renal transplant recipients. Transplant.Proc. 34:1651-1652

101. Sindhi R, Webber S, Goyal R, Reyes J, Venkataramanan R, Shaw L (2002) Pharmacodynamics of sirolimus in transplanted children receiving tacrolimus. Transplant.Proc. 34:1960

102. Sindhi R, Webber S, Goyal R, Reyes J, Venkataramanan R, Shaw L (2002) Pharmacodynamics of sirolimus in transplanted children receiving tacrolimus. Transplant.Proc. 34:1960

103. Slaton JW, Kahan BD (1996) Case report--sirolimus rescue therapy for refractory renal allograft rejection. Transplantation 61:977-979

104. Smith KD, Wrenshall LE, Nicosia RF (2003) Delayed graft function and cast nephropathy associated with tacrolimus plus rapamycin use. J Am Soc Nephrolin press

105. Stallone G, Infante B, Schena A, DiPaolo S, Gesualdo L, Ditonno P, Battaglia M, Grandaliano G, Schena FP (2003) Sirolimus prolongs delayed graft function in recipients of sub-optimal cadaveric kidney donors. Am J Transplantation 3:Abstract 1601

106. Swanson SJ, Hale DA, Mannon RB, Kleiner DE, Cendales LC, Chamberlain CE, Polly SM, Harlan DM, Kirk AD (2002) Kidney transplantation with rabbit antithymocyte globulin induction and sirolimus monotherapy. Lancet 360:1662-1664

107. Undre NA (2003) Pharmacokinetics of tacrolimus-based combination therapies. Nephrol.Dial.Transplant. 18:I12-I15

108. Wali RK, Richards A, Cunningham R, Drachenberg C, Ramos E, Brisco M, Wiland AM, Philosophe B, Bartlett S, Weir M (2003) Can we change the progressive decay in graft function after the onest of chronic allograft nephropahty in the recipients of kidney allografts?(preleminary results of the ongon study). Am J Transplantation 3:Abstract 720

109. Whelchel J, Paczek L, Bechstein WO, Russ G (2003) A regimen of sirolimus and reduced-dose tacrolimus results in improved renal allograft function: combined analysis of the north american target, european and australian sirolimus-tacrolimus trials. Am J Transplantation 3:Abstract 1218

110. Woodle ES, Vincenti F, Lorber M, Gritsch A, Washburm K, Matas A, Gallichio M (2003) A multicenter, open label pilot study of early corticosteroid cessation in *de novo* renaltransplant recipients under simulect, tacrolimus, and sirolimus therapy: interim analysis. Am J Transplantation 3:Abstract 1128

111. Wyzgal J, Paczek L, Senatorski G, Zygier J, Rowinski W, Szmidt J, Perkowska A (2002) Sirolimus rescue treatment in calcineurin-inhibitor nephrotoxicity after kidney transplantation. Transplant.Proc. 34:3185-3187

112. Youseff N, Small S (2002) A retrospective analysis of a sirolimus/prograf regimen for the prevention of acute rejection in recipients of primary mismatched renal allografts. Transplant.Proc. 34:1653-1655

113. Youseff N, Small S (2002) A retrospective analysis of a sirolimus/prograf regimen for the prevention of acute rejection in recipients of primary mismatched renal allografts. Transplant.Proc. 34:1653-1655

114. Youseff N, Small S (2002) A retrospective analysis of a sirolimus/prograf regimen for the prevention of acute rejection in recipients of primary mismatched renal allografts. Transplant.Proc. 34:1653-1655