African Journal of Nephrology (2004) 8:97-103

AJN

Original Article

Sirolimus based therapy in live-donor renal transplantation: A prospective randomized study

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Abstract

Background/Aim: Calcineurin inhibitor nephrotoxicity has been one of the major clinical problems in clinical practice after renal transplantation. This study was conducted assuming that the advent of novel, potent and non-nephrotoxic immunosuppressant, sirolimus may counterbalance the calcineurin inhibitor dose reduction or avoidance to guard against nephrotoxicity.
Methods: Between May 2001 and June 2002, 80 live donor renal allotransplant recipients were subjected to a prospective, randomized controlled trial where they were divided into two equal demographically matched groups to receive either low dose tacrolimus (0.03 mg/kg/day) {Group A} or mycophenolate mofetil (MMF 2gm/day) {Group B} in combination with sirolimus (5 and 10 mg/day in group A and B respectively). All patients received steroids, according to local protocol, and basiliximab induction therapy. One year follow up for all patients was carried out including histological evaluation of renal allograft tissue at the end of first year.
Results: One-year patient and graft survival rates were not significantly different between group A (97.5%, 94.6%) and group B (100%, 97.4%) respectively. However, group B patients experienced lower incidence of biopsy proven acute rejection, albeit statistically insignificant, being 10% in group B and 25% in group A. Moreover, group B patients demonstrated better renal allograft function as measured by serum creatinine at all studied time points. In addition, 1-year protocol biopsies showed significant lower incidence of tubular atrophy and interstitial fibrosis among group B patients.
Conclusion: The present study demonstrates that excellent one year kidney transplant outcome can be achieved by sirolimus administration, especially with avoidance of calcineurin inhibitors.

Key words: Immunosuppression; Renal transplantation; Sirolimus

Introduction

Although short term renal allograft survival has improved since the introduction of cyclosporine (CsA) in 1976, long term renal allograft survival remains a major concern with chronic renal allograft dysfunction (CRAD) being the principal cause of late renal allograft loss after the first year [1].
While acute rejection episodes and HLA mismatching remain the most important alloantigen-dependent factors predictive of future CRAD, alloantigen-independent factors also contribute to its pathogenesis. Nephrotoxicity induced by calcineurin inhibitors (CsA and tacrolimus) is considered one of the most significant alloantigen-independent causes of CRAD [2].
Sirolimus, an immunosuppressant that has not been associated with nephrotoxicity in phase I or II studies [3] and has been shown to have only marginal effects on renal and glomerular dynamics in an experimental study of rats [4], may offer the advantage of providing both prophylaxis against acute rejection episodes and permitting maximal recovery of kidney function after transplantation.
Synergistic interaction between sirolimus and tacrolimus in prolongation of heart allograft survival in rats [5] had encouraged McAlister and colleagues [6] to examine sirolimus and tacrolimus regimen in human transplantation which proved to be safe and highly effective in prevention of acute rejection inspite of steroid withdrawal from all patients beyond 3 months.

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However, this trial was uncontrolled, non-randomized including different organ transplantation.
Calcineurin inhibitors free regimens using sirolimus as base therapy in combination with an antiproliferative agent, either azathioprine or MMF, have been evaluated in two phase II multicenter studies conducted in Europe [7,8]. Both studies showed that renal function was superior among patients receiving sirolimus-based therapy compared with those receiving CsA-based therapy, however higher than desired rates of acute rejection were obtained being 41% and 27.5% in the previous two studies respectively.
The objective of this work is to assess safety and efficacy profiles of sirolimus in combination with either low dose tacrolimus or mycophenolate mofetil after live donor kidney transplantation.

Materials and methods

Patients: Between May 2001 and June 2002, a total of 80 patients of either sex, aging 18-60 years with end stage renal disease, who had undergone live donor renal allotransplantation in Urology and Nephrology Center Mansoura University, were recruited into the study. Exclusion criteria consisted of prior transplantation or pretransplant chemistries demonstrating a total serum cholesterol greater than 300 mg/dl, triglycerides greater than 400 mg/dl, white blood cell count less than $4000/mm^3$ or platelets less than $150,000/mm^3$. All patients had a pretransplant negative lymphocytotoxic cross match test and at least 50% DR match.
Immunosuppression protocol: The patients were prospectively randomized prior to transplantation into two groups; group (A) patients received sirolimus solution (Rapamune, Wyeth-Ayerst) within 24 hours after completion of surgery in a dose of 10 mg/day orally (single morning dose) for 3 days and then maintained on 5 mg/day. Further doses were concentration controlled to keep 24 hour whole blood trough level between 6-12 ng/ml. Tacrolimus (Prograf; Fujisawa Healthcare, Inc) was also administered to this group of patients on the third day postoperative, provided that creatinine clearance is above 50 ml/min. Tacrolimus was started at 0.03 mg/kg/day in two epually divided doses. Further doses were subsequently adjusted to maintain 12 hour whole blood trough level of 3-7 ng/ml (6). Group (B) patients received sirolimus and maintained on single oral morning dose of 10mg/day targeting 24 hour whole blood trough level between 10-15 ng/ml. Mycophenolate Mofetil (Cellcept, Hoffman-La Roche) 1 gm twice daily was begun the morning after surgery. Patients remained on this dose unless side effects such as gastrointestinal toxicity or leukopenia necessitated dose reduction. All patients in both groups received basiliximab (Simulect, Novartis) 20 mg intravenously at surgery and on day 4 postoperative. Patients in both groups received intravenous methyl prednisolone 500 mg one day before and on day of surgery. Oral prednisolone was then given at a dose of 1 mg/kg/day which is then gradually tapered down to 0.1 mg/kg by the 10^{th} month post-transplantation.
Parameters of Prospective evaluation: All patients were followed up for a minimum of 12 months period.

1) Clinical assessment: A patient is considered hypertensive if blood pressure exceeds 140/90 mm/Hg. Number of antihypertensive drugs was reported for every patient to express severity of hypertension. Clinical tolerance to given medications was assessed which included the safety profile and occurrence of any adverse events.
2) Laboratory Investigations: The renal allograft function was assessed each visit by estimation of serum creatinine. Other laboratory tests included complete urine analysis, serum electrolytes, liver function tests, fasting blood sugar, uric acid, calcium, phosphorus and complete lipid profile. Therapeutic drug monitoring of sirolimus and tacrolimus was carried out. Sirolimus assay was performed using high performance liquid chromatography (HPLC) technique with mass spectroscopy detection. Blood samples were regularly collected from patients and sent frozen to a qualified laboratory in Germany (Zentrum Innere Medizin, Abt. Klinische, chemie/ Zentrallabor, 37075 Gottingen). The assay was performed every 3 weeks post-transplantation for the first 2 months and then every 6 weeks for all patients. Tacrolimus assay was carried out each visit by estimation of tacrolimus whole blood trough level (12 hours) using micro-particulate enzyme immunoassay method based on Abbott IMX analyzer in a semi-automated technique.
3) Histopathological examination of the graft biopsy: In this work, renal allograft tissue histopathologic examination was carried out in case of; delayed graft function, nephrotic range proteinuria, episodes of renal dysfunction (25% increase in creatinine from base line), in addition to routine protocol core biopsy at 1 year post-transplantation. Histological examination was performed according to Banff Schema 1997 .The histological "chronic allograft damage index; CADI" was used for estimation of the protocol graft biopsies performed at 1 year post-transplantation. This index was created for comparison of the impact of different treatment options on renal allograft histology [9].

Statistical analysis

The findings were recorded, tabulated and analyzed using SPSS for windows (SPSS inc. Chicago). T-test was used to compare between the two groups in continuous data while non continuous data were compared using Mann-whitney U test. Chi square and chi square with Yates' correction were used to compare categorical variables. The survival of the graft was computed using the Kaplan-Meier technique.

Differences in survival were calculated by the log rank test. P value < 0.05 was considered statistically significant.

Results

Demography: Both groups were homogenous regarding demographic and base line characteristics (table 1).

Table 1. Demography and base line Characteristics

	Group A (FK 506)	*Group B (MMF)*	*P-value*
Number of patients	40	40	
Recipients' age (year)	32.8 ± 10.8	31.3 ± 7.9	0.484
Recipients'sex (male:female)	30 : 10	25 : 15	0.292
Recipients' body weight (kg)	65 ± 13.1	67.2 ± 16	0.503
Original kidney disease:			
Mesangiocapillary GN	3	2	
FSGS	1	4	
Obstructive Uropathy	-	1	
Chronic pyelonephritis	10	6	
Polycystic kidney	-	1	
Hereditary Nephritis	3	2	
Renal Amyloidosis	1	1	
End stage kidney (Biopsy)	9	6	
Unknown	7	10	
Others	6	7	0.439
Pretransplant hypertension	30	31	0.792
History of Urinary bilharziasis	15	12	0.478
Recipient HCV antibody: - (Positive: negative)	15:25	20:30	0.259
Donors' age (year)	37.2 ± 10.8	36.1 ± 10.5	0.632
Tissue matching:			
Number of HLA (A&B) Matches:			
Four mismatch	2	1	
Three mismatch	5	4	
Two mismatch	23	26	0.731
One mismatch	4	6	
Zero mismatch	6	3	
Number of DR Matches:			
One mismatch	31	31	1.00
Zero mismatch	9	9	

Values are expressed as mean ± standard deviation.

Immunosuppressive drugs: Mean tacrolimus dose required to achieve target trough level reached the maximum value 7.57 mg/day (0.1 mg/kg/day) by the end of second week post-transplantation. Temporal significant reduction of mean tacrolimus dose was noticed (p=0.008) down to 2.98 mg/day (0.04 mg/kg/day) by the end of the first year. On the other hand, mean tacrolimus trough level was kept within the target window (3-7 ng/ml) throughout the whole study follow up period. Starting dose of MMF was reduced form 2 gm/day to a mean of 1.72 gm/day by the second week post-transplantation after which the dose remained more or less stable till the end of the first year (P=0.656). Significant reduction of mean sirolimus dose was noticeded over time in both groups (P=0.001) (figure 1). Mean sirolimus levels were kept within target therapeutic window in each group correspondingly except for the first 3 months at which mean levels were above targets. Group B patients had significantly higher mean sirolimus trough levels than group A at most follow up periods (figure2).

Graft function: A trend towards better graft function as measured by serum creatinine was noticed among patients of group B at different time points; however it did not rank to statistical significance (table 2).

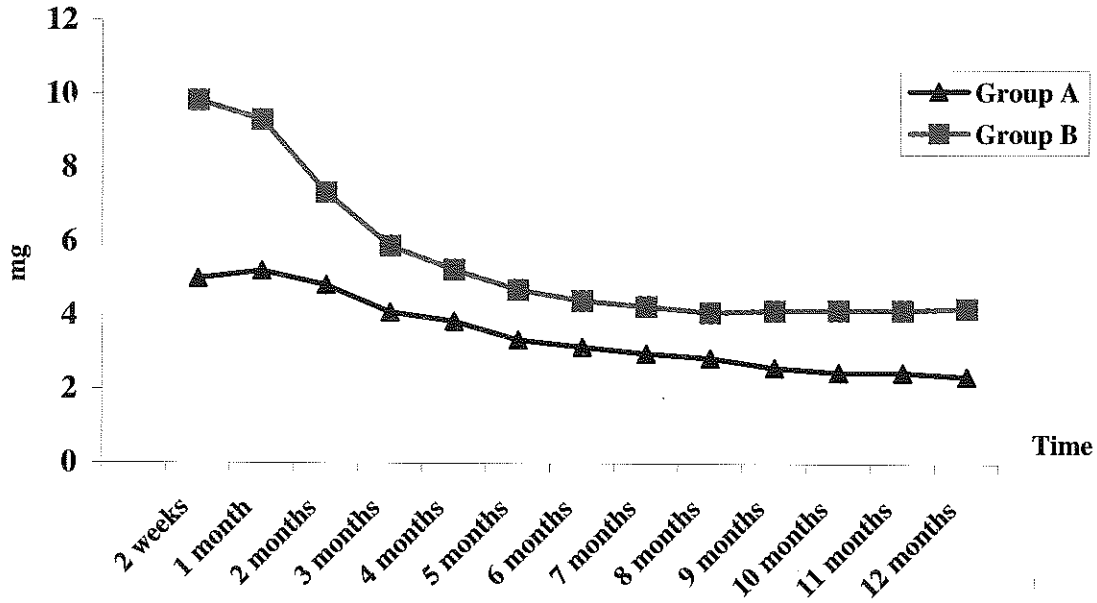

Fig. 1. Mean Sirolimus dose

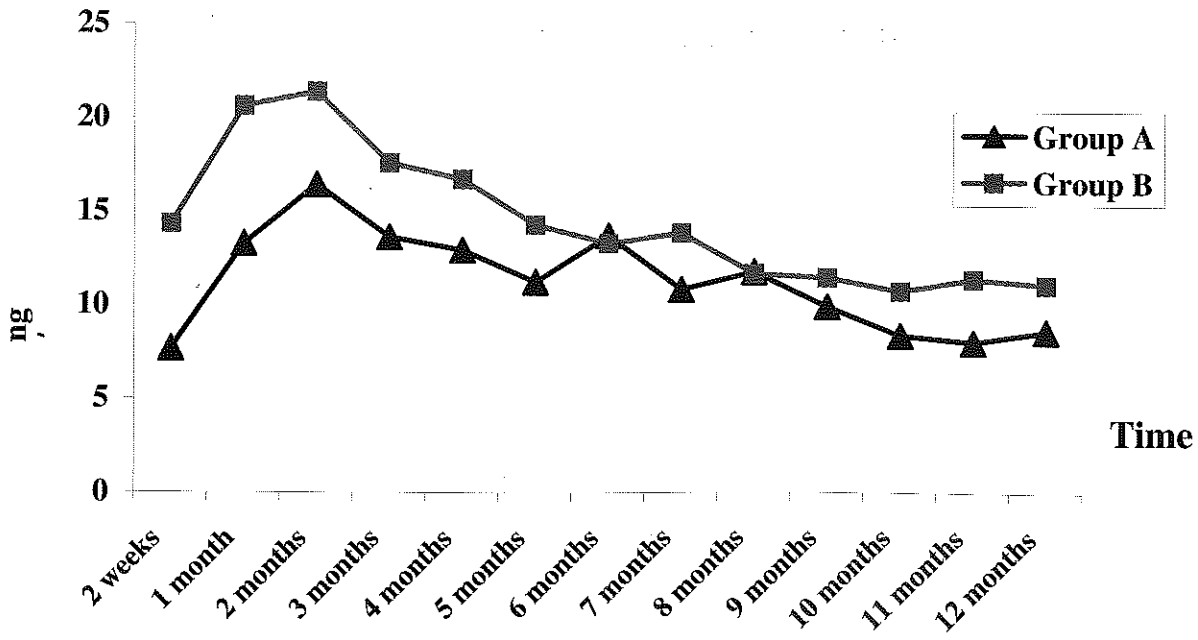

Fig. 2. Mean Sirolimus level (ng/ml) in both groups at different follow up periods

Table 2. Graft function: Mean serum creatinine (mg/dL)

Time	*Group A*	*Group B*	*P-value*
	(Mean ± SD)	(Mean ± SD)	
2 weeks	1.18 ± 0.21	1.12 ± 0.24	0.253
1 month	1.27 ± 0.49	1.12 ± 0.26	0.119
3 months	1.27 ± 0.35	1.21 ± 0.40	0.516
6 months	1.28 ± 0.35	1.24 ± 0.54	0.675
12 months	1.32 ± 0.47	1.18 ± 0.37	0.168

Histopathological findings: The impact of immunosuppression was reflected on the incidence and frequency of acute rejection episodes being less frequent in group B patients (10% versus 25% in group A) and also less severe however it did not rank to statistical significance (table 3). De novo glomerulonephritis had been diagnosed in 2 cases among group A [minimal change disease and membranoproliferative glomerulonephritis (MPGN) type I] and 3 cases among group B [all have focal segmental glomerulosclerosis (FSGS)]. Recurrent original kidney disease was diagnosed in one and three patients in group A and B respectively. Higher CADI score in group A (2.70) than group B patients (2.44) was noticed however it did not reach statistical significance (P=0.303). Regarding incidence of histopathologic findings in renal allograft protocol biopsies, tubular atrophy and interstitial fibrosis were found to be significantly higher among group A than group B patients (table 4).

Table 3. Frequency and severity of acute rejection episodes

	Group A	*Group B*	*P-value*
No rejection	30	36	0.077
One episode	7	2	0.076
Two episodes	3	2	0.644
Acute rejection episodes:			
- Total number	13	6	0.065
- Banff. Grade			
* Border line	6	2	0.598
* Grade I	4	4	0.140
* Grade II	3	--	0.199

Table 4. Histopathological findings in renal allograft protocol biopsies (1 year)

	Group A	*Group B*	*P.value*
Mesangial Matrix Increase	40%	23.1%	0.192
Glomerular sclerosis	12%	30.8%	0.103
Tubular Atrophy	88.9%	61.5%	0.020
Interstitial inflammation	18.5%	23.1%	0.682
Interstitial fibrosis	77.8%	46.2%	0.017
Vascular intimal proliferation	8%	19.2%	0.243

Medical complications: No significant difference was found regarding number of antihypertensive medications in either group along follow up periods. The majority of patients in both groups suffered from hyperlipidemia requiring statin therapy being 60% in group A and 87.5% in group B. No significant differences were encountered regarding the incidence of different types of infections between the two groups except for urinary tract infections and herpes zoster being more common among group B patients. Among group A and B, 47.5% and 57.5% of patients were encountered to have high SGPT and SGOT serum values at least at one occasion. High incidence of avascular bone necrosis was encountered being 7.5% and 12.5% in group A and B respectively. Significant higher incidence of new onset diabetes mellitus was observed among group A patients (30%) in comparison to group B (10%), (P =0.025). On the other hand, higher incidence of proteinuria was reported among group B patients being 35% versus 22.5% in group A (table 5).

Table 5. Medical complications

	Group A	*Group B*	*P-value*
Diabetes Mellitus	12 (30%)	4 (10%)	0.025
Hyperlipidemia	24 (60%)	35 (87.5%)	0.999
Leukopenia	7 (17%)	10 (25%)	0.412
Thrombocytopenia	4 (10%)	2 (5%)	0.395
Infections:			
- UTI	8 (20%)	17 (42.5%)	0.029
- H.Z.	--	4 (10%)	0.040
- T.B	2 (5%)	1 (2.5%)	0.556
- Fungal infection	4 (10%)	2 (5%)	0.315
Proteinuria:			
1-3 gm	4 (10%)	8 (20%)	0.210
>3 gm	5 (12.5%)	6 (!5%)	0.745
Total	9 (22.5%)	14 (35%)	0.370
High liver Enzyme	19 (47.5%)	23 (57.5%)	0.370
Avascular necrosis (hip joint)	3 (7.5%)	5 (12.5%)	0.456
Diarrhea	8 (20%)	2 (5%)	0.042

Surgical complications: Both groups were equally affected regarding the incidence of lymphoceles (3 cases in each group) as well as urinary fistulae being a single case in each group. Complicated wound healing was encountered among 4 and 5 patients in group A and B respectively.

Patient and graft outcome: One-year graft survival was 94.6% and 97.4% for group A and B respectively. Two graft losses were encountered in group A, the first was due to patient death secondary to miliary T.B, 6 months post-transplantation while the second was due to chronic allograft nephropathy and the patient returned to hemodialysis 4.5 months post-transplantation. The sole graft loss in group B was due to recurrent FSGS and the patient returned to hemodialysis 8 months post-transplantation.

Discussion

Estimation of renal allograft function by serum creatinine revealed better renal function in group B

patients as compared to group A at all time points however it did not rank to statistical significance. This finding came in accordance with what had been previously reported by Groth et al [7], and Kreis et al [8], that calcineurin inhibitor free regimens based on sirolimus have better renal function than calcineurin inhibitor based regimens. Recently, a prospective randomized trial has been conducted by Flechner and coworkers [10], who compared sirolimus against CsA in combination with steroids, MMF plus basiliximab induction in 61 adult primary kidney transplant recipients. The authors found that, at 6 and 12 months, the sirolimus treated patients enjoyed significant better renal function than CsA treated patients.

Regarding severity of acute rejection and response to treatment, group A patients had 10 episodes (out of 13) diagnosed as borderline and grade I acute rejection according to Banff classification and all were steroid sensitive. The rest 3 episodes were grade II and two of them required ATG therapy. On the other hand, group B patients had not only lower incidence of acute rejection episodes, although insignificant, but also less severe forms, being all graded as borderline and grade I according to Banff classification, besides, all were steroid sensitive. The incidence of acute rejection at 1 year in the rapamune US trial [11] and global trial [12] was 14.6% and 23.3% respectively for the sirolimus arm of 5 mg in combination with full dose CsA and steroids. In our study, we thought that sirolimus in combination with tacrolimus would be a better combination than sirolimus and CsA combination in terms of acute rejection prophylaxis based on data from McAlister and colleagues [6]. Good results obtained from previous trials regarding the incidence of acute rejection may be explained by that 70% of cases were liver transplants and only 21% of cases had renal transplantation in combination with pancreas and liver. Kreis and associates [8], were able to obtain one-year acute rejection rate of 27.5% in renal transplant patients treated with steroids, sirolimus and MMF. In our study, by adding an interleukin II receptor antagonist (basiliximab) to the previous regimen, we succeeded to obtain lower rate of acute rejection being 10% among group B patients after 1 year. Flechner and Coworkers [10], had also advocated low incidence of acute rejection (6.4%) at 1 year in patients treated with steroids, sirolimus, MMF and basiliximab. The authors demonstrated that sirolimus permits trough blood levels of mycophenolic acid two to three times those observed in CsA, MMF treated patients. Furthermore, there was a significant prolongation of CD 25 T-cell suppression beyond month 2 by steroid, sirolimus, MMF and basiliximab combination regimen. Data from our study and Flechner et al. [10] study, supported the observation that steroid, sirolimus, MMF and basiliximab combination regimen could potentially provide a wide umbrella of protection from acute rejection.

Relevant to cardiovascular risks, there were no statistically significant differences in the incidence of patients displaying hyperglycemia, suggestive of new onset diabetes mellitus among cohorts in US and Global trials [13]. Conversely our study demonstrated significant higher incidence of new onset diabetes mellitus among group A patients (30%) in comparison to group B (10%). Our findings come in accordance with what have been reported by Hricik et al [14], about high incidence of post-transplant diabetes mellitus (36%) among African-American kidney transplant recipients treated with steroid, sirolimus and tacrolimus. The authors explained that combination of sirolimus and calcineurin inhibitors may be synergistic not only in preventing rejection but also in promoting nephro- or neurotoxicity as well as enhancement of tacrolimus induced islet cell toxicity [14].

Sirolimus has been observed to elevate blood lipids in almost all clinical trials [15]. In our study the incidence of post-transplant hyperlipidemia requiring statin therapy was 60% in group A and 87.5% in group B patients. Mean values for total serum cholesterol were significantly higher among group B patients than group A, throughout the first 6 months post-transplant, which may be attributed to significant higher sirolimus dose and level among group B. Mean values for serum triglycerides, HDL and LDL were comparable among both groups at different time points. Pravastatin was used for treatment of hypercholesterolemia and it was found to be safe and moderately effective.

The lower incidence of leukopenia and thrombocytopenia in group B compared with other sirolimus-based, calcineurin inhibitor-free therapies may be explained by low sirolimus dose and level obtained in our study compared to others. However group A patients had an approximately equal incidence of leukopenia and thrombocytopenia compared to other calcineurin inhibitor-based therapies combined with sirolimus [11,12].

No cases of malignancy had been diagnosed in our series supporting the hypothesis of Luan and coworkers [16], that sirolimus might prevent rather than promote tumor progression however, longer term assessment is recommended.

Striking high incidence of proteinuria was noted in our study. Nine patients of group A (22.5%) were diagnosed to have proteinuria at different time points of follow up. On the other hand 14 patients (35%) of group B patients had proteinuria. To the best of our knowledge, proteinuria as a specific complication of sirolimus therapy was not known, neither in sirolimus based regimens [7,8] nor in CsA based regimens in combination with sirolimus [11,12]. Therefore proteinuria as a potential complication of sirolimus therapy needs further evaluation.

High liver enzymes as a metabolic complication of sirolimus therapy was encountered in various studies, however its incidence did not exceed 20% [7]. In our study significant higher incidence was reported, being 19 cases (47.5%) and 23 cases (57.5%) in group A & B respectively. Mean values of SGPT and SGOT were found to be higher than normal early post-transplant and returned gradually to normal values by the third month

post-transplantation. The outstanding high liver enzymes encountered in our study may be related to high prevalence of pretransplant positive hepatitis C viral infection being 37.5% and 50% in group A and B respectively.

Unexpectedly, the incidence of diarrhea was significantly higher among group A patients than group B. Diarrhea is not unexpected considering the macrolide structure of tacrolimus and it was found to occur significantly more frequent with tacrolimus than CsA in 2 of 3 studies [17]. We believe that sirolimus may enhance the tacrolimus induced gastrointestinal disturbances.

In our study, no base line biopsies were available, however estimation of mean CADI score at 1 year revealed a non significant difference between the 2 groups being 2.70 in group A and 2.44 in group B (p=0.303). Further analysis of histological findings of protocol biopsies revealed significant higher incidence of tubular atrophy and interstitial fibrosis among group A patients which is most probably attributed to tacrolimus therapy.

Conclusion

Sirolimus administration in renal allo-transplant recipients of this study was found to be safe and effective regarding both patients and grafts outcome. In addition, our calcineurin inhibitor free regimen consisting of sirolimus, MMF, steroids and basiliximab induction was found to be associated with better renal allograft function, lower incidence of acute rejection and hopeful histological findings of protocol biopsies than the low dose tacrolimus regimen. The impact of improved renal function and histologic evidence of graft integrity on eventual graft survival and chronic rejection rates awaits longer follow up.

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