



Conversion from Cyclosporine to Tacrolimus in Renal Allograft Recipients with Chronic Allograft Nephropathy: Assessment of Efficacy by Repeated Biopsies

KEYWORDS

Renal transplantation, Chronic allograft nephropathy, Cyclosporine A, Tacrolimus, Pathology

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ABSTRACT *Objectives:* This study evaluated the efficacy and safety of tacrolimus (FK506) as secondary intervention in cyclosporine A (CsA) treated renal allograft recipients with chronic allograft nephropathy(CAN).

Methods: 176 Patients were either converted to tacrolimus (FK506 group, n=112) or remained on their initial CsA-based immunosuppression (CsA group, n=64) followed over 5-year survey by repeated biopsies. The rate of decline of renal function before and after the FK506 conversion was represented by the regression line (slope) of the reciprocal of serum creatinine versus time.

Results: After 5-year of follow-up, serum creatinine was markedly decreased from (160.7±46.3) umol/L to (149.8±49.8) umol/L, P<0.001. Chronic allograft damage index(CADI) significantly decreased from 8.3±2.6 to 3.0±0.7 (P<0.001) in FK506 group. Repeated renal biopsy revealed that in FK506 group 56 cases (65.9%) became C4d negative in renal tissue and no case become positive, and 4 case (4.7%) showed steady C4d positive; and in CsA group, no case became C4d negative, 7 cases (13.7%) showed steady C4d positive, and vice versa, there are 16 cases from negative to positive (31.4%). Graft survival rate was significantly increased in the FK506 group than in the CsA group, 98.2% vs. 85.9% and 89.3% vs. 56.3% follow-up 5-year, respectively.

Conclusion: Conversion from a CsA-based regimen to a tacrolimus-based regimen was an effective alternative for salvage of patients with abnormal graft renal function induced by CAN.

INTRODUCTION

Renal transplantation is universally considered to be the treatment of choice for patients with end-stage renal failure¹. However, chronic allograft nephropathy(CAN) has still remained a major long-term clinical problem in renal transplantation, in which progressive and relentless deterioration in allograft function leads to eventual graft loss^{2,3,4}. The cyclosporine(CsA)-based regimen of maintenance therapy has been widely practiced without lasting success^{5,6}. Tacrolimus (FK506) and CsA are both strong calcineurin inhibitors (CNIs), which can inhibit lymphocyte activation effectively and prevent the occurrence of early acute rejection⁷. However, the long-term clinical application of CsA is limited, because of its side effect of inducing hypertension, hyperlipemia and atherosclerotic disease etc.^{8,9}. FK506 has

proved to be effective in renal transplantation recipients both de novo and in refractory rejection^{10,11}, but there is no current data regarding its role in the treatment of patients suffering from chronic allograft nephropathy. There are also few prospective studies about conversion from original immunosuppressive agent to FK506 for patients who have undergone CAN. In this study, we investigate the effect of conversion from CsA based- regimen to FK506-based regimen on the course delay of grafted renal function induced by chronic allograft nephropathy.

MATERIALS AND METHODS

Patient enrollment

There were 1044 consecutive adult first cadaveric renal transplant recipients at our center in the past five years

(Jan.1998 to Jun. 2008). Inclusion criteria: post-transplantation renal function declines slowly and progressively (serum creatinine level $\geq 132.6\mu\text{mol/L}$), duration of at least 3 months. Exclusion criteria: excluding surgical complications, infection, tumor, urinary tract obstruction, acute rejection, primary or secondary diabetes, CsA nephrotoxicity, allograft dysfunction caused by new or recurrent kidney disease. 176 renal transplant recipients with biopsy-proven chronic allograft nephropathy were enrolled in this study. 125 male, 51 female, with ages 34.8 ± 11.6 (18-51) years.

Clinical trial design

Patients were grouped randomly into one of the protocols which consisted of treatment with CsA group ($n = 64$) and the FK506 group ($n = 112$) for 5 years. There was no significant difference between the two groups in gender, age, dialysis time, mean time after transplantation, cold and hot ischemia time, lymphocytes complement activation test, reactive antibodies, HLA mismatch previous incidence of acute rejection and the average daily doses of CsA and mycophenolate mofetil (MMF) (Table 1.); Two groups were not significantly different on blood urea nitrogen (BUN), serum creatinine (SCr) levels, total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL-c), high density lipoprotein (HDL-c), fasting blood glucose, glycosylated hemoglobin, serum albumin and urinary protein levels. All subjects have signed informed consent.

CsA groups:

The patients who continued to maintain the original immunosuppressive regimen: CsA + MMF + prednisone, CsA dose adjustments based on the time after transplantation, CsA levels were maintained between 100-120 $\mu\text{g/L}$. The dose of MMF was unchanged (1.5g/d, orally), and adjusted based on the standard MMF plasma levels (MMF AUC 0-12 35-45 mg/h/L). Corticosteroid dosage was of the same.

FK506 group: Conversion from CsA to FK506, the dosage and usage of MMF and prednisone were the same with CsA group.

Switch scheme from CsA to FK506

All subjects had received a CsA-MMF-prednisolone immunosuppressive regimen before conversion. Patients were selected for conversion of the maintenance therapy from a CsA-based regimen to an FK506-based regimen. Conversion to FK506 was undertaken at an initial dose of 0.15 mg/kg per day, which was subsequently adjusted to maintain FK506 whole blood trough levels between 5 and 10 $\mu\text{g/L}$ as detected using a cellular enzyme-linked immunosorbant assay. After conversion, MMF and prednisolone were continued according to the posttransplant immunosuppressive protocol in our center.

Renal allograft pathology

Protocol and repeated biopsy were managed in the selected recipients, with the method of B ultrasonic- positioning negative pressure suction percutaneous paracentesis. Two needle biopsy cores were obtained from each renal allograft for morphologic studies. These were divided into two parts: one for formalin fixation and one for quick freezing. Hematoxylin and eosin, periodic acid Schiff, and masson trichrome stains were routinely used for formalin-fixed tissue. Fresh-frozen tissue was analyzed by immunofluorescence microscopy using a conventional panel of antibodies against immunoglobulin (Ig) G, IgM, IgA, complement component (C)3, C4, C4d and C1q.

C4d detection by immunofluorescence

C4d staining was performed using an indirect immunofluorescence technique, as described previously¹². C4d manifested deposition ring in the peritubular capillary (PTC), and showed diffused distribution (at least 25% of the existence of peritubular capillaries), which are considered as C4d positive¹³. The intensity of C4d staining is graded as^{14,15}: negative (C4d 0, C4d PTC deposition <10%), mild (C4d 1, 10-24%), moderate (C4d 2, 25-50%) and severe (C4d 3, > 50%).

Diagnosis of chronic allograft nephropathy

Chronic allograft nephropathy is pathologically diagnosed according to the Banff 97 criteria^{16,17}, which was classified as grade I, II, III based on the degree of nephropathy.

Serologic evaluation

Flow cytometry panel reactive antibody (PRA) test (The FlowPRA™ screening test) is that purified HLA-I and HLA-II antigens, including all common and rare HLA antigens, are coated outside dozens of micro-particles. These particles were binded with fluorescent labeled anti-human IgG antibody, after incubated with the tested serum for a period of time. The specificity and intensity of HLA antibodies (Flow-PRA%) in serum samples can be detected by flow cytometry. It is positive that Flow-PRA I and II antibody $\geq 10\%$.

Statistical analysis

All measurement data are expressed by mean \pm standard deviation ($\bar{x} \pm s$), different groups were compared by analysis of variance, using t test between the two groups; count data shows the number of cases for each category, calculating rates if necessary, using chi-square test between the two groups. All statistical analysis was managed by SPSS11.0 statistics software. $P \leq 0.05$ shows statistical significance. Make the use of linear regression analysis to calculate the reciprocal of serum creatinine and time slope; calculate the person, renal survival rate and the incidence rate of adverse events.

RESULTS

Clinical efficiency after conversion

The mean time of conversion from CsA based- regimen to FK506-based regimen was 34.1 ± 16.2 months. Changes of clinical parameters at pro- and post-conversion (Table 2.).

Comparison of allograft function

After 5-year of follow-up, SCr in CsA group had risen from (158.3 ± 37.1) $\mu\text{mol/L}$ at the beginning of the study to (295.2 ± 65.2) $\mu\text{mol/L}$, $P < 0.01$; SCr in FK506 group had reduced from (160.7 ± 46.3) $\mu\text{mol/L}$ before the conversion to (149.8 ± 49.8) $\mu\text{mol/L}$, $P < 0.001$. The changes of 1/SCr level and time slope between two groups are shown in Figure 1.

Histopathological changes of graft after conversion

There were both with mild to moderate interstitial infiltration of inflammatory cells, interstitial fibrosis, tubular atrophy, mesangial matrix proliferation, glomerular sclerosis, intimal hyperplasia between two groups before the conversion ($P = \text{NS}$). By the time of 5-year follow-up, pathological changes had been significantly improved in accordance with the 97' Banff classification (Table 3.). Repeated biopsy prompted that the degree of allograft pathological changes was significantly reduced (Table 4.).

Evolution of C4d deposition in allograft

One hundred thirty six cases of repeated biopsy specimens were stained by immunofluorescence, C4d positive 63 cases (46.3%) in the all of allograft. Evolution of C4d

deposition in allografts during the 5-year follow-up is shown in Figure 2. Repeated renal biopsy revealed that in FK506 group 56 cases (65.9%) became C4d negative in renal tissue and no case become positive, and 4 case (4.7%) showed steady C4d positive accompany with hepatitis C (renal graft biopsy showed membranous nephropathy); and in CsA group, no case became C4d negative, 7 cases (13.7%) showed steady C4d positive, and vice versa, there are 16 cases from negative to positive(31.4%). Classification according to the Banff 07 criteria: 73 cases of C4d0, 4 cases of C4d1, the 15 cases of C4d2, 44 cases (32.4%) of C4d3. The degree of C4d deposition was significantly reduced in 5 years after the conversion.

C4d deposition in allograft and PRA levels

Flow-PRA determination was undergone in a total of 136 patients: HLA-I class of pure antibodies 4 cases (> 10%), HLA-I and HLA-II class of antibodies 2 cases (> 10%), HLA-II class of pure antibodies 130 cases (> 10%), the average HLA-II class of antibody levels $56 \pm 9\%$ (36-88.5%), and the ratio of C4d positive rate in pathology of patients whose HLA-II class of antibodies increased was 93.1% (121/130), while the ratio of C4d positive of those whose PRA were not elevated was only 26.4%. After the treatment with FK506, with the disappearance of C4d deposition in allograft, HLA-II class antibody levels decreased to $6.1 \pm 1.2\%$ (3.9-7.3%).

Patient and graft survival

No deaths during the 5-year follow-up. Renal function was deteriorated in 28 cases in CsA group, and the patients returned to dialysis due to renal dysfunction: 4 cases in the 1st year, 1 case in the 2nd year, 4 cases in the 3rd year, 6 cases in the 4th and 13 cases in the 5th year; and no case of renal dysfunction happened in FK506 group within 2 years after the switching, but 2 cases in the 3rd year, 3 cases in the 4th and 7 cases in the 5th year. Allograft loss rate of CsA group was significantly higher than that of FK506 group, 28 cases (25.7%) vs. 12 cases (10.7%), $P < 0.05$. Graft survival rate in the FK506 group and the CsA group: 98.2% vs. 85.9% and 89.3% vs. 56.3% at follow-up 3-year and 5-year, respectively.

Safety after conversion

No case of acute rejection occurred during 5-year follow-up in the two groups. FK506 group had a higher incidence of tremor, 31 cases (27.7%) in 2-3weeks after the conversion to FK506, and the tremor became negative with the reduction of dose, appropriately. 11 cases (9.8%) of patients had hyperglycemia, and 3 of them were given hypoglycemic agents and insulin to maintain blood glucose, and the blood glucose of the remaining patients was back to normal after low-sugar diet. The incidence of adverse events in two groups (Table 5). The incidence of nausea, vomiting, loss of appetite, bloating, diarrhea and other gastrointestinal reactions had no significant difference between two groups.

DISCUSSION

With the advent and extensive application of new potent immunosuppressive agents, the incidence of acute allograft rejection have decreased significantly over the past 10 years. The incidence of acute rejection within 1 year after kidney transplantation has decreased from 40.9% in 1993 to 13.6% in 2004 [2], but long-term survival rate is still not improved. The rate of CAN occurrence is as much as 60-70% in conventional biopsy within 1 year after transplantation, the main factor for long-term allograft survival is still chronic renal nephropathy [2,4]. Numerous studies

have confirmed that FK506 has incomparable advantage over CsA in lipid metabolism, induction of the expression of fibrogenic cytokines, etc. . FK506 can significantly ameliorate abnormal lipid metabolism, reduce the side effects caused by CsA, such as hyperlipidemia, hypertension, gingival hyperplasia, hirsutism and so on [19,20]. Although many literature report that it can improve chronic renal function and reduce cardiovascular complications in renal transplant recipients with the conversion from CsA to FK506, it is difficult to make clear conclusion due to the lack of long-term comparative study of large sample and complete pathological data [21,22,23]. This study observed long-term progress of renal dysfunction in patients who used CsA and were proven CAN by biopsy, and the pathological changes in repeated biopsies. This article investigates the efficacy and safety of the treatment of conversion to FK506 for patients with renal-dysfunction CAN.

In this study, we confirmed that FK506 can slow down the progress of renal dysfunction proven CAN by biopsy, with 5-year clinical and pathological follow-up. After the conversion to FK506, TC, TG, and LDL decreased significantly, average serum creatinine levels in FK506 group were significantly lower than that of CsA group, decreasing from (160.7 ± 46.3) $\mu\text{mol/L}$ to (149.8 ± 49.8) $\mu\text{mol/L}$, $P < 0.001$. The changes of $1/\text{SCr}$ levels and time slope were also different from that of CsA group, who maintained the original CsA therapy. Chronic allograft damage index (CADI) significantly decreased from 8.3 ± 2.6 to 3.0 ± 0.7 ($P < 0.001$) in FK506 group. Thus, FK506 delayed the occurrence and development of CAN. No death during follow-up period of 5 years. Renal function was deteriorated in 28 cases in CsA group, and the patients returned to dialysis due to renal dysfunction; and no case of renal dysfunction happened in FK506 group within 2 years after the switching, but 2 cases in the 3rd year, 3 cases in the 4th and 7 cases in the 5th year. Allograft loss rate of CsA group was significantly higher than that of FK506 group, 28 cases (25.7%) vs. 12 cases (10.7%), $P < 0.05$. Graft survival rate in the FK506 group and the CsA group: 98.2% vs. 85.9% and 89.3% vs. 56.3% at follow-up 3-year and 5-year, respectively. It further proved that the conversion from CsA to FK506 can delay the progress of CAN, and help to improve long-term survival rate of allograft [24].

The essence of allograft dysfunction caused by CAN is that reversible or irreversible pathological changes of varying severity occurred 25-28, including hyaline degeneration of renal vascular, glomerulosclerosis, tubular atrophy and interstitial fibrosis. Early prevention of the occurrence of CAN is the most effective way, so this study emphasizes the conversion of FK506 for CAN should be early: usually 3 months postoperative, SCr levels before switching should not exceed $200 - 300 \mu\text{mol/L}$, proteinuria $< 0.8\text{-}1\text{g}/24\text{h}$. To switch at such an opportunity can get good results. Not only were lipid levels changed significantly, but renal function in patients with CAN has also been significantly improved, after conversion to FK506. It should be taken into consideration that CAN of early stage could be predictable and treated by dynamic observation of histological evidence from protocol biopsy in long-term follow-up, in order to improve the long-term effects of renal transplantation [29]. Repeated renal biopsy prompted the markedly reduction in the degree of renal disease after conversion to FK506. According to the selected patients in this study, the more severe pathological changes of CAN before switching they had, the lower achievement rate after switching it is. Once the pathological changes of CAN up to the Banff 97 IIb or more, the results were less effective.

Many previous studies focused on the best immunosuppressive regimen in patients with CAN, including raising MMF dosage, stop using CNI immunosuppression, switch CNI to mTOR inhibitor, or switch CsA to FK506. However, without large sample of domestic control study, the result was not very satisfied. By 5-year follow-up observation, we confirmed that the combination of FK506 and MMF can not only effectively alleviate the pathological changes of CAN, but also effectively treat antibody-mediated C4d positive chronic rejection. 136 cases were subjected to repeated allograft biopsy and C4d immunofluorescence stained, and the incidence of C4d positive was 46.3%, among the total, CsA group 13.7% and FK506 group 65.9%. In CsA group, no case became C4d negative, and vice versa, there are 16 cases from negative to positive(31.4%), 7 cases showed steady C4d positive; in FK506 group, 56 cases (65.9%) became C4d negative and no case became positive, and 4 case (4.7%) showed steady C4d positive accompanied with hepatitis C (renal graft biopsy showed membranous nephropathy). The degree of C4d deposition significantly decreased or even disappeared within 5 years after conversion to FK506, with HLA-II class antibody levels decreasing to $6.1 \pm 1.2\%$ (3.9-7.3%). It was proved once again that it is valid for FK506 combined with MMF to treat chronic C4d positive antibody-mediated rejection. In the view of mechanism of drug action, FK506 and CsA are both CNI drugs, but FK506 has stronger immunosuppressive effects than CsA, and FK506 has better effect on the humoral immune injury when combined with MMF 30,31. FK506 can reduce the IL-10 expression, and adjust humoral immunity through the role of B cells 32,33. Therefore, it can be explained that FK506 has better effect in patients mainly with humoral immune injury.

CONCLUSION

Combining FK506 and MMF for long-term treatment showed small toxicity and few side effects, the most suitable for renal transplant recipients of long-term treatment 34,35. Although there happened to be some side effects occurring in some patients, such as hyperglycemia, new onset of diabetes and peripheral leukopenia, as long as we pay attention to monitoring the blood concentration and timely adjustment of dose, we can completely avoid the side effects of these two drugs. The author believe that the adjustment of FK506 and MMF dose should base on clinical condition and allograft pathology among different individuals. To maintain FK506 lowest concentration at 5-8 ug/L and MMF AUC 0-12 35-45 mg.h/L is safe.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the **Indian Journal of Applied Research (IJAR)**

Table 1. clinical information of two groups before study

	CsA group	FK506 group	P value
Gender female/male(%)	18/46(39.1)	33/79(41.8)	NS.
Age (years)	34.2±12.1	34.8±11.6	NS.
Dialysis time (months)	7.1±4.5	7.3±3.6	NS.
Time after transplantation(months)	34.1±13.5	34.0±14.1	NS.
Hot ischemia time (min)	7.1±1.0	7.3±1.4	NS.
Cold ischemia time (hr)	15.6±5.4	15.8±4.1	NS.
CDC(%)	5.2±1.6	5.4±1.3	NS.
PRA(%) I	5.1±2.5	5.3±1.9	NS.
II	4.9±0.8	4.3±0.9	NS.
HLA mismatch			
A	2.0±0.6	2.1±0.2	NS
B	2.6±1.0	2.5±0.9	NS.
DR	1.4±0.5	1.4±0.5	NS.
Acute rejection (%)	11(17.2)	22(19.6)	NS.
MMF dosage(mg/d)	1363.0±628.0	1364.0±589.0	NS.
MPA-AUC0-12 (mg.h/L)	35.9±11.1	35.8±10.1	NS.
CsA trough concentration (ug/L)	109.3±20.1	107.3±19.1	NS.

N.S.: no significantly difference. FK506 group vs. CsA group

Table 2. Clinical parameters before and after the FK506 conversion

	CsA group(n=44)		FK506 group(n=112)	
	Pre-conversion	Post-conversion	Pre-conversion	Post-conversion
Mean arterial pressure (mmHg)	140±11	95±7	139±5	90±7**
Number of Antihypertensive drugs	9.1±0.2	8.3±0.2	9.5±0.2	3.3±0.2**
Proteinuria(g/24hr)	1.5±0.8	1.2±0.7	1.6±0.7	0.8±0.5**
Serum albumin level(g/L)	36.2±8.1	34.1±9.1	36.0±8.2	45.1±2.2*
Fasting blood glucose (mmol/L)	6.3±2.2	6.0±2.2	6.4±1.4	5.3±1.2
Glycated hemoglobin(%)	5.3±1.2	4.2±1.1	5.3±1.2	4.2±1.1
Serum creatinine(umol/L)	158.2±32.2	238.3±35.9	169.3±35.9	155.4±18.4**
Cholesterol levels (mmol/L)	7.10±1.13	6.60±1.22	6.63±1.27	5.23±1.02*
TG (mmol/L)	2.49±1.32	2.47±1.48	2.34±1.21	2.04±0.93
HDL-cholesterol (mmol/L)	1.9±0.1	1.9±0.1	1.1±0.1	2.0±0.5*
LDL-cholesterol (mmol/L)	5.11±1.21	4.01±0.99	4.19±1.20	2.04±0.96**

*P<0.001, post-conversion FK506 vs. post-conversion CsA;

**P<0.001, post-conversion FK506 vs. pre-conversion FK506

Table 3. Allograft histological changes after repeated biopsies

	CsA group		FK506 group	
	Pre-conversion (n=64, %)	Post-conversion (n=51, %)	Pre-conversion (n=112, %)	Post-conversion (n=85, %)
Glomerulitis	2(3.1)	0(0)	4(3.6)	0(0)
Tubulitis	4(6.3)	0(0)	7(6.3)	0(0)
Interstitial cell infiltration	6(9.4)	4(7.8)	11(9.8)	1(7.7)
Vasculitis	2(3.1)	2(3.9)	4(3.6)	0(0)
Glomerulosclerosis	21(32.8)	42(82.4)*	40(35.7)	45(52.9)**
Tubular atrophy	36(56.3)	48(94.1)*	65(58.0)	39(45.9)**
Interstitial fibrosis	30(46.9)	51(100.0)*	58(51.8)	26(30.6)**
Arterial hyalinosis	34(53.1)	51(100.0)*	61(54.5)	21(24.7)**
CADI	8.8±2.5	5.9±2.1	8.3±2.6	3.0±0.7**

CADI¹⁵: chronic allograft damage index, including interstitial cell infiltration, interstitial fibrosis, tubular atrophy, mesangial matrix proliferation, glomerulosclerosis, intima hyperplasia.

*P<0.001, Pre-conversion vs. Post-conversion;

#P<0.001, Post-conversion FK506 vs. Post-conversion CsA

Table 4. The degree of allograft pathological changes after conversion to FK506

Banff classification	CsA group		FK506 group	
	Pre-conversion (n=64, %)	Post-conversion (n=51, %)	Pre-conversion (n=112, %)	Post-conversion (n=85, %)
I	23(35.9)	6(11.8)*	36(32.1)	3(3.5)**
IIa	39(60.9)	15(29.4)*	70(62.5)	16(18.8)**
IIb	2(3.1)	2(3.9)	6(5.4)	0
III	0	0	0	0

*P<0.001, post-conversion vs. pre-conversion;

#P<0.001, post-conversion FK506 vs. pre-conversion FK506

Table 5. The incidence of adverse events in two groups(%)

	CsA group (n=64)	FK506 group (n=112)	P value
Acute rejection	0	0	
Tremor	20.3	27.7	<0.05
Hyperglycemia	4.7	9.8	<0.05
Hypertension	82.8	41.1	<0.001
Hirsutism	54.7	23.2	<0.001
Gum hyperplasia	51.6	8.9	<0.001
Abnormal liver function	17.2	6.3	<0.001
Pulmonary cytomegalovirus (CMV) infection	10.9	6.3	<0.05

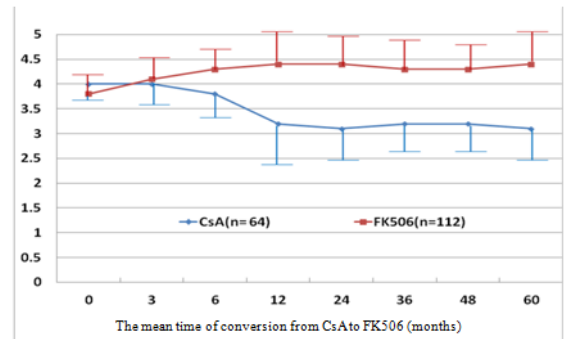


Figure 1. 1/SCr level and time slope of two groups calculated by linear regression analysis

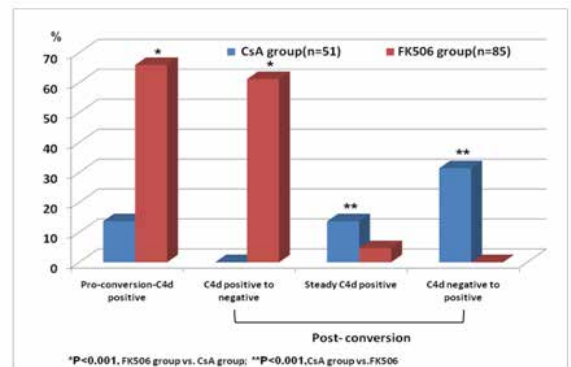


Figure 2. Evolution of C4d deposition in allograft pro- and post- conversion to FK506

1/SCr(umol/LX 1000)-1

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