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RETROSPECTIVE STUDY

Effect of low-dose tacrolimus with mycophenolate mofetil on renal function following liver transplantation

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Abstract

AIM: To determine whether low-dose tacrolimus (TAC) combined with mycophenolate mofetil (MMF) is a safe approach to decrease the incidence of chronic kidney disease (CKD) in liver transplantation (LT) recipients.

METHODS: We analyzed the medical records of 689 patients who underwent LT between March 1999 and December 2012 in a single Chinese center. Immunosuppression was initiated with a calcineurin inhibitor (TAC or CSA) and prednisone with or without MMF. CKD is defined by the glomerular filtration rate (GFR), estimated by an abbreviated Modification of Diet in Renal Disease formula, < 60 mL/min per 1.73 m^2 for at least 3 consecutive months after LT. Individuals with TAC trough concentrations ⩽ 8 ng/mL at 3 mo after LT were defined as the low-dose group. The incidence of CKD within 5 years was compared between the TAC group and the CSA group, as well as between four subgroups (low-dose and high-dose TAC groups with or without MMF).

RESULTS: No difference regarding the occurrence of pre-LT renal dysfunction or that of post-LT rejection was found between the TAC and CSA groups or between the four subgroups. With a definition of GFR < 60 mL/min per 1.73 m^2, the overall incidence of CKD was significantly higher in the CSA group than in the TAC group. The incidence of CKD in the low-dose TAC + MMF group (7.7%) was significantly lower than that observed in the low-dose TAC group (15.9%), high-dose TAC group (24.6%) and high-dose TAC + MMF group (18.5%). The cumulative 1-, 3- and 5-year incidence rates of CKD were 12.7%, 14.5% and 16.7%, respectively. The cumulative 5-year survival rates were 61.7% and 82.2% in patients with or without CKD, respectively.

CONCLUSION: In LT patients, the choice of immunosuppressive therapy appears to affect renal function and patient survival.

Key words: Liver transplantation; Chronic kidney disease; Calcineurin inhibitor; Mycophenolate mofetil

Core tip: Calcineurin inhibitor nephrotoxicity has been proposed to have a central role in chronic kidney disease, which has become a leading cause of long-term morbidity and mortality after liver transplantation. This study was conducted in 689 consecutive liver transplantation recipients and suggested that the choice of the immunosuppression therapy should be low-dose tacrolimus combined with mycophenolate mofetil, as this treatment was associated with better renal function and a higher patient survival rate.

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INTRODUCTION

The use of the calcineurin inhibitors (CNIs) cyclosporine A (CSA) and tacrolimus (TAC) in liver transplantation (LT) has greatly increased recipient survival rates and reduced graft rejection rates[1]. However, CNI nephrotoxicity has been proposed to have a central role in chronic kidney disease (CKD) after LT[2-4]. CKD has become a leading cause of long-term morbidity and mortality[5]. Ojo *et al*[5] reported that 18% of 36849 LT recipients had chronic renal dysfunction defined as a glomerular filtration rate (GFR) < 29 mL/min per square meter 5 years after LT.

Although the different impacts of TAC and CSA on renal function remains controversial, there has been substantial evidence that TAC has lower nephrotoxicity potential than CSA, especially in kidney transplant recipients. Numerous studies have shown that recipients treated with TAC display better renal function than those who receive CSA[6-9]. However, Alghamdi *et al*[10] found no difference in the mean levels of serum creatinine between the CSA and TAC groups, but this effect remains inconclusive in LT patients[11,12].

The most direct strategies to prevent CNI nephrotoxicity are avoidance and withdrawal of the drug. However, the exclusion of CNIs from immunosuppressive regimens does not preserve allograft function due to inadequate acute rejection prophylaxis by other immunosuppressive regimens[13-16]. Herein, novel CNI minimization protocols, in which the doses of cyclosporine or tacrolimus are adjusted to lower target levels, were conducted to balance potent immunosuppression and reduce CNI exposure. Morard *et al*[17] showed that independent risk factors associated with impaired renal function were trough levels of CSA ≥ 150 ng/mL or TAC ≥ 10 ng/mL at 1 year and CSA ≥ 100 ng/mL or TAC ≥ 8 ng/mL at 5 years. Our previous study showed that groups with ideal trough concentrations (CSA trough concentrations ≤ 150 ng/mL, TAC trough concentrations ≤ 8 ng/mL) had a significantly lower incidence of CKD[18]. A recent meta-analysis of 64 studies demonstrated that lower trough concentrations of TAC (6-10 ng/mL during the first month) had no significant influence on acute rejection and that TAC would be more appropriate after LT[19].

Immunosuppressive drugs without renal side effects have been increasingly used as CNI-sparing agents. Mycophenolate mofetil (MMF) is a non-nephrotoxic drug that inhibits the proliferation of T and B lymphocytes and has proven efficacy in the field of LT[20]. Substantial evidence has been found to suggest that MMF induction and maintenance used in conjunction with CNI following LT resulted in a significant improvement in renal function[21-25].

The aims of the present study were to determine whether TAC yields a lower incidence of CKD than CSA in recipients undergoing LT, as well as to investigate whether the use of reduced-dose TAC combined with MMF is a relatively safe approach to decrease the incidence of CKD.

MATERIALS AND METHODS

Study population
In this retrospective study, data from the clinical records of 940 consecutive patients who underwent LT between March 1999 and December 2012 in a single Chinese center were analyzed. The observation period ended on August 31, 2013, or at the time of patient death. Recipients who were followed up for less than 3 mo or died within 3 mo after transplantation, as well as those younger than 18 years, were excluded from the current study. All liver grafts were obtained from brain-dead or living donors. Living and deceased donations were voluntary in all cases, were approved by the West China Hospital Ethics Committee and were in accord with the ethical guidelines of the Declaration of Helsinki.

Evaluation of renal function
Renal function was assessed by the estimated GFR (eGFR) obtained using the abbreviated Modification of Diet in Renal Disease formula: eGFR = 186 × creatinine $(mg/dL)^{-1.154} \times (age)^{-0.203} \times (0.742$ if female)[26]. CKD was defined as having a GFR < 60 mL/min per 1.73 m^2 for at least 3 consecutive months after LT. Renal dysfunction before LT was also defined as having an eGFR < 60 mL/min per 1.73 m^2. Acute kidney injury (AKI) was defined as a > 25% decrease in GFR in the first post-operative week compared with the pre-operative level[27].

Definitions of other clinical parameters
Acute rejection (AR) and chronic rejection (CR) were confirmed by liver biopsy. Mayo end-stage liver disease scores were calculated for each patient.

Immunosuppressive protocols
Immunosuppression was initiated with a CNI (TAC or CSA) and prednisone with or without MMF. The initial dose of CNI was 0.05-0.10 mg/kg daily for TAC and 5-10 mg/kg daily for CSA. The dose of MMF was determined individually and ranged from 1.0-1.5 g/d. At our center, patients were only administered MMF during the early phase after transplantation when they were diagnosed with hypertension or diabetes mellitus; however, all recipients in the late post-transplant period were administered MMF unless severe gastrointestinal side effects or myelosuppression occurred. Prednisone was generally discontinued within 3 mo after transplantation.

Adjustment of calcineurin inhibitor dose during follow-up
CNI trough concentrations were checked daily for the first week, weekly for the next three weeks during the first post-operative month, monthly within 3 mo and ev-
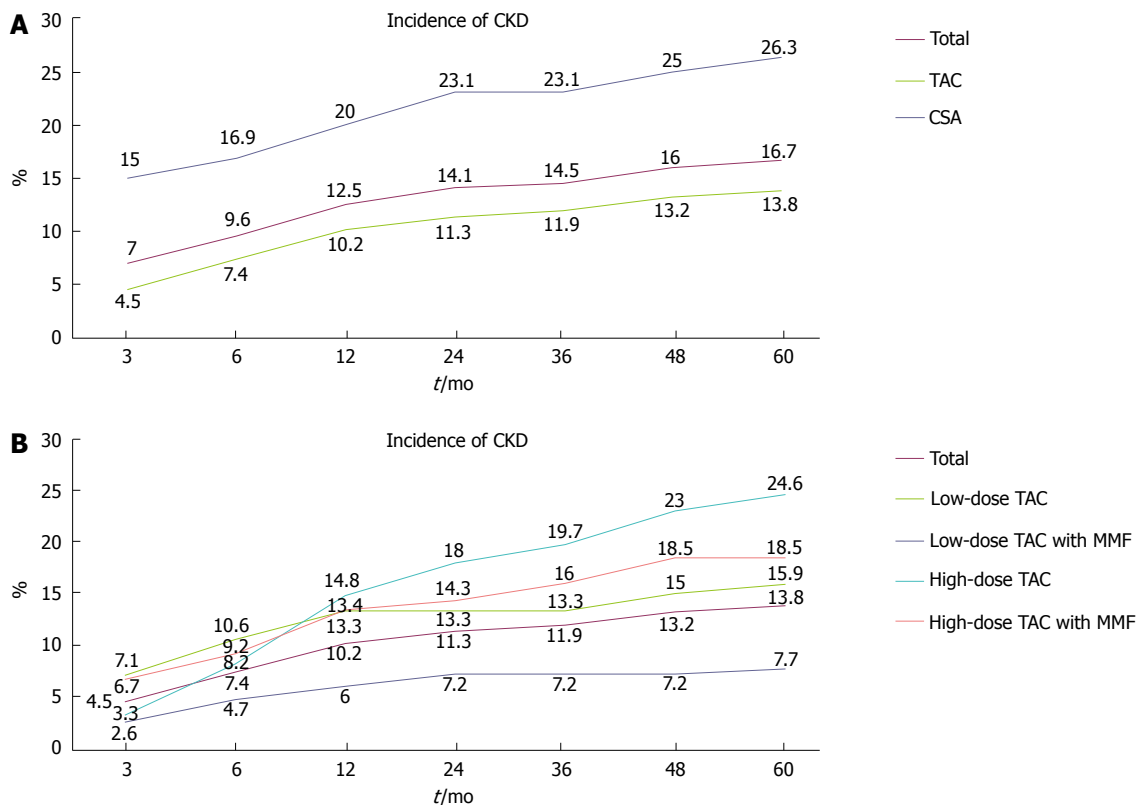
Figure 1 Incidence of chronic kidney disease. A: Incidence of chronic kidney disease (CKD) in the tacrolimus (TAC) and cyclosporine A (CSA) groups (*P* < 0.05); B: Incidence of CKD in the four TAC subgroups (*P* < 0.05). The estimated glomerular filtration rate (eGFR) was calculated by the abbreviated modification of diet in renal disease formula after each patient visit. Once the criterion for CKD (eGFR < 60 mL/min per 1.73 m^2) was met, the patient was registered in the CKD group.

ery 3 mo thereafter. The ideal serum trough level of CNI was 6-8 ng/mL for TAC and 120-150 ng/mL for CSA at 3 mo after operation. We classified patients with a TAC trough concentration ⩽ 8 ng/mL at 3 mo after LT as the low-dose group. Liver function was monitored intensely while adjusting the CNI dose. If AR occurred, the previous dosage was restarted with an increased prednisone dosage or high-dose methylprednisolone administration. Dose reduction was carefully and slowly carried out. A trough level of 4-6 ng/mL for TAC and 80-120 ng/mL for CSA one year after transplantation was expected to achieve stable liver function.

Statistical analysis
Numerical data are presented as the mean ± SD or as the median. The χ^2 test or Fisher's exact test was used to compare categorical variables. Continuous data were compared using the independent *t* test if data were normally distributed or using the rank-sum test if data were non-normally distributed. All analyses were performed using SPSS 22.0 statistical software (IBM Corporation, Armonk, NY). *P* < 0.05 was considered statistically significant.

RESULTS
Demographics
The medical records of 689 patients who met the inclu-

sion criteria, including 575 males and 114 females with a mean age of 44.94 years, were retrospectively reviewed. The median follow-up duration was 24 (3-120) mo. The two most common primary diagnoses for recipients were tumors and cirrhosis, with 344 (49.9%) and 232 (33.7%) patients, respectively. More than 80% of cases were found to be hepatitis B virus (HBV)-related. The deceased donor transplantation rate was 74.2%. TAC group patients were divided into two groups based on the critical ideal trough concentration of ⩽ 8 ng/mL at 3 mo after transplantation. Furthermore, four subgroups were created depending on whether MMF therapy was adopted.

Incidence of chronic kidney disease
The eGFR was calculated after each patient visit. Once the criterion for CKD was met, the patient was registered in the CKD group. As shown in Figure 1, 16.7% of the entire patient population (115 cases) developed CKD during the 5-year follow-up.

No differences were found in renal dysfunction before LT or in AKI, AR and CR after LT between the TAC and CSA groups (Table 1) as well as between the four TAC subgroups (low-dose and high dose TAC with or without MMF, Table 2). The cumulative incidence of CKD at 3, 6, 12, 24, 36, 48 and 60 mo was 15.0%, 16.9%, 20.0%, 23.1%, 25.0% and 26.3%, respectively, in the CSA group and 4.5%, 7.4%, 10.2%, 11.3%, 11.9%, 13.2% and

Table 1 Baseline patient demographics and clinical characteristics in the tacrolimus and cyclosporine A groups *n* (%)

	Total (*n* = 689)	TAC (*n* = 529)	CSA (*n* = 160)	*P* value
Age (yr)	44.94 ± 9.68	44.70 ± 9.25	45.73 ± 10.98	NS
Gender (male/female)	575/114	448/81	127/33	NS
Donor type (DDLT/LDLT)	511/178	368/161	143/17	< 0.001
MELD score	13.77 ± 7.77	13.54 ± 7.96	14.54 ± 7.07	NS
Pre-LT renal dysfunction	61 (8.9)	46 (8.7)	15 (9.4)	NS
Post-LT AKI	108 (15.7)	80 (15.1)	28 (17.5)	NS
Post-LT AR	78 (11.3)	53 (10.0)	25 (15.6)	NS
Post-LT CR	18 (2.6)	13 (2.5)	5 (3.1)	NS
Primary diagnosis				NS
Tumors	344 (49.9)	265 (50.1)	79 (49.4)	
Cirrhosis	232 (33.7)	182 (34.4)	50 (31.3)	
Chronic active hepatitis	54 (7.8)	36 (6.8)	18 (11.3)	
Others	59 (8.6)	46 (8.7)	13 (8.1)	
Viral infection				NS
HBV infection	564 (81.9)	435 (82.2)	129 (80.6)	
HCV infection	9 (1.3)	8 (1.5)	1 (0.6)	

Age: Age at transplantation; LT: Liver transplantation; DDLT: Deceased donor liver transplantation; LDLT: Living donor liver transplantation; MELD: Mayo end-stage liver disease; AKI: Acute kidney injury; AR: Acute rejection; CR: Chronic rejection; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NS: No significance; TAC: Tacrolimus; CSA: Cyclosporine A.

Table 2 Baseline patient demographics and clinical characteristics in the tacrolimus group *n* (%)

	Total (*n* = 529)	Low-dose TAC (*n* = 113)	Low-dose TAC with MMF (*n* = 235)	High-dose TAC (*n* = 61)	High-dose TAC with MMF (*n* = 120)	*P* value
Age (yr)	44.00 ± 9.25	45.00 ± 9.61	44.86 ± 9.21	42.93 ± 8.83	44.98 ± 9.20	NS
Gender	448/81	95/18	200/35	51/10	102/18	NS
Donor type	368/161	102/11	143/92	49/12	74/46	< 0.001
MELD score	13.54 ± 7.96	15.03 ± 8.34	13.15 ± 7.85	13.48 ± 6.59	12.94 ± 8.37	NS
Renal dysfunction pre-LT	46 (8.7)	15 (13.3)	16 (6.8)	8 (13.1)	7 (5.8)	NS
Post-LT AKI	80 (15.1)	22 (19.5)	33 (14.0)	11 (18.0)	14 (11.7)	NS
Post-LT AR	53 (10.0)	15 (13.3)	18 (7.7)	10 (16.4)	10 (8.3)	NS
Post-LT CR	13 (2.5)	3 (2.7)	5 (2.1)	2 (3.2)	3 (2.5)	NS
Primary diagnosis						NS
Tumors	265 (50.1)	61 (54.0)	107 (45.5)	35 (57.4)	62 (51.7)	
Cirrhosis	182 (34.4)	39 (34.5)	89 (37.9)	17 (27.9)	37 (30.8)	
Chronic active hepatitis	36 (6.8)	9 (8.0)	12 (5.1)	4 (6.6)	11 (9.2)	
Others	46 (8.7)	4 (3.5)	27 (11.5)	5 (8.2)	10 (8.3)	
Viral infection						NS
HBV infection	435 (82.2)	95 (84.1)	191 (81.3)	48 (78.7)	101 (84.2)	
HCV infection	8 (1.5)	2 (1.8)	6 (2.6)	0	0	

Age: Age at transplantation; LT: Liver transplantation; DDLT: Deceased donor liver transplantation; LDLT: Living donor liver transplantation; MELD: Mayo end-stage liver disease; AKI: Acute kidney injury; AR: Acute rejection; CR: Chronic rejection; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NS: Not significance; TAC: Tacrolimus; CSA: Cyclosporine A.

13.8%, respectively, in the TAC group (Figure 1A, *P* < 0.05). The intragroup analysis of TAC showed that the low-dose TAC with MMF group had a significantly lower incidence of CKD at these times compared with the other three groups (2.6%, 4.7%, 6%, 7.2%, 7.2%, 7.2% and 7.7%, respectively; Figure 1B, *P* < 0.05).

The cumulative survival rates at 5 years after LT in patients with and without CKD were 61.7% and 82.2%, respectively (log-rank test, *P* < 0.05) (Figure 2).

DISCUSSION

The present study demonstrated a cumulative incidence of CKD of 12.5% within 1 year, 14.5% at 3 years and 16.7% at 5 years after LT. We observed that TAC sup-

ported better renal function than CSA, especially when used at a low dose and in combination with MMF. This combined regimen showed the most stable long-term outcome, with a CKD incidence of only 7.7% at 5 years after LT. We also confirmed that CKD yielded a lower patient survival rate.

All of the comparisons made before transplantation were similar, even if a difference appeared concerning donor type. These similarities were most likely due to the chronological aspect of the study. In our previous research, we confirmed that donor type had no significant impact on renal dysfunction[18].

There is substantial evidence that TAC has a lower nephrotoxicity potential than CSA. Animal studies have demonstrated that the vasoconstrictive effect of TAC is
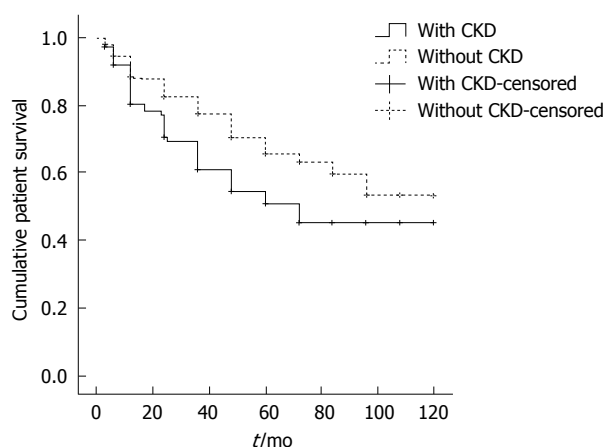
Figure 2 Kaplan-Meier analysis of cumulative patient survival in patients with and without chronic kidney disease. The cumulative survival was significantly higher in the non-chronic kidney disease (CKD) group (log-rank test, $P < 0.05$).

weaker than that of CSA[28-30], and this effect was also apparent in humans[31,32]. Moreover, the fibrogenic potential of TAC appears to be lower than that of CSA[33], although these results could not be confirmed in a more recent study[34]. For nonrenal solid organ transplantation, there have been single and multicenter studies, as well as registry analyses, that demonstrate the benefit of TAC over CSA with regard to renal function[5,35-37]. However, other studies exist that do not report this benefit of TAC over CSA[38].

In contrast to CSA, for which no dose-finding studies were performed before its introduction into clinical practice, extensive studies on TAC were performed before its introduction, and these demonstrated significant correlations between concentration and rejection and between concentration and toxicity[39]. To avoid CNI nephrotoxicity, minimizing CNI levels may be a better option, but it has become clear that the increased risk of allograft rejection could negate these positive effects. The positive effects observed following the introduction of MMF, which does not interfere with CNI actions or cause renal toxicity, as a rescue treatment for renal dysfunction due to CNI toxicity have been reported in several studies[40-42]. Moreover, MMF could have nephroprotective properties. Romero *et al*[43] noted that MMF prevented progressive renal failure in rats that underwent 5/6 renal ablation and hypothesized that MMF has an antiproliferative effect. In fact, in various cell lines (*e.g.*, smooth muscle cells, renal tubular cells and mesangial cells), MMF reduced or even abrogated proliferation in response to proliferative stimuli[44]. These same effects on endothelial cells may counteract the harmful vascular effects of CNI and explain the beneficial effects of MMF in the prevention and treatment of CNI toxicity apart from the effect of a CNI dose decrease. As a result, the lower decrease in the GFR observed in patients receiving MMF may not be due only to the CNI dose reduction.

In conclusion, we showed that in LT patients, the optimal calcineurin inhibitor is low-dose TAC combined with MMF, as this treatment was associated with a better long-term GFR (10 mL/min per 1.73 m^2), thereby decreasing renal toxicity, and a higher patient survival rate.

COMMENTS

Background
Calcineurin inhibitors (CNI), since their introduction in the 1980s, have been the cornerstone of maintenance immunosuppressive regimens in liver transplantation. The use of CNI has substantially decreased the risk of acute rejection and improved short-term outcomes. However, CNI is associated with severe adverse effects, such as nephrotoxicity, dyslipidemia and hypertension especially in cyclosporine A (CSA). Recent studies showed that tacrolimus is preferred over CSA as an immunosuppressive agent. Low dose administration of immunosuppressive agents, such as tacrolimus, might reduce the risk of graft rejection, as well as cut down the cost of immunosuppressive therapy. However, correlation between the dosage of tacrolimus and the associated side effects and survival rates in liver transplant (LT) patients is largely unknown.

Research frontiers
Tacrolimus (TAC) has been proved with a less nephrotoxicity than CSA as well as mycophenolate mofetil (MMF), which have been used commonly in transplantations. In the area of prevention of chronic kidney disease (CKD) after LT, the research hotspot is how to balance the potent immunosuppression and less CNI exposure.

Innovations and breakthroughs
This article focused on developing and validating a low-dose tacrolimus combined with MMF as a better choice of immunosuppression. The study included 689 consecutive liver transplantation recipients. Glomerular filtration rate, estimated by an abbreviated modification of diet in renal disease formula, suggested CKD when it is lower than 60 mL/min per 1.73 m^2 for at least 3 consecutive months after LT. TAC trough concentrations $\leqslant$ 8 ng/mL at 3 mo after LT was defined as low-dose group. Incidence of CKD within 5 years was compared between TAC group and CSA group, as well as among four subgroups (low-dose and high-dose TAC groups with or without MMF). This study was with a high volume cohort and suggested that the choice of the immunosuppression should be low-dose TAC combined with MMF because it was associated with a better renal function and a higher patient survival rate.

Applications
The study results suggest that the choice of immunosuppressive therapy appears to affect renal function and patient survival in LT.

Terminology
Tacrolimus (trade name Prograf) is a product of the bacterium *Streptomyces tsukubaensis*. It is a macrolide lactone and acts by inhibiting calcineurin. The drug is used primarily in liver and kidney transplantations, although in some clinics it is used in heart, lung, and heart/lung transplantations. It binds to the immunophilin FKBP1A, followed by the binding of the complex to calcineurin and the inhibition of its phosphatase activity. In this way, it prevents the cell from transitioning from the G0 into G1 phase of the cell cycle. Tacrolimus is more potent than ciclosporin and has less pronounced side-effects. CKD, also known as chronic renal disease, is a progressive loss in renal function over a period of months or years. The symptoms of worsening kidney function are non-specific, and might include feeling generally unwell and experiencing a reduced appetite. Often, chronic kidney disease is diagnosed as a result of screening of people known to be at risk of kidney problems, such as those with high blood pressure or diabetes and those with a blood relative with chronic kidney disease. Chronic kidney disease may also be identified when it leads to one of its recognized complications, such as cardiovascular disease, anemia or pericarditis. It is differentiated from acute kidney disease in that the reduction in kidney function must be present for over 3 mo.

Peer review
This is a good retrospective study in which the authors analyzed the effect of low-dose tacrolimus with mycophenolate mofetil on the incidence of chronic kidney disease following liver transplantation. The results are interesting and

suggest that the choice of the immunosuppression appears to affect renal function and patient survival following LT.

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