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Long-Term Effects of Calcineurin Inhibitors on Renal Function After Liver Transplantation

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Abstract

The longer survival of liver transplant recipients has emphasized the need to consider complications that develop several years after liver transplantation, such as chronic renal dysfunction. Renal dysfunction has an impact on long-term posttransplant morbidity and mortality. The prevalence of chronic renal disease among liver transplant recipients varies widely from 10 to 78%. This renal dysfunction is multifactorial in origin, but is customarily considered to be secondary to calcineurin inhibitors, tacrolimus and cyclosporine, acute dose-dependent and chronic non dose-dependent nephrotoxicity. With the occurrence of powerful immunosuppressive drugs without renal side-effects (i.e. mycophenolate mofetil and sirolimus), there have been several reports on the management of calcineurin inhibitor-induced nephrotoxicity, with either reduction or complete withdrawal of calcineurin inhibitors. Most of them resulted in an improvement in renal function. The point is to assess if reduction is sufficient to reverse renal lesions. Concerning prevention of renal function deterioration, the best way is on the one hand to try to control the potential contributors to chronic renal failure, such as hypertension, hyperlipidemia, and diabetes mellitus, and on the other hand to decrease the cumulative doses of calcineurin inhibitors. In an attempt to prevent renal dysfunction after liver transplantation, several investigators have published studies designed to reduce the dose and/or to delay the introduction of calcineurin inhibitors, with the use of mycophenolate mofetil and/or anti-CD25 antibodies induction.

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Introduction

From 1988 to 2004, 66,393 liver transplantations (LT) have been performed in Europe[1]. As operative techniques and immunosuppressive management have improved, long-term survival has increased, with five-year and 10-year patient survival of 70 and 60%, respectively. The main threats to the graft currently are those associated with rejection episodes, biliary and vascular complications, and recurrence of the initial liver disease, particularly hepatitis C and hepatocellular carcinoma. However, the longer survival of LT recipients has emphasized the need to consider other complications which develop several years after LT such as chronic renal dysfunction.

Renal dysfunction is a major problem after LT, and has an impact on long-term morbidity and mortality. The prevalence of chronic renal disease among LT recipients varies widely from 10 to 78%[2-5]. These variations have many explanations: lack of standard definition of posttransplant renal disease, confusion between acute (reversible or not) and chronic dysfunction, and variable periods of follow-up. This renal dysfunction is multifactorial in origin, but is customarily considered to be secondary to calcineurin inhibitors (tacrolimus and cyclosporine) and acute dose-dependent and chronic non dose-dependent nephrotoxicity[6]. One important point is the possible interplay of preexisting renal disease and calcineurin inhibitor (CNI) therapy. Moreover, LT recipients may develop diabetes mellitus and hypertension, two conditions associated with renal failure.

Prevalence and consequences of renal dysfunction after liver transplantation

Before considering posttransplant renal dysfunction, two points need to be emphasized.

The first point concerns the definition of renal dysfunction. Numerous studies used a definition of chronic renal failure as an elevated serum creatinine level. For instance, using a serum creatinine level > 2.5 mg/dl, Gonwa, et al. found an incidence of chronic renal failure at 13 years of 6%[3]. Limitations of the diagnostic use of creatinine in patients with impaired liver function, as well as LT recipients, are well known: reduced muscle mass, impaired hepatic biosynthesis[7]. Since "gold standard" methods using direct measurements of glomerular filtration rate (GFR), such as isotopic or non-isotopic iothalamate clearances, are cumbersome, time-consuming, and too expensive for use in clinical practice, determination of GFR remains difficult in these patients. Several creatinine-based equations, including biochemical, demographic, and anthropometric data, have been evaluated in LT recipients[8]. It seems that the Modification of Diet in Renal Disease formula, rather than the Cockcroft and Gault formula, is the most accurate to assess renal function after LT. Recently, Gerhardt, et al. have suggested that cystatin C-based equations had the best overall performance to GFR estimates after LT[7].

The second point concerns pretransplant renal function. In patients with cirrhosis, renal failure may be due to prerenal failure, mainly hepatorenal syndrome which is a potentially functional state, and intrinsic renal failure (tubular necrosis or glomerulonephritis), which is a potentially irreversible parenchymal injury[9]. This point allows to distinguish *de novo* posttransplant renal dysfunction from preexisting renal dysfunction. The absence of parenchymal kidney disease is usually indicated by proteinuria < 500 mg/day, microhematuria < 50 red blood cells per high-power field, and normal renal ultrasonography[10].

The heterogeneity of the definitions used in the literature to assess the incidence and the prevalence of renal dysfunction after LT makes it difficult to understand the results. Acute renal dysfunction, defined by an increased serum creatinine during the first month posttransplant, has been reported with an incidence ranging

from 12 to 64%[11]. The etiology of acute renal dysfunction is multifactorial, associating preexisting renal impairment resulting from hepatorenal syndrome, diabetic nephropathy, and cryoglobulinemia, and posttransplant conditions such as acute tubular necrosis, sepsis, and CNI toxicity[12].

Concerning chronic renal dysfunction, Ojo, et al. have reported the results of a population-based cohort analysis involving recipients of nonrenal solid organs in order to determine the incidence of chronic renal failure, the risk factors for this condition, and the risk of death associated with it[13]. The sample in the analysis included 69,321 patients who received a first nonrenal solid organ transplant in the USA between January 1, 1990 and December 31, 2000. Among them, 36,849 patients were LT recipients. The primary endpoint analyzed was chronic renal failure, defined as GFR ≤ 29 ml/minute/1.73 m^2 of body-surface area, or the onset of end-stage renal disease, as determined by the initiation of dialysis therapy or preemptive kidney transplantation. The cumulative incidence of chronic renal failure after LT was 8 ± 0.1% at one year, 13.9 ± 0.2% at three years, and 18.1 ± 0.2% at five years. End-stage renal disease occurred at a rate of 1-1.5% per year among LT recipients. Multivariate Cox regression analysis revealed that the risk of chronic renal failure after LT was associated with a number of variables: age, male sex, non-Asian race, pretransplantation GFR, dialysis treatment before transplantation, diabetes mellitus before transplantation, hepatitis C, postoperative acute renal failure, year of transplantation (before 1994), and use of cyclosporine therapy. Chronic renal failure was associated with an elevated risk of death after LT (RR: 4.55; 95% CI: 4.38-4.74).

As already mentioned, chronic renal dysfunction after LT is multifactorial. In a renal histopathologic study performed in 26 LT recipients with chronic renal failure, Pillebout, et al. have demonstrated that renal involvement is often severe and that renal destruction is in fact multifactorial: not only specific lesions of CNI toxicity, but also lesions related to diabetes mellitus, arterial hypertension, or to volume-expansion products used in the 1990s in patients with ascites awaiting LT[14].

As demonstrated in numerous studies, one of the prevalent causes of renal dysfunction is the long-term use of CNI. High trough cyclosporine levels early after LT and higher cumulative cyclosporine dosage later after the LT are significant risk factors identified for late, severe renal dysfunction[2,15]. In a study about long-term renal function after LT, Morard, et al. found that trough levels of cyclosporine ≥ 150 µg/l and of tacrolimus ≥ 10 µg/l one year after LT and of cyclosporine ≥ 100 µg/l and of tacrolimus ≥ 8 µg/l five years after LT were independent risk factors associated with impaired renal function at five years[16]. Early clinical studies comparing the chronic nephrotoxic effects of cyclosporine versus tacrolimus have yielded variable and conflicting results, suggesting a better preservation of renal function with tacrolimus compared to cyclosporine[5]. However, in recent studies designed to compare cyclosporine microemulsion with tacrolimus, it was always concluded that renal dysfunction was the same in both groups[17-19].

Preservation of calcineurin inhibitor-altered renal function after liver transplantation

With the occurrence of powerful immunosuppressive drugs without renal side effects, i.e. mycophenolate mofetil (MMF) and sirolimus, there have been several reports on the management of CNI-induced nephrotoxicity, with either reduction or complete withdrawal of CNI. Most of them resulted in an improvement in renal function. The point is to assess if reduction is sufficient to reverse renal lesions. It is acknowledged that chronic renal nephrotoxicity is partly dose-dependent, but can occur in the presence of low blood levels[20]. Thus, it was often considered to represent an

Table 1. Partial replacement of calcineurin inhibitors with mycophenolate mofetil

Study	(n)	IS	Time to LT (months)	Follow-up (months)	Baseline creatinine	Improvement	Rejection
Raimondo, et al.[23]	18	MMF ↓ 50%	32	26	142 µM/l	60%	0%
Cantarovich, et al.[24]	19	MMF ↓ 50%	> 12	12	141 µM/l	71%	29%
Reich, et al.[25]	18	MMF ↓ 50%	13	12	19 mg/l	50%	11%
Pageaux, et al.[26]	27	MMF ↓ 50%	62	12	162 µM/l	72%	0%

IS: immunosuppressor; MMF: mycophenolate mofetil; LT: liver transplant.

Table 2. Complete replacement of calcineurin inhibitors with mycophenolate mofetil

Study	(n)	IS	Time to LT (months)	Follow-up (months)	Baseline creatinine	Improvement	Rejection
Schlitt, et al.[27]	14	MMF	76	6	168 µM/l	78%	21%
Stewart, et al.[28]	9	MMF	> 12	3	Not detected	83%	33%
Raimondo, et al.[23]	16	MMF	45	35	179 µM/l	62%	6%
Fairbanks, et al.[29]	15	MMF	67	19	29 mg/l	73%	20%
Reich, et al.[25]	20	MMF	16	12	19 mg/l	63%	30%

IS: immunosuppressor; MMF: mycophenolate mofetil; LT: liver transplant.

irreversible damage[21]. It is now suggested by the efficacy of CNI dosage reduction on improvement of renal function, that there is a part of reversible functional impairment in chronic CNI renal dysfunction[15-22].

In several prospective (most often open) and retrospective studies, the partial (Table 1) or complete (Table 2) replacement of CNI with MMF, in patients with chronic renal dysfunction, resulted in a significant improvement in renal function, but sometimes an increased risk of acute and chronic rejection[23-29]. We have to be very cautious with the late-onset rejection episodes, which are responsible for decreased graft survival, contrary to the early episodes. Moreover, it is critical to consider the risks associated with rejection therapy, such as a worsening of recurrent hepatitis C with corticosteroid pulses[30]. We consider that CNI reduction must be preferred to complete withdrawal, especially in the absence of validated monitoring of MMF therapy in the setting of LT. Thus, we have designed a prospective, multicenter, randomized study, which was the first with an untreated control arm, and the results at one year have shown that the introduction of MMF combined with the reduction of at least 50% of CNI dose allowed to significantly improve the renal function of LT recipients, without any rejection episode and without significant side-effects[26]. The two-year results of this study have been presented during the Association for the Study of Liver Diseases (AASLD) meeting in November 2007[31]. They emphasized, on the one hand, the significant improvement of renal function at two years compared to baseline but, on the other hand, the absence of significant improvement between one and two years, suggesting an incomplete benefit of reducing CNI doses.

Sirolimus has also been used to eliminate CNI because of nephrotoxicity (Table 3)[29,32-34]. In summary, GFR improved or remained stable in the CNI-withdrawal groups at both one and two years. Complete CNI withdrawal was achieved in 50-100% of patients, and rejection episodes were unusual[35]. However, these promising

Table 3. Complete replacement of calcineurin inhibitor with sirolimus

Study	(n)	IS	Time to LT (months)	Follow-up (months)	Baseline creatinine	Improvement	Rejection
Cotterell, et al.[32]	8	SRL	60	ND	24 mg/l	62%	0%
Fairbanks, et al.[29]	21	SRL	72	16	28 mg/l	71%	5%
Kniepeiss, et al.[33]	6	SRL	62	4.5	29 mg/l	83%	0%
Sanchez, et al.[34]	35	SRL	6	24	17 mg /l GFR 42	44%	2.8%
			Withdrawn 34%				

IS: immunosuppressor; SRL: sirolimus; LT: liver transplant; GFR: glomerular filtration rate.

results are hampered by lack of experience and possible sirolimus-induced side effects.

Prevention of calcineurin inhibitor-induced renal dysfunction after liver transplantation

Concerning prevention, the best way is, on the one hand, to try to control the potential contributors to chronic renal failure, such as hypertension, hyperlipidemia, and diabetes mellitus and, on the other hand, to decrease the cumulative doses of CNI. Thus, it has been demonstrated that optimal treatment of diabetes considerably diminishes the risk of developing diabetic nephropathy[14]. Moreover, identification of microalbuminuria should lead to institution of angiotensin converting enzyme inhibitor treatment, which has also been shown to slow the progression of diabetic nephropathy[36]. The opportunity to use non-nephrotoxic, immunosuppressive drugs, such as MMF, sirolimus, everolimus, or anti-CD25 antibodies, could allow to decrease the cumulative dose of CNI in immunosuppressive regimens. In addition, it could be preferable not to begin CNI until 48-72 hours post-LT, when renal hemodynamic has returned toward normal. At least, we have to take into account the possibility that cirrhosis itself and the attendant abnormalities in renal function may predispose the LT recipient to permanent renal damage when treated with CNI.

In an attempt to prevent renal dysfunction after LT, several investigators have published studies designed to reduce the dose and/or to delay the introduction of CNI, with the use of MMF and/or anti-CD25 antibodies induction. Yoshida, et al. have suggested that delayed low-dose tacrolimus, in combination with daclizumab and MMF, preserved early (month 1 and 6) renal function post-LT without the cost of increased rejection[37]. During the AASLD meeting held in Boston in 2007, two studies were presented with conflicting results. In the first one, a prospective, randomized trial on 525 patients, it was suggested that lower (trough target level < 8 ng/ml) and delayed introduction (on day 5) of tacrolimus, together with MMF and daclizumab was associated with better preservation of renal function at one year without any significant adverse impact on patient and graft[38]. It must be emphasized that in the three groups of this study (standard tacrolimus, low-dose tacrolimus plus MMF, low-dose and delayed introduction of tacrolimus plus MMF plus daclizumab), renal impairment assessed by the Cockcroft-Gault formula was observed, but significantly less in the third group. In the second one, a prospective, randomized trial on 207 patients, delayed tacrolimus administration with MMF and daclizumab was not statistically different to that with immediate tacrolimus administration in terms of benefit on renal function at six months, assessed by serum creatinine[39].

In conclusion, LT recipients need to be informed about the long-term risk of chronic renal dysfunction. In case of preexisting renal

disease, the possibility of combined liver and kidney transplantation may be considered. Immunosuppressive regimens using CNI-sparing drugs need to be evaluated in clinical trials.

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