

Immunosuppression in liver transplant recipients with renal impairment

C. Duvoux^{1,*}, G.P. Pageaux²

¹Department of Hepatology and Gastroenterology, Liver Transplant Unit, Hospital Henri Mondor AP-HP, University Paris Est, Créteil, France;

²Medico-Surgical Federation of Digestive Diseases, Liver Transplant Unit, Hospital Saint-Eloi, Montpellier, France

Introduction

Renal injury has been recognized as an increasingly prevalent complication of liver transplantation (LT) over the last decade. Both acute and chronic renal injuries occur with high frequency in liver transplant recipients and are associated with increased morbidity and mortality. The risk of immediate post-LT kidney dysfunction is increased in patients with pre-transplant kidney failure, hepato-renal syndrome (HRS), and intra-operative or post-operative hypotension. Thus with the improvement in life expectancy after LT, chronic kidney disease (CKD) has emerged as an increasingly prevalent complication among long-term survivors. Although post-LT renal injury is often multifactorial, one of the dominant mediators is the use of calcineurin inhibitors (CNI), namely Cyclosporine (CsA) and Tacrolimus (Tac), which are the cornerstone of immunosuppression in LT recipients. These drugs indeed intrinsically share a variety of renal toxicities, ranging from oligoanuric acute renal failure to chronic kidney disease.

Optimization of immunosuppression for protection of kidney function must, therefore, be considered a major goal after LT, in particular for patients with already impaired renal function.

The aim of this article is to review the epidemiology, risk factors, and consequences of post-LT renal dysfunction and to discuss the current approaches to overcome CNI toxicity after LT, both in the early post-operative period and in the long-term, focusing on manipulation of immunosuppressive agents.

The issue of combined liver/kidney transplantation in LT candidates with renal failure is beyond the scope of this review and will not be considered herein.

Immunosuppression for patients in the early post-operative period

The issue of early renal dysfunction after liver transplantation

Acute post-operative renal injury frequently occurs after LT [1–6]. The high frequency of acute renal dysfunction results from variable, multi-factorial insults to the kidney, including pre-existing hepato-renal syndrome, the use of nephrotoxic antimicrobial agents and, obviously, the use of CNI immediately after LT. In fact, one of the strongest predictors is the dose and level of CNI in the early post-transplantation period [7,8]. An important objective in the early post-operative period is, therefore, to optimize the immunosuppressive regimen in order to protect kidney function and prevent long-term consequences.

Depending on the criteria used to define “acute renal failure,” post-operative renal injury has been reported in 17–94% of patients undergoing LT [1–6]. Using the RIFLE (Risk–Injury–Failure–Loss–Endstage) criteria (Table 1) for acute renal dysfunction, renal “injury” (increase in serum creatinine $\geq 2.0 \times$ baseline or decrease in GFR $\geq 50\%$) was observed in 41.5% of the patients in the first month post-LT [7]. In two studies, in which renal failure was defined by an increase in serum creatinine $\geq 50\%$ above baseline values, the incidence of renal failure was 42% and 48% [5,6].

Severe forms of acute renal “failure” (RIFLE) requiring renal replacement therapy (RRT) have been reported in 6.5–18.3% [9–12,4,13] of cases, usually early, within the first week post-LT. In this setting, acute renal failure results from major post-operative stresses frequently associated with acute tubular necrosis, including prolonged hypotension, sepsis or septic shock, sustained pre-renal failure, primary graft non-function, or delayed function of the liver.

Post-operative renal injury is responsible for significant mid- and long-term consequences and impacts both on kidney function and survival. Renal replacement therapy has consistently been associated with a significant reduction in 1-year survival compared to patients not requiring RRT: 1-year survival in RRT patients is close to 50% (Fig. 1) [9,12]. Among survivors, RRT is considered a significant predictor of impaired renal function in the long term, with a more than 2-fold increase in the risk of chronic renal failure [14]. Early acute renal injury not requiring RRT is also considered a major contributor to the long-term risk of chronic kidney disease [8,15,16]. In most studies, early

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*Corresponding author. Address: Service d'Hépatogastroentérologie, Unité de Transplantation Hépatique, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, 94000 Créteil, France. Tel.: +33 1 49 81 23 53; fax: +33 1 49 81 23 52.

E-mail address: christophe.duvoux@hmn.aphp.fr (C. Duvoux).

Abbreviations: CKD, chronic kidney disease; CNI, calcineurin inhibitors; CsA, Cyclosporine A; GFR, glomerular filtration rate; HRS, hepato-renal syndrome; LT, liver transplantation; MPA, mycophenolic acid; mTOR, mammalian target of Rapamycin; RRT, renal replacement therapy; Tac, Tacrolimus.



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Table 1. The acute dialysis quality initiative (ADQI) criteria for the definition and classification of acute kidney injury: the RIFLE (Risk–Injury–Failure–Loss–Endstage renal disease) criteria^a.

RIFLE category	Serum creatinine criteria	Urine output criteria
Risk	Increase in serum creatinine $\geq 1.5 \times$ baseline or decrease in GFR $\geq 25\%$	<0.5 ml/kg/h for ≥ 6 h
Injury	Increase in serum creatinine $\geq 2.0 \times$ baseline or decrease in GFR $\geq 50\%$	<0.5 ml/kg/h for ≥ 12 h
Failure	Increase in serum creatinine $\geq 3.0 \times$ baseline or decrease in GFR $\geq 75\%$ or an absolute serum creatinine ≥ 354 $\mu\text{mol/L}$ with an acute rise of at least 44 $\mu\text{mol/L}$	<0.3 ml/kg/h ≥ 24 h or anuria ≥ 12 h

RIFLE classification is an attempt to define the presence or absence of the clinical syndrome of acute kidney injury in a given patient, and to describe the severity of this syndrome.

^a In Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P: Acute Dialysis Quality Initiative workgroup: acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8:R204–R212.

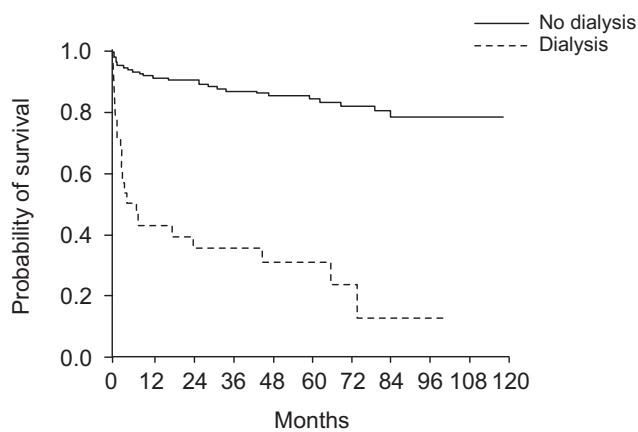


Fig. 1. Probability of survival after liver transplantation according to dialysis in the early post transplant period ($p = 0.0001$). Adapted from Singh et al. [12].

elevation in serum creatinine at 1, 3, or 6 months post-LT was an independent predictor of chronic renal failure [8,15,16]. And in a recent retrospective study [17] of 1075 patients, the onset of chronic renal dysfunction within the first year after LT was even correlated with reduced survival.

Limiting early insults of any kind to the kidney and especially CNI toxicity is, therefore, of major importance in order to preserve renal function and survival in the long-term. With respect to this, understanding the mechanism of CNI nephrotoxicity is essential.

Mechanism of acute CNI renal toxicity and the relationship with end-stage liver disease

Cyclosporine and Tac are two CNI which share a similar mechanism of action, as well as a pattern of nephrotoxicity. Acute CNI nephrotoxicity is caused by an intense, predominantly afferent, arteriolar vasoconstriction (Fig. 2) which thereby alters renal hemodynamics (reviewed in [18,19]. This pre-renal, dose-related, renal dysfunction results in an acute and reversible decrease in the glomerular filtration rate (GFR), renal blood flow, and urine output. The vasoconstriction is in part related to an imbalance in the release of vasodilator substances, such as prostaglandin E2 [20] or NO [21], and increased vasoconstrictor factors, such

as thromboxane A2, endothelin 1 [22], and angiotensin II [20]. Local activation of the sympathetic nervous system may also contribute. Following discontinuation of CNI, renal function usually returns to baseline without any major histological or cytological abnormalities. However, in some instances, prolonged vasoconstriction may directly damage renal tubular cells causing acute tubular vacuolization (Fig. 3) or necrosis, with subsequent tubule-interstitial lesions and chronic/irreversible nephrotoxicity [19].

Immunosuppressive approaches to prevent acute renal dysfunction

Prevention of acute CNI nephrotoxicity can in principle be achieved by: (A) excluding CNI from immunosuppressive regimens; (B) delaying the introduction of CNI beyond the very early post-operative phase during which the kidney is particularly susceptible to CNI acute injury; and, (C) early minimization of CNI levels.

Excluding CNI from immunosuppression

Withdrawing CsA in patients with HRS or significant renal dysfunction and replacement with Azathioprine and steroids was first proposed [23] in the early nineties. Such an approach must be used with caution in the early post-operative phase because elimination of CNI even when substituted by more recent antiproliferative agents than Azathioprine, such as MPA has been associated with a notable rate of rejection [24,25] and even graft loss.

Sirolimus and Everolimus are two mammalian targets of Rapamycin inhibitors (mTOR) which when given without CNI in patients with normal baseline renal function are not considered nephrotoxic. Yet, mTOR inhibitors are usually avoided in the immediate post-LT period. A pivotal study combining Sirolimus and Tacrolimus as a primary immunosuppressive regimen demonstrated a significant reduction in 1-year survival because of an unexpected incidence of infections and vascular thrombotic complications. In addition, wound healing complications may also be caused by the antiproliferative effects of this class of agents. For these reasons, very early use of mTOR inhibitors post-LT cannot yet be recommended. However, a study in 145 liver transplant recipients on maintenance regimens supported that concentration-controlled Everolimus allows for the elimination of CNI without increasing the risk of acute rejection [26]. Early introduction of mTOR inhibitors, 4 weeks post-LT, followed

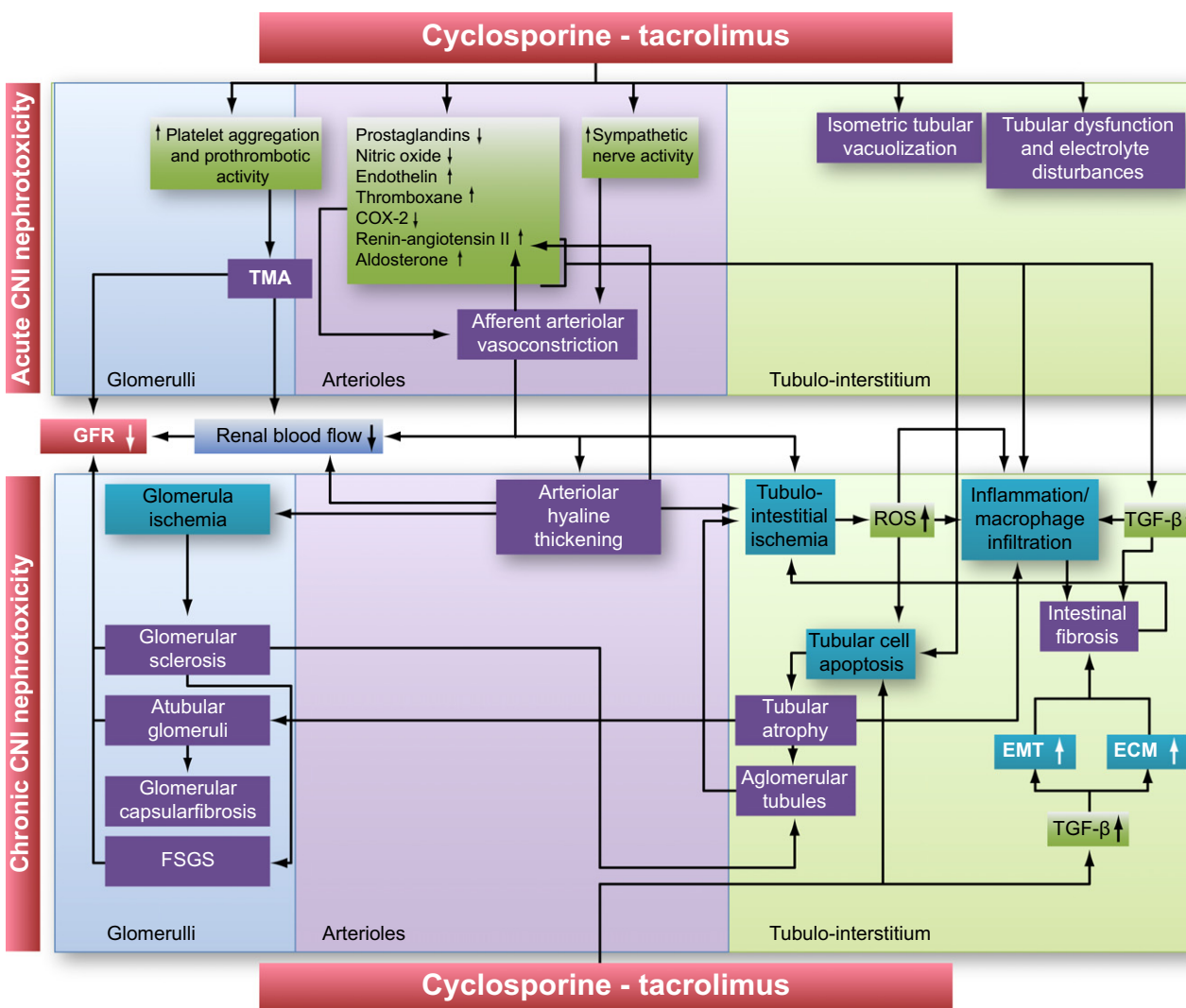


Fig. 2. Schematic representation of the pathophysiology of calcineurin inhibitors nephrotoxicity. Reprinted from Naesens et al. [45], with permission from the American Society of Nephrology.

by early reduction or discontinuation of CNI may provide superior renal function compared to CNI-based standard therapy and, is currently under investigation (Clinical Trials.gov identifier: NCT00622869).

Another option which has achieved encouraging results in kidney transplantation [27] is the blockade of the T-cell co-stimulation pathway. Belatacept is a fusion protein derived from CTLA4-Ig which blocks the interactions of CD28 with CD80 and CD86 with a 10-fold greater inhibition of T-cell activation *in vitro* as compared with CTLA4-Ig alone. In kidney transplantation, a Phase II study involving 218 recipients of *de novo* renal allografts compared the efficacy of Belatacept to CsA as a maintenance immunosuppressant together with Basiliximab induction, steroids, and MPA [27]. Belatacept-based therapy (intravenous infusion every 4 or 8 weeks) showed similar efficacy in preventing acute rejection at 6 months versus CsA-based treatment: 6–7% for Belatacept versus 8% for CsA. Furthermore, Belatacept-treated patients showed a significant improvement in renal function at one year compared with CsA-treated patients (63 ml/mn versus 53.5 ml/mn/1.73 m²). Whether such a beneficial impact

on renal function can be achieved in LT recipients on maintenance Belatacept therapy is currently being investigated (Belatacept in liver transplantation; Clinical Trials.gov identifier: NCT00555321).

Delaying introduction of CNI (Table 2)

The challenge of such an approach is to ensure adequate immunosuppression despite delayed introduction of CNI. To achieve this goal, induction therapy with anti-lymphocyte/thymocyte antibody preparations or anti-interleukin-2-receptor antibodies, with or without MPA have been proposed (Table 2). This approach can be particularly useful in instances where pre- or immediate post-LT renal function is significantly altered.

Anti-lymphocyte antibodies

In a retrospective study [28] comparing 129 patients receiving standard CNI, with 262 patients receiving 3-day induction therapy with Thymoglobulin (2.5 mg/kg/d) followed by CNI introduction as the local standard prophylactic treatment, Soliman and colleagues reported better renal function at 1-year

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Table 2. Impact of induction therapies and delayed introduction of calcineurin inhibitors on renal function after [28,30–33]. [36]

References	No. Patients	Design	Time of IS change	Type of induction	Immunosuppression /groups	Acute rejection	Renal function
Soliman et al. [29]	391	Retrospective, controlled	<i>De novo</i>	ATG	A (n = 129): CNi B (n = 262): delayed CNi + ATG	A: 31.8% B: 14.5% $p = 0.0008$	A: 72 ml/min B: 81 ml $p = 0.02$, at 1 yr
Bajjoka et al. [30]	198	Retrospective 2 consecutive arms	<i>De novo</i>	ATG	A (n = 118) : delayed CNi + ATG + MMF B (n = 80) : standard CNi		A : 57.4 ml/min/1.73 m ² B: 43.7 ml/min/1.73 m ² $p < 0.001$, at 1 yr
Lin et al. [31]	47	Prospective non randomized Open label	<i>De novo</i>	IL2 R Ab basiliximab	A (n = 27) : delayed CNi + IL2R Ab + MMF B (n = 18) : CNi + MMF therapy		A: 72 ml/minute B : 57 ml/minute, $p = 0.04$
Yoshida et al. [32]	148	Prospective, controlled	<i>De novo</i>	IL2 R Ab daclizumab	A (n = 72): MMF + delayed reduced Tac + IL2 R Ab B (n = 76): MMF + normal dose Tac + IL2R Ab		Month 1 A: 86.8 ml/min B: 70.1 ml/min $p < 0.001$ Still significant at M6
Neuberger et al. [33]	485	Prospective Randomized Multicenter 3 arms	<i>De novo</i>	IL2 R Ab daclizumab	A: Standard Tac + IL2R Ab B: MMF + reduced Tac + IL2 C: MMF + reduced delayed Tac + IL2	lower BPAP in group C: $p = 0.0054$ A: 23.2% B: 27.7% $p = 0.68$	At 1 yr Reduction in GFR lower in group C vs A and B 13.6 vs 23.6 vs 21.2 ml/mn, $p = 0.007$

CNI, calcineurin inhibitors; IL 2R Ab, IL2 receptors Antibodies; ATG, anti-thymocyte globulins; MMF, mycophenolate mofetil. Overall, delayed-reduced introduction of CNI, in combination with induction therapy + MMF was associated with an improvement in renal function without increasing the risk of rejection in the short and mid-term.

in the Thymoglobulin induction group (GFR: 81 versus 72 ml/min, $p = 0.02$). In addition, Thymoglobulin patients experienced less frequent rejection with similar 1-year survival and a similar incidence of *de novo* tumors. Interestingly, the same group recently reported that a longer (10-day) Thymoglobulin-based induction therapy [29] was associated with an increased risk of infection, supporting the concept that the best risk–benefit ratio was achieved with the short induction phase. Similar results were observed by Bajjoka et al. [30]. In this study, all the patients had post-operative renal dysfunction defined by the need for hemodialysis or a creatinine >1.5 mg/dl, and received MPA. Anti-thymocyte globulin (0.5–1 mg/kg/d) was given for a maximum of 5 days or until creatinine had decreased <1.2 mg/dl. Delayed CNi initiation after anti-thymocyte globulin induction was associated with a significant improvement in renal function with a higher estimated glomerular filtration rate (57.4 versus 43.7 ml/min/1.73 m², $p < 0.001$) and less dependence on dialysis (0.8% versus 13%, $p < 0.001$) at 12 months post-transplant, with no impact on CMV infection or severity of HCV recurrence.

Anti-interleukin-2-receptor antibodies

When complexed with anti-IL2 receptor antibodies, IL-2 receptors on T-lymphocytes are no longer available for IL-2 binding, and the proliferation of associated T-lymphocytes is inhibited. The duration of IL-2 receptor saturation in adults is longer than 4 weeks and several studies have tested whether a delayed introduction of CNi after Daclizumab or Basiliximab induction therapy was beneficial to kidney function. In a prospective non-randomized open label study [31], 47 consecutive living donor

LT recipients were treated either with Basiliximab induction therapy + MPA and delayed introduction of Tacrolimus, or with conventional CNi + MPA therapy. Basiliximab was preferentially used in the sickest patients at transplantation and in those with significant blood loss. In such cases, Tac was introduced as a median of 36 h post-LT [24–108 h]. The creatinine clearance rate was higher (median 72 versus 57 ml/min, $p = 0.04$) and the incidence of renal insufficiency was lower in the induction group (26% versus 67%, $p < 0.01$) at three months post-transplant.

A beneficial impact of delayed introduction of CNi on renal function in patients receiving Daclizumab induction therapy has also been reported in two randomized controlled studies [32,33] (Table 2) without increasing the risk of rejection. In both studies, Daclizumab was given in combination with MPA, followed by delayed introduction of Tac at normal or even reduced doses. In the Yoshida and colleagues study [32], GFR calculated by the Modification of Diet in Renal Disease [34] method was significantly better in the delayed, low-dose (4–8 ng/ml) Tac group than in the standard Tac group, at 1 week, 1 and 6 months post-LT. In the ReSPECT trial [33], the decrease in GFR [ml/min] from baseline to week 52 was significantly lower in the induction/delayed–reduced Tac group than the standard group (GFR reduction: 13.63 ml/min versus 23.61 ml/mn, $p = 0.007$). Renal replacement therapy was also required less frequently in the induction group (4.2% versus 9.9%; $p = 0.037$).

In conclusion, these results highly suggest that delayed-reduced introduction of CNi under the protection of MPA and anti-IL2 receptor antibodies is associated with an improvement in renal function in the short and mid-term, without increasing

the risk of rejection when compared with conventional CNI-based immunosuppression.

Minimizing CNI doses: combining reduced doses of CNI with MPA

MPA is a non-competitive reversible inhibitor of IMPDH, an enzyme required for *de novo* purine synthesis, which selectively inhibits lymphocyte proliferation without nephrotoxicity.

The combination of MPA and reduced Tac has been proven to be an efficacious and well tolerated immunosuppressive regimen in large randomized, multicenter studies. Investigated as a specific trial arm in the ReSpECT trial [33], the minimized Tac triple therapy (MPA, 2 g/day + reduced-dose Tacrolimus with target trough levels ≤ 8 ng/ml + corticosteroids) showed similar efficacy in preventing rejection than the standard dual group (Tacrolimus with target trough levels >10 ng/ml and corticosteroids) with only a marginal, non-significant reduction in GFR at 52 weeks (21.22 versus 23.61 ml/min).

In summary, liver transplant recipients, especially those with severe end-stage liver disease and those with early post-operative complications, are exposed to a high risk of early renal dysfunction, which is predictive of chronic renal injury. In this setting there is a growing body of evidence that early

manipulation of immunosuppression with delayed introduction of CNI, under the protection of induction therapy and MPA, is beneficial to the kidney in the short-term, and, therefore, probably in the long-term, without increasing the risk of rejection. The reasons for this impact have not been fully elucidated.

As stated above, pre-transplant renal failure, in particular HRS, is a predictor of post-transplant renal dysfunction. Since HRS is one of the most common causes of renal failure pre-LT [35] and is characterized by a pre-renal dysfunction with intense arterial vasoconstriction, it can be reasonably hypothesized that HRS patients and to a lesser extent ascitic patients, could be more susceptible to the vasoactive effects of CNI post-transplant. These patients, therefore, could be more prone to develop acute CNI-induced nephrotoxicity and even tubular cell injury. Delayed introduction or even avoidance of CNI might be particularly protective to the kidney in the short term, resulting in a beneficial effect in the long-term. To prevent nephrotoxicity, immunosuppression could be tailored to each patient and the impact of individualized immunosuppressive regimens tested in specific populations.

In patients with HRS, interleukin 2 receptor blockers or short-term antithymocyte globulin induction therapy + MPA, with delayed, reduced-dose CNI could be proposed. In LT candidates

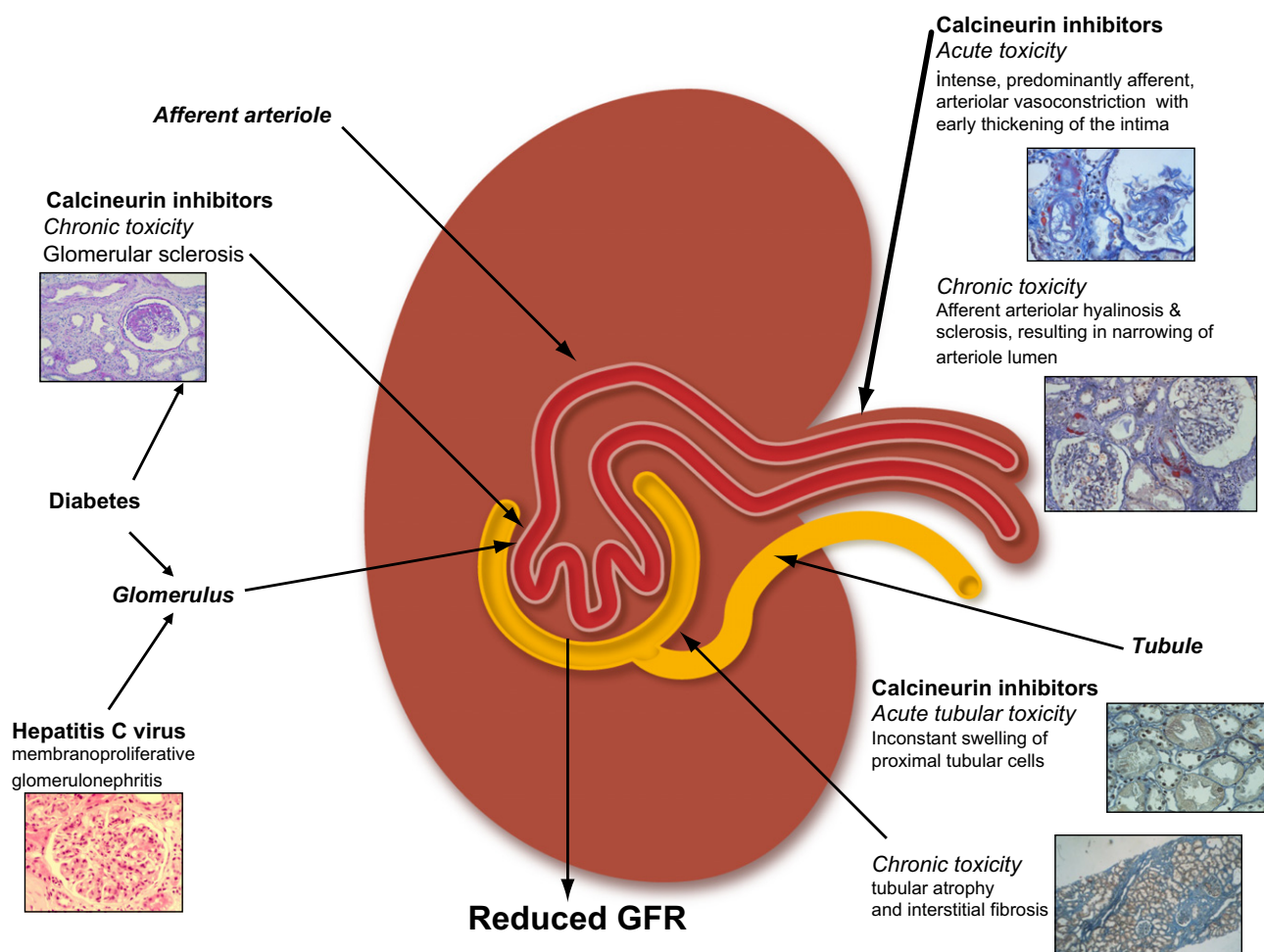


Fig. 3. Renal injury after liver transplantation. Role of calcineurin inhibitors and other co-factors.

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with refractory ascites, but apparent normal renal function pre-LT, low-dose CNI in conjunction with MPA and standard steroid therapy could be considered. Standard immunosuppression could be used in elective situations in patients with strictly pre- and post-LT normal kidney function (Fig. 4 summarizes the options for protecting the kidney in the early post-operative phase).

Immunosuppression in liver transplant patients with chronic renal injury in the long-term

The issue of renal dysfunction in the long-term

Definition and frequency

Chronic renal impairment is one of the major complications after LT and is largely caused by prolonged exposure to CNI. Renal impairment is associated with increased risks of morbidity and mortality after transplantation and one of the major long-term goals is to prevent renal function deterioration.

The definition and classification of chronic kidney disease [CKD] has been recently revised by the Kidney Disease Improving Global Outcome conference [37,38]. Chronic Kidney Disease is defined by “structural or functional abnormalities of the kidney, with or without decreased GFR, evidenced by abnormalities in the composition of the blood or urine, or abnormalities in imaging tests,” or $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$, with or without kidney damage. The K/DOQI-KIDIGO classification of CKD stratified renal alterations into five stages which are summarized in Table 3.

The exact prevalence of CKD in LT is difficult to determine because it varies widely according to the definition of CKD and length of follow-up (1–13 years), but appears to range between 4% [39] and 79% [40]. In some reports [39,41] the definition of CKD relies on serum creatinine, which is not appropriate for evaluating renal function if not interpreted together with sex, age, and weight. Others use GFR but with different methods of estimation and with non-standardized cut-off values. For instance, according to Cohen et al., the prevalence of $\text{GFR} < 40 \text{ ml/min/1.73 m}^2$ as determined by iothalamate clearance was 27.5% at

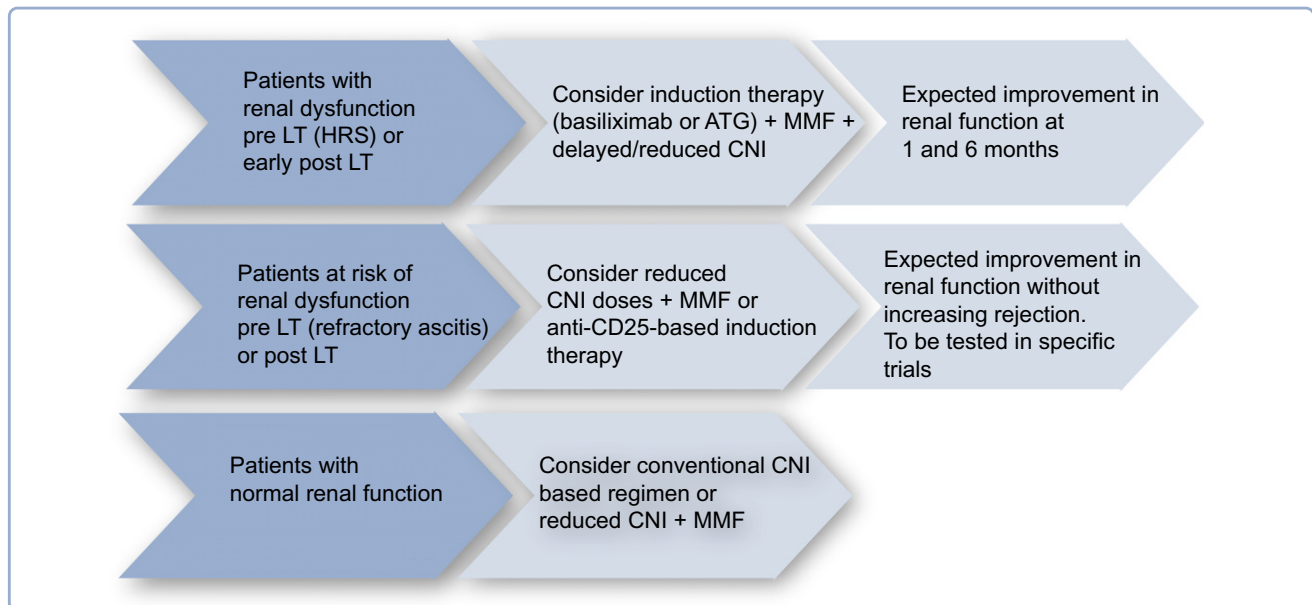


Fig. 4. Protection of the kidney in the early post-operative period: how to tailor immunosuppression to the individual profile of the LT recipient? ATG, anti-thymocytes globulins; CNI, calcineurin inhibitors; HRS, hepato-renal syndrome; LT, liver transplantation; MMF, mycophenolate mofetil.

Table 3. Chronic kidney diseases: the KIDIGO classification. [38]

Stage	Description	GFR, ml/min per 1.73m ²	Related terms
1	Kidney damage with normal or increased GFR	≥90	Albuminuria, Proteinuria, Hematuria
2	Kidney damage with decreased GFR	60-89	Albuminuria, Proteinuria, Hematuria
3	Moderately decreased GFR	30-59	Chronic renal insufficiency, early renal insufficiency
4	Severely decreased GFR	15-29	Chronic renal insufficiency, late renal insufficiency
			pre end stage renal disease
5	Kidney failure	<15 (or dialysis)	Renal failure, end stage renal disease, uremia

GFR, glomerular filtration rate.

Table 4. Frequency of chronic kidney disease in liver transplant recipients according to calculated GFR and K/DOGI-K/DIGO [6,14,43,44] (for classification see Table 3).

Study	Number of patients	End point	GFR assessment	Frequency of CKD according to stage
Ojo AO et al. [15]	36,849	5-year cumulative incidence	MDRD	Stage 4 = 18.1%
O'Riordan A et al. [44]	230	10-year cumulative incidence	MDRD	Stage 1 = 9.6% Stage 2 = 53.7% Stage 3 = 56.7% Stage 4 = 6.1% Stage 5 = 2.6%
Burra P et al. [45]	223	5-year prevalence	ND	Stage 3 = 36% Stage 4 = 2.7%
Karie-Guigues J et al. [6]	1508	5-year prevalence	MDRD	Stage 1 = 5.7% Stage 2 = 36.6% Stage 3 = 52.7% Stage 4 = 3.7% Stage 5 = 1.3%

CKD, chronic kidney disease; GFR, glomerular filtration rate; ND, not determined; MDRD, modification of diet in renal disease.

5-years [42], while Sheiner et al. [40] reported that the prevalence of GFR <43 ml/min/1.73 m² was 79.5% at 5-years. In the latter study, renal function was estimated using the Cockcroft–Gault formula and standardized to a body surface area of 1.73 m² [40].

Because of these major discrepancies, a better estimation is given in cohort studies in which the frequency of CKD has been assessed according to a calculated GFR [6,14,43,44]. The frequency of CKD after LT as reported in major cohort studies is described in Table 4. In the largest study based on the analysis of 36,849 liver transplant recipients, Ojo et al. reported a cumulative incidence of advanced CKD (defined as GFR ≤ 29 ml/min/1.73 m² as assessed by the aMDRD formula) of 8.0% at 1-year and 18.1% at 5-years. This incidence was higher than in heart, lung, or heart–lung transplant recipients [14]. Overall, these results indicate that deterioration of renal function almost universally occurs after LT. On average, moderate but significant renal dysfunction (Stage 2–3) occurs in 40–50% of LT recipients and severe renal dysfunction (Stage 4) in 5–15% of patients, 5 years post-LT.

Mechanism of CNI-chronic renal injury

CNI not only induces reversible alterations in renal vascular resistance, but is also associated with irreversible damage to the renal architecture. Detailed histological analyses have shown the three compartments of kidney that can be irreversibly injured by both CsA and Tac treatment: vessels (arteriolar hyaline sclerosis), tubulointerstitium (tubular atrophy and interstitial fibrosis), and glomeruli (thickening and fibrosis of Bowman's capsule and focal segmental or global glomerular sclerosis) (Figs. 2 and 3) [45]. The mechanism of chronic CNI nephrotoxicity has been studied extensively. A combination of CNI-induced hemodynamic changes and direct effects on tubular epithelial cells is thought to play a role. Nodular hyaline deposits in the media of afferent arterioles (arteriolar hyaline sclerosis) are regarded as a hallmark of CNI nephrotoxicity. Arteriolar hyaline sclerosis is commonly regarded

as irreversible, although it has been reported that complete regression of severe CsA-associated arteriolopathy can occur after stopping or reducing CsA exposure following kidney transplantation [46]. In the setting of chronic use of CNI, it is likely that narrowing of the arteriolar lumen is a major contributor to the development of interstitial fibrosis and tubular atrophy, as well as glomerular sclerosis (Fig. 3).

Other risk factors of CKD post-LT

In combination with CNI toxicity, pre-transplant renal dysfunction [47] and early post-operative renal injury are probably the most important predictors of post-transplant CKD. Yet, the onset of CKD after LT is usually multifactorial, also promoted by hypertension, diabetes mellitus, hepatitis C virus, and even alcohol intake [6,14,43,44,47,48]. The impact and site of action of these co-factors are summarized in Fig. 3.

Impact on outcome

Several reports indicate that chronic renal alterations significantly impact on morbidity and mortality after LT. Ojo et al. found that non-renal solid organ transplant recipients with CKD had a 4.55-fold increase in the risk of death, compared to transplant recipients without CKD [14]. Moreno et al. reported that 6-year survival was significantly lower among liver transplant patients with CKD than those without (63% versus 71%) [49]. Gonwa et al. reported that the 13-year survival rate in patients with severe CKD was only 28.2% compared to 54.6% in those without post-transplant CKD [8].

The long-term management of CKD after LT

Optimal management of CKD post-LT relies first on prevention: early CNI minimization, aggressive blood glucose, and blood pressure controls and treatment of HCV infection when appropriate. In the case of hypertension, two classes of antihypertensive drugs

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Table 5. Calcineurin inhibitors reduction (at least 50%) with introduction of mycophenolic acid.

Reference	N	Design	Time of IS change	Baseline Creatinine	Baseline GFR (ml/mn)	Follow up (years)	% of pts with renal function improvement *	Rejection* N (%)
Cantarovich M 2003 [51]	19	Uncontrolled case study	≥1 year post Tx	141 ± 24 µmol/L	53 ± 9	1	90	5/19 (29)
Koch MO 2004 [52]	32	Uncontrolled case study	25.6 ± 34.7 months	2.63 ± 0.39 mg/dl	ND	4.8 ± 0.6	88	2/32 (6)
Reich DJ 2005 [53]	18	Prospective randomized	13 months	1.8 mg/dl	46.7 ± 11.8	1	50	2/18 (11)
Créput C 2007 [54]	49	Prospective uncontrolled	7.7 ± 4.3 years	ND	42.9 ± 14	3.4 ± 1.5	80	0
Pageaux GP 2006 [55]	56 MMF/C : 27/29	Prospective randomized	≥1 year post Tx	172 µmol/L	43	1	72	0
Cicinatti VR 2007 [56]	75 MMF/C: 50/25	Prospective randomized	72.4 ± 54.9 months	1.9 ± 0.4 mg/dl	ND	1	62	ND
Biselli M 2009 (57)	60 MMF/C: 30/30	Prospective controlled	62.5 months	1.65 mg/dl	51	2	53	0

CN, calcineurin inhibitors; MMF, Mycophenolate mofetil; IS, immunosuppression; GFR, glomerular filtration rate. In the five controlled studies in which this approach was tested, the incidence of rejection ranged from 0–11%, for a crude number of rejection episodes of 2/234 patients (8/°°). Taking into account all the available studies, 10 rejection episodes occurred in 285 patients, for an incidence of 3.5%. This approach was associated with an improvement in renal function, although modest, in 50–90% of the cases.

may be beneficial to prevent CNI renal toxicity (reviewed in [45]): on the one hand, vasodilators as calcium channel blockers may counteract the vasoconstrictive effects of CNI and prevent the fall in renal plasma flow and GFR associated with CNI administration. On the other hand, ACE inhibitors and angiotensin II receptor blockers could counteract the pivotal role of the renine angiotensin system in the development of CNI nephrotoxicity. Spironolactone could as well counteract the pivotal role of aldosterone.

Early detection of renal injury is also required based on careful assessment of renal function. This includes sequential monitoring of serum creatinine and assessment of calculated glomerular filtration rate at least every 6 months, in combination with sequential measurements of proteinuria and hematuria, and in patients without proteinuria, measurement of microalbuminuria. In patients in whom renal dysfunction is detected, a strict cooperation with a nephrologist is mandatory. There is currently no guideline regarding the place of renal biopsy in the setting of kidney injury after LT. The decision should be taken on a case by case basis, taking into account associated co-morbidities, timing, and course of renal dysfunction as well as the risk/benefit ratio of kidney biopsy. Kidney biopsy should be particularly considered in the case of early rapid dysfunction with significant proteinuria, or on the long term in patients with proteinuria >1.5 g/24 h, especially in HCV-infected patients, to differentiate between CNI and HCV-related injury. Indeed, in the case of HCV-related injury, IFN

based-antiviral therapy may be considered instead of CNI minimization. In patients with early stages of renal injury (Stages 1 and 2 of the KIDIGO classification), measures to protect the kidney must be undertaken including the use of ACE inhibitors and angiotensin II receptor blockers, further minimization of CNI and if possible conversion to non-nephrotoxic immunosuppressive agents.

CNI minimization protocols

CNI minimization protocols have been intensively developed and evaluated in an attempt to stabilize and even improve renal function and patient outcome in LT recipients [36]. Non-nephrotoxic immunosuppressive drugs, such as azathioprine, MPA, and mTOR inhibitors (i.e. Sirolimus and Everolimus) have been studied according to two approaches: CNI reduction with introduction of non-nephrotoxic agents, and CNI withdrawal with replacement by non-nephrotoxic drugs. Of note, the approaches discussed below, including subtherapeutic levels of CNI or CNI withdrawal together with MPA or mTOR inhibitors have been proposed to be licensed.

CNI reduction

Beneficial effects of MPA combined with CNI minimization have been reported in several studies [48–54]. The results of these studies are summarized in Table 5. Most enrolled a small number

Table 6. Calcineurin inhibitors withdrawal and replacement by mycophenolic acid.

Reference	N	Design	Time of IS change (months)	Baseline Creatinine	Baseline GFR (ml/mn)	Follow up (months)	% of pts with renal function improvement *	Rejection* N (%)
Schlitt HJ 2001 [24]	28 MMF/C: 14/14	Prospective randomized	≥6	168.1 µmol/L	50	6	78	3/14 (21)
Barkman A 2000 [58]	22	Prospective uncontrolled	>6	201 µmol/L	ND	15	74	2/22 (5)
Raimondo ML 2003 [59]	45 MMF/C: 16/29	Prospective Case-control	45	179 µmol/L	ND	35	62	1/16 (6)
Moreno-P JM 2004 [60]	50	Uncontrolled	81	1.8 mg/dl	44.7	18	80	6/50 (12)
Reich DJ 2005 [53]	20	Prospective uncontrolled	16	1.8 mg/dl	53	12	63	6/20 (30)
Dharancy S 2009 [61]	52	Retrospective Uncontrolled	70 ± 53	ND	37 ± 10	24	86	2/52 (3)

CNI, Calcineurin Inhibitors; MMF, Mycophenolate Mofetil; C, control; IS, immunosuppression; GFR, glomerular filtration rate; Tx, Transplantation. * In MMF group. CNI withdrawal followed by MMF monotherapy was associated with a higher risk of rejection (21% to 30%) and sometimes leading to graft loss, in the 2 randomized controlled studies in which monotherapy was started early post-LT. In the retrospective studies with late CNI withdrawal, the risk of rejection was lower, ranging from 3 to 12%. A total of 22 rejection episodes were observed in 188 patients for an incidence of 12%. An improvement in renal function was observed in 74% of the cases.

of patients with moderate renal impairment [Stage 3 in K/DOQI–KDIGO classification] at the time of MPA introduction. With an average follow-up of one year, these studies showed that introduction of MPA combined with at least a 50% reduction in CNI dosage was associated with a significant improvement in renal function and a low risk of biopsy-proven rejection. In MPA studies, the overall incidence of acute rejection was 3.5%, and only 0.8% in the MPA arm of the randomized controlled studies.

In a prospective randomized study [52] we investigated the effects of MPA introduction followed by reduction in CNI dose on renal function in patients who had developed CNI-related CKD more than 1-year post-LT. Fifty-six patients were randomly assigned to receive MPA followed by at least a 50% CNI dose reduction ($n = 29$), or CNI without addition of MPA ($n = 27$). In the MPA group, there was a significant decrease in serum creatinine values from 171.7 ± 24.2 µmol/l at day 0 to 143.4 ± 19 µmol/l at month 12 and a significant increase in creatinine clearance from 42.6 ± 10.9 to 51.7 ± 13.8 ml/mn. No episode of rejection was observed. In the control group, there was no improvement in renal function. That is, serum creatinine values of 175.4 ± 23.4 µmol/l at day 0 and 181.6 ± 63 µmol/l at month 12, and creatinine clearance of 42.8 ± 12.8 ml/mn at day 0 and 44.8 ± 19.7 ml/mn at month 12 were observed. The differences between the two groups were significant ($p = 0.001$ for serum creatinine, and $p = 0.04$ for creatinine clearance). It must be emphasized that improvement in renal function was observed early after CNI reduction, usually during the first 3 months, with stabilization thereafter. MPA introduction in combination with CNI minimization, therefore, seems an efficacious and safe

approach to limit CNI toxicity and to prevent further renal function deterioration in the mid-term Table 5.

CNI withdrawal

Several studies have evaluated CNI conversion to MPA [24,52,57–60] (Table 6) or mTOR inhibitors [61–66] (Table 7).

Introduction of MPA in combination with CNI withdrawal was generally associated with an improvement in serum creatinine in 60–80% of patients and an increase of GFR by 9–12 ml/min [24,52,56–60]. However, episodes of graft rejection, reversible or not, have been observed in 3–30% of patients, 12% on average. Thus, in a retrospective analysis of MPA monotherapy in 16 patients converted after a median of 2056 days post-LT, three episodes [47, 107, and 1203 days after conversion] of severe, irreversible graft rejection were observed. This resulted in death in two patients and required retransplantation in one patient [67]. In all studies using MPA monotherapy, there was no pharmacological monitoring of mycophenolic acid (the active form of MPA) blood levels, although significant inter-individual and intra-individual variability in the pharmacokinetics is well established [68].

Interestingly, three studies in the mid-nineties also explored the efficacy and safety of azathioprine after CNI reduction/interruption [69–72] in patients with renal impairment. Although limited, this experiment suggested here again that CNI interruption under the control of antiproliferative agents was associated with an improvement in renal function at the cost of rejection. Randomized controlled trials directly comparing azathioprine and MPA monotherapy in LT recipients with impaired renal function had never been designed.

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Table 7. CNI withdrawal and replacement by Sirolimus/Everolimus.

Reference	N	Design	Time of IS change	Baseline Creatinine	Baseline GFR (ml/mn)	Follow up (months)	% of pts with renal function improvement *	Rejection* N (%)
Fairbanks KD 2003 [62] <i>Sirolimus</i>	21	Prospective uncontrolled	6 years	2.2 mg/dl	34	67 ± 39	71	1/21 (5)
Watson CJ 2007 [63] <i>Sirolimus</i>	27 S/C: 13/14	Prospective randomized controlled	≥11 months	122 μmol/L	49.8	12	68 ns	2/13 (17)
Shenoy S 2007 [64] <i>Sirolimus</i>	40 S/C: 20/20	Prospective randomized controlled	≥6 months	1.5 mg/dl	64	12	90 ns at 1 yr	2/20 (5)
Dubay D 2008 [66] <i>Sirolimus</i>	114 S/C: 57/57	Retrospective Case-control	≥63 months	ND	37	18	79 ns	(5)
Campbell MS 2007 [65] <i>Sirolimus</i>	179 S/C: 79/100	Retrospective Case-control	≥2 months	1.2 mg/dl	ND	24	ns at 2 yrs	1/79 (1.2)
Castroagudin JF 2009 [67] <i>Everolimus</i>	21	Prospective uncontrolled	62 months	1.79 ± 0.39 mg/dl	54.6 ± 12.4	19.8	43	0
De Simone P 2009 [26] <i>Everolimus</i>	145 E:72 C:73	Prospective randomized	>12 months <60 months	ND	51 ± 11.7	12	ns at 6 & 12 months	3/72 (4.1)

CNI, Calcineurin Inhibitors; S, sirolimus; E, everolimus; C, control; IS, immunosuppression; Tx, Transplantation; ND, not determined; * In mTOR inhibitors group. Significant improvement in renal function was inconsistently observed after conversion to mTOR inhibitors with an overall risk of rejection of 11/169 (6.5%) after conversion.

The use of mTOR inhibitors has shown contrasting results (Table 7). Overall, CNI interruption after mTOR inhibitor introduction was associated with a 6.5% incidence of rejection. Several small, uncontrolled, single-center reports have suggested renal sparing effects in patients with CNI-induced nephrotoxicity converted to either Sirolimus alone, or Sirolimus in conjunction with a low-dose CNI regimen [61,73–79]. Yet, recent, usually controlled studies suggest that the advantage of Sirolimus-based immunosuppression on long-term renal function may be overstated [26,61–66]. In an open-label, randomized controlled trial comparing CNI-based immunosuppression to Sirolimus-based immunosuppression in patients with post-transplant CNI-related nephrotoxicity, the difference in absolute GFR between the two groups was significant at 3 months ($p = 0.02$), but not at 12 months ($p = 0.07$) [63]. Shenoy et al. in a prospective comparison of Sirolimus conversion with unmodified immunosuppression in a similar population showed an early (3 month) significant improvement in creatinine clearance. However, this was not maintained at 1-year [63]. In a case-control study of LT recipients with relatively preserved renal function, Campbell

et al. showed the risk of renal dysfunction after a median follow-up of 1-year was similar whether the patients were switched to Sirolimus or maintained on CNI [64]. Finally, in a retrospective case-control series [65], 57 patients with renal insufficiency who had been started on Sirolimus >90 days postoperatively and treated longer than 90 days were compared to 57 matched patients maintained on low-dose CNI. At 1 year post-intervention, creatinine clearance, rates of progression to renal replacement therapy, rejection, and death did not differ between the groups. Furthermore, an overall increased prevalence of side-effects in the Sirolimus group was observed.

Data about the efficacy and safety of Everolimus in LT recipients are scarce and inconclusive. In a prospective open-label study, 21 liver transplant recipients with chronic renal dysfunction were switched from CNI to Everolimus [66]. A significant improvement in creatinine clearance (Cockcroft and Gault) without any rejection episode was observed at 1-year: 54.6 ± 12.4 to 64.4 ± 16.7 ml/min. By contrast, a prospective, randomized, multicenter study evaluated the impact of Everolimus with CNI reduction or discontinuation on renal function in maintenance

liver transplant recipients with CNI-related renal dysfunction [26]. The mean change in creatinine clearance from baseline to month-6 (2 and 3 ml/mn, respectively) was similar between the two groups (72 Everolimus and 73 control). In addition, study drug discontinuation was higher in Everolimus patients due to a higher incidence of adverse events.

Of note, the recent CONVERT trial in kidney transplant recipients [80] demonstrated that conversion from CNI to Sirolimus was beneficial in the subgroup of patients with GFR >40 ml/mn at baseline. In patients with more severe alterations in renal function, the switch to Sirolimus was associated with more adverse events and more frequent proteinuria. Pre-existing proteinuria was also a risk factor for poor outcomes. These results indicate that in patients with already advanced renal dysfunction, mTOR inhibitors are also nephrotoxic, and that in the setting of kidney transplantation, a substantial number of patients actually develop proteinuria when converted to Sirolimus [81]. *In vitro* studies suggest that glomerular proteinuria may reflect direct Sirolimus toxicity to the glomerular podocyte–endothelial axis through inhibition of vascular endothelial growth factor [82]. Impairment in tubular uptake of protein has also been postulated to be a mechanism for proteinuria. Unfortunately, one can assume that these findings could be extrapolated to liver transplant recipients. Thus conversion to mTOR inhibitors may be only attempted in LT recipients with GFR >40 ml/mn and with no, or mild proteinuria (<0.8 g/L).

Tailoring immunosuppression to co-morbidities

- As stated above, renal function deterioration often results from a multifactorial process and is more frequent in patients with HCV infection post-LT. An important issue is, therefore, to determine whether immunosuppression can be tailored to the individual profile of the patient to protect the kidney. This particular aspect has been poorly studied so far.

- In patients with HCV recurrence, it is assumed that renal deterioration is accelerated by latent membranoproliferative glomerulonephritis often pre-existing LT [83] or detected post-LT [84]. This results in a higher incidence of significant proteinuria in HCV + compared to HCV-LT recipients [85]. Some preliminary results indicate that treatment of HCV infection can result in stabilization [86] or improvement [87] of renal dysfunction and cryoglobulinemia-related symptoms.
- Two studies also suggested that the combination of MPA + CNI minimization can slow down renal function deterioration in HCV + LT recipients [88,89]. In one study [88], 19 patients were assigned to MPA introduction and CsA tapering or to CsA alone. Renal function improved significantly (serum creatinine: 239.3 ± 90.2 versus 175.8 ± 46.0 $\mu\text{mol/L}$; $p = 0.008$) in the treatment group, while deteriorating (serum creatinine: 156.8 ± 44.6 versus 214.8 ± 120.1 $\mu\text{mol/L}$; $p = 0.06$) in the controls.
- In another study comparing 4946 HCV + recipients discharged with a triple immunosuppressive regimen containing MPA and 3884 HCV + patients receiving a dual immunosuppressive regimen without MPA [89], the risk for post-transplant renal dysfunction and death was evaluated after controlling for baseline characteristics and extended steroid use. At 3-years post-transplant, triple drug therapy was associated with a 6% lower adjusted risk of renal dysfunction. Death rate and adjusted risk for death were also lower for recipients on a three- versus two-drug regimen.
- There is currently no evidence indicating that a specific immunosuppressive regimen can be protective to the kidney in case of diabetes or hypertension. Uncontrolled studies have suggested that conversion from Tac to CsA in cases of diabetes can improve glucose metabolism [90] but the

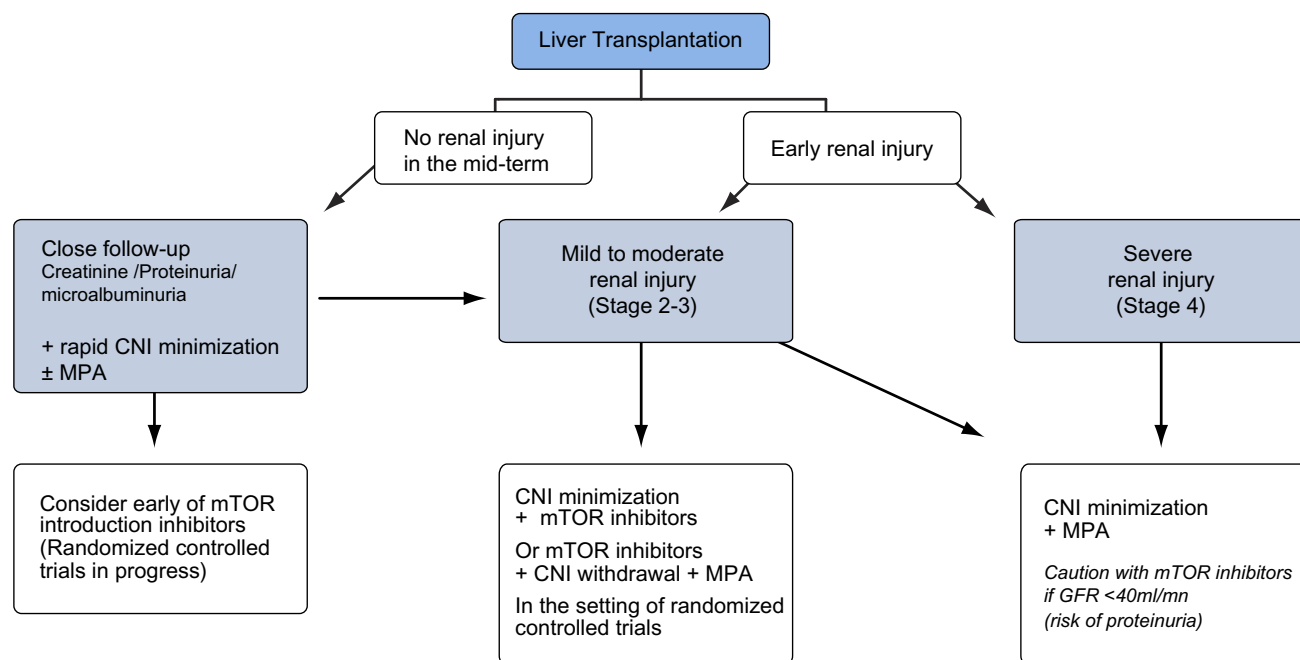


Fig. 5. Immunosuppressive strategies after liver transplantation: an algorithm for mid/long term kidney protection. CNI calcineurin inhibitors; GFR, glomerular filtration rate; MPA, mycophenolate acid.

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impact on renal function has not been studied in the mid-term. On the other hand, in Ojo's study [14] Tac was less nephrotoxic compared to CsA. Specific studies aimed at defining the optimal immunosuppressive regimen in patients with diabetes or hypertension are, therefore, mandatory. In patients with cardio-vascular risk factors, mTOR inhibitors may offer an interesting alternative to CNI due to their different toxicity profile, to prevent renal deterioration.

In summary, (Fig. 4), the development of irreversible renal damage after LT is a frequent and serious problem that impacts on survival. The best treatment of CNI-induced CKD should be prophylactic (Fig. 5). With this respect, early conversion to mTOR inhibitors before the occurrence of significant injury is a promising approach which is currently being investigated in a large phase III clinical trial, whose mid- and long-term results are eagerly anticipated. Fig. 5.

In the future, the identification of molecular signatures of operational tolerance [91] could even allow complete withdrawal of immunosuppressive drugs and optimal prevention in tolerant patients.

In LT recipients with overt CKD, MPA in combination with CNI minimization seems to be a safe approach that usually results in a significant, although modest, improvement in renal function or at least stabilization. This is even true in HCV patients.

MPA monotherapy after CNI withdrawal is considered too risky due to a 12–15% risk of rejection, but safety could be improved by pharmacological monitoring of MPA [68], an approach which is currently under investigation [92].

Late CNI withdrawal and conversion to mTOR inhibitors has achieved variable results in the mid-term, although sometimes disappointing due to matters of tolerability, or because withdrawal was attempted in patients already with advanced kidney damage. Thus in patients with GRF <40 ml/mn, minimization of CNI under the protection of MPA can be considered less risky (Fig. 5).

Conclusions

Renal dysfunction has emerged as one of the most important issues in the short, medium, and long term after LT because of the significant impact on survival. Manipulation of immunosuppression to avoid or limit CNI nephrotoxicity is one of the major tools to overcome this problem. Delayed introduction of CNI in the post-operative phase under the protection of induction therapy plus MPA in high risk patients and early withdrawal of CNI under the protection of mTOR inhibitors are two approaches that could be easily implemented to prevent irreversible renal damage. Their impact on survival requires further investigation. The role of co-stimulation blockade as a CNI sparing regimen and the impact on kidney function also deserve study. Among the large cohorts of LT recipients with preexisting significant renal function impairment, minimization of CNI, and introduction of MPA currently offer the best risk/benefit ratio. However, new policies based on early CNI withdrawal/minimization and conversion to mTOR inhibitors are promising approaches that could radically change the management of LT recipients in the future.

Key points

- Significant acute renal dysfunction occurs in 40% of liver transplant (LT) recipients in the post operative period and it is a major predictor of late, chronic renal insufficiency.
- Acute renal failure requiring renal replacement therapy occurs in 15% of LT recipients in the post operative period and significantly alters mid-term survival.
- Acute calcineurin inhibitor (CNI) induced nephrotoxicity is caused by an intense arteriolar vasoconstriction, resulting in a pre-renal, dose related renal dysfunction. This causes a decreased, yet reversible, glomerular filtration rate.
- Delayed introduction of CNI after LT, under the protection of induction therapy and mycophenolate acid (MPA) significantly improves renal function in the short- and mid-terms.
- By 5-years post-LT, a significant multi-factorial chronic alteration of renal function occurs in 40–50% of LT recipients and severe renal dysfunction is observed in 5–15% of cases.
- Chronic renal dysfunction significantly impacts on long-term survival.
- In the case of significant chronic renal dysfunction, MPA introduction and CNI minimization is associated with an improvement/stabilization of renal function.
- Late introduction of mTOR inhibitors with CNI minimization/interruption can also be considered before GFR <40 ml/mn, provided no proteinuria is detectable.
- Prophylactic approaches based on early elimination/reduction of CNI and early introduction of mTOR inhibitors, or co-stimulation blockade are currently under investigation

Conflict of interest

The authors who have taken part in this study have declared a relationship with the manufacturers of the drugs involved. C. Duvoux has acted as advisor and lecturer for Novartis and Astellas and has received research support from Roche. G.P. Pageaux has acted as advisor for Astellas and Roche and as lecturer for Roche.

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