Les fonctions glomérulaires et tubulaires chez les enfants ayant subi une transplantation hépatique et traités par tacrolimus

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Abstract

Genève est aujourd'hui le centre pédiatrique suisse de référence pour les transplantations hépatiques par décision de la commission fédérale de la Médecine Hautement Spécialisée. La néphrotoxicité du tacrolimus étant une complication redoutée chez les patients traités par tacrolimus, nous souhaitions évaluer l’impact du tacrolimus sur la fonction rénale et notamment sur la fonction tubulaire, peu étudiée dans la littérature. Le but de notre étude a été d’analyser de façon rétrospective l’impact à moyen terme (3 ans de suivi) du tacrolimus sur la fonction rénale, tant d’un point de vue glomérulaire que tubulaire, chez 24 patients âgés de 6 mois à 16 ans ayant subi une transplantation hépatique. Nous avons pu démontrer que malgré les effets néphrotoxiques dans la phase précoce qui suivait la greffe, 65.5% des patients avaient une fonction rénale normale 3 ans après la greffe hépatique et que les indices tubulaires corrélaient avec les taux de tacrolimus.

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Glomerular and tubular function following orthotopic liver transplantation in children treated with tacrolimus

As CNI, CsA and TAC were introduced as first-line immunosuppressants for solid organ transplantation, survival of patients has considerably increased. Nephrotoxicity is one of the most notorious side effects of these drugs and is associated with significant morbidity and mortality in both children and adults (1–3). The etiology of CNI-induced nephrotoxicity is not yet elucidated. It appears that it can be separated in two different phases. The first is acute, reversible and dose-dependent, probably owing to impaired endothelial cell function and secondary afferent and efferent glomerular arteriolar vasoconstriction leading to reduced GFR (4–7). The second is chronic, irreversible and not dose-dependent, and correlates with a complex vascular, tubular, and glomerular lesions (4–7). There are no good prognostic indicators of long-term renal function in either children or adults following liver transplantation.

Most studies to date were performed in adult patients on CsA, but the mechanism of TAC injury seems to be the same (4, 8). There is some debate about the relative nephrotoxicity of CsA and TAC. Previous studies looking at GFR showed no difference between CsA and TAC (9–11), while others suggest a safer renal profile for TAC (4, 12, 13). In adults, in whom hypertension and diabetes contribute significantly to renal

Abbreviations: CNI, calcineurin inhibitors; CrCl, creatinine clearance; CsA, ciclosporine; GFR, glomerular filtration rate; OLT, orthotopic liver transplantations; SMg, serum magnesium; TAC, tacrolimus; TRP, tubular phosphate reabsorption; UCa/Cr, urine calcium/creatinine ratio; UPr/Cr, urine protein/creatinine ratio.
dysfunction, the contribution of CNI toxicity to post-transplant renal dysfunction may be relatively small (14). In children, one might postulate that CNI toxicity may be a greater contributor to renal dysfunction because the other factors are less prevalent.

That CNIs affect glomerular function is commonly accepted. However, the impact of CNIs on tubular function is comparatively less well studied. Thus, we aimed to examine both glomerular and tubular functions in pediatric liver transplant recipients treated by TAC.

**Patients and methods**

All patients having undergone liver transplant between the January 1, 2003, and June 30, 2009, at the Geneva Children’s Hospital were retrospectively included in this study. A total of 39 patients underwent OLT. Among these, two patients retransplanted at 3 and 10 days postoperatively were included. Fifteen patients were excluded from the analysis (Table 1). We performed a chart review on a total of 24 patients with 8.3% of patients presenting as acute liver failure. Table 1 summarizes the study population and Table 2 the indications for OLT.

All patients were treated with TAC as primary immunosuppressant. Target TAC trough levels were 8–12 ng/L in the first three months post-OLT and then 4–7 ng/L by one yr post-transplant. Median trough level of TAC was 7.2 ng/L at one yr. All patients received basiliximab induction at day 0 and day 4. Steroids, mycophenolate, diuretics, or antihypertensive treatments were used in selected patients.

We performed a retrospective cohort study over the course of five and a half yr at our institution to evaluate the impact of TAC on the glomerular and tubular functions of patients following OLT. Because of the retrospective nature of the study, the number of patients at each visit varied slightly: pre-OLT; n = 24, one month: n = 23, three months: n = 23, six months: n = 23, 12 months: n = 22, 24 months: n = 18, 36 months: n = 15. The number of patients at four and five yr was too small to reach significance; thus, the study was stopped at three yr post-OLT. All follow-up visits were performed in our hospital; follow-up was regular and there were very few missed visits (limited missing data). The study was approved by the Ethical Committee of the University Hospitals Geneva.

The following preoperative variables were obtained from patient charts: age, sex, diagnosis, weight, and length. Blood and urine biochemistries and TAC levels were collected from anniversary visit records. Glomerular function was assessed using CrCl, determined by 24-h urine collection and considered abnormal below 90 mL/min/1.73 m². National Kidney Foundation Criteria were used for the classification of renal insufficiency (15).

In young patients, urine collection was performed over 12 h using a urine bag (16) or a catheter. Urine collection was repeated in cases where the sample was incomplete. Tubular function was assessed using the TRP index, urate/Cr, 24-h Ca excretion (U24h-Ca) and SMg. Twenty-four-hour proteinuria (U-24hPr) and UPr/Cr were also recorded as a mixed marker of glomerular and tubular function and were expressed in UPr/Cr. All patients with blood pressure greater than the 75th percentile for age and gender were treated using calcium-channel blockers as first-line drugs and angiotensin-converting enzyme inhibitors as second-line anti-hypertensives.

**Statistical methods**

The Statistical Package for Social Sciences SPSS 17.0 software was used for generating statistical data. Results were expressed as median ± standard error of the mean (s.e.m.) unless indicated otherwise. Median was chosen owing to sample size. Confidence intervals were 95%. The correlation between the variables and TAC levels was performed using the Kendall coefficient and the Wald’s chi-square test. A p-value <0.05 was considered significant.

**Results**

Twenty-four of 39 eligible patients were enrolled (Table 1) and their charts reviewed. Actuarial patient survival for the entire cohort was 91%, and the survival for our study was 85%. One patient required renal-replacement therapy perioperatively and for the first two months post-OLT. No patient received pre-operative chemotherapy because hepatoblastoma was not an indication for OLT in this small series.
Glomerular function

CrCl
Before OLT, 39% patients had a GFR below 90 mL/min/1.73 m² including one patient on renal-replacement therapy. Twenty-five percent of patients needed diuretic therapy (furosemide and spironolactone) for ascites before OLT. At one month, 58.33% of patients presented with a GFR below 90 mL/min/1.73 m², and 8.33% below 30 mL/min/1.73 m². At one month, 8.33% needed diuretic therapy for ascites; no patient required diuretics beyond 30-day post-transplant. After three yr, 20% patients had a GFR below 90 mL/min/1.73 m², but > 60 mL/min/1.73 m². The prevalence of impaired glomerular function as measured by GFR <90 mL/min/1.73 m² varied significantly between 1 and 24 months post-OLT (p = 0.045). Further, no patient had a GFR <60 mL/min/1.73 m² at 36 months compared to 16% pre-OLT population, mostly accounted for by the patient requiring dialysis (Fig. 1).

A small subset of patients had pre-existing renal disease (n = 7) prior to OLT. Two of the patients had metabolic liver disease (Wilson’s disease, methylmalonic academia), while the remainder had cholestatic diseases. Immunosuppressant regimen was not adjusted in these patients. Among those patients with pre-existing renal disease, the kinetics of post-transplant renal function were similar to the whole cohort and are summarized in Table 3.

Tubular function

TRP
The TRP values were normal (N > 80%) throughout the observation period with mean values from 89% to 91%. There was no effect of time post-OLT (p = 0.871) and no correlation with TAC trough levels.

UCa/Cr
The UCa/Cr values were normalized by the third-month post-OLT (N < 0.6 before one yr and 0.4 after one yr). We observed a significant decrease over time during all the study (p < 0.001). However, there was no significant correlation with TAC trough level (p = 0.588). When calcium was assessed using 24-h calcium excretion, it always remained within the normal range.

SMg
Magnesemia (N > 0.7 mm) progressively decreased during the first year post-OLT with a median value at one yr of 0.69 mm compared to 0.9 mm pre-OLT and 0.72 mm one month post-OLT. Patients received magnesium supplements on an as-needed basis. By three yr post-OLT, the median was within the normal range: 0.7 mm. There was no significant correlation with TAC trough level (p = 0.23).

Mixed marker of glomerular and tubular function: UPr/Cr
The UPr/Cr was increased before OLT and at one month post-OLT but did not reach the nephrotic range (>0.2 g/mmol) (Fig. 2). Indeed, 36.7% patients had increased UPr/Cr pre-OLT and 46% at one month. The prevalence declined thereafter: 21% at three months, 11.7% at six months, 11% at 12 months, 6% at 24 months, 18% at 36 months. Among the patients with persistent proteinuria, two children
had a primary diagnosis of biliary atresia, and two patients with Alagille syndrome had persistent proteinuria for the duration of the observation period. As a whole, UPr/Cr decreased steadily post-OLT but this decline never reached statistical significance (p = 0.432). However, there was a significant positive correlation between UPr/Cr and TAC trough levels (p = 0.031).

**Antihypertensive therapy**

Only one patient who had primary non-function and required retransplantation was on antihypertensive therapy before the second graft. At three months post-OLT, 65.2% of patients needed antihypertensive therapy, while only 33% were receiving antihypertensives 36 months post-OLT. At three months, two children needed two drugs and one child three drugs. At six months post-OLT, two children needed two drugs. No patient needed more than one antihypertensive treatment beyond the first anniversary visit.

**Discussion**

The primary objective of this retrospective study of 24 orthotopic liver transplant recipients followed over five and a half years was to evaluate the effect of TAC on both glomerular and tubular functions. The overall finding is that TAC was associated with renal impairment which was mostly reversible one yr following OLT.

**Glomerular function**

Assessment of glomerular function in this small but representative cohort was remarkable for a decline in CrCl during the early post-operative phase (first month). Median values pre-OLT and one month post-OLT were 92.4 and 83.2 mL/min/1.73 m², respectively, followed by
a progressive recuperation after the first year post-OLT (median value: 108.5 mL/min/1.73 m²). Importantly, 80% of patients had moderate renal dysfunction as measured by a GFR < 90 and > 60 mL/min/1.73 m² (stage 2 according to the National Kidney Foundation criteria).

Among those patients with pre-existing kidney disease, a similar trend was observed: there was a transitory worsening of kidney function in the early postoperative phase, followed by notable improvement in excess of pre-transplant values. This finding is of clinical significance for two reasons. First, it suggests that moderate to severe renal insufficiency does not necessarily require combined liver–kidney transplant. Second, it suggests that in those patients with pre-existing renal disease, the benefit of liver transplantation on renal function may outweigh the risks of CNI-nephrotoxicity in the medium term. In patients with cirrhotic liver disease, one might ascribe the betterment of renal function to improved renal hemodynamics. In those with non-cirrhotic metabolic liver disease, elimination of the toxic metabolite by OLT may contribute to recovering what dysfunction was reversible.

Our findings mirror those of other studies that have shown a transient impairment of renal function in the first year following liver transplantation, an effect that seems independent of CNI choice (9–11, 17). Among the many studies seeking to identify predictors of long-term renal function, the work by Campbell et al. (18) makes a strong case for GFR at one yr post-OLT as predictor of long-term renal function. If indeed this is the most reliable predictor, the results of this study are auspicious for minimal long-term kidney dysfunction.

**Tubular function**

In this series, tubular function mirrors glomerular function by showing a transient decline in the first few months post-OLT followed by full recovery. The different tubular indices did not all fluctuate in the same way, suggesting that other factors than CNI exposure may affect tubular function following pediatric liver transplant. First, TRP was within the normal range throughout the duration of the study. Second, the UCa/Cr ratio was elevated in the early post-transplant phase, but normalized by the end of the third-month post-OLT. The significance of this finding is unclear since 24-h calcium excretion was normal at all time points. Importantly, it appeared that following OLT, children do not have excessive calcium losses, at least in a selected group of patients with a steroid-free immunosuppressive regimen. We suspect that this result reflects the limitations of using ratios with creatinine in children who are undernourished: abnormally low serum creatinine will lead to low urinary creatinine, thus elevating the ratio. Third, magnesiumemia declined progressively during the first year post-OLT and normalized by three yr post-OLT. Although there are adult reports of TRPM6 downregulation and associated renal Mg wasting (19, 20), our findings suggest that there is no statistically significant association between SMg and TAC trough levels, corroborating the findings of others (21). Nonetheless, magnesium serum levels are lower when TAC trough levels are high, but this finding is of unclear significance in the long-term as it normalized after one yr.

We used UPr/Cr as markers of both glomerular and tubular function. However, in a large fraction of our children, the UPr/Cr ratio was elevated both pretransplant and during the first three months post-OLT. It normalized thereafter and this correlated significantly with the drop in TAC trough levels. Importantly, the values never reached the nephrotic range and at two-yr post-OLT all patients had normalized their ratios. The clinical relevance of this finding is unclear. First, as for the UCa/Cr ratio, it could be a reflection of impaired or low urinary creatinine excretion, thus reflective of nutritional status. Second, it raises the question of how to follow proteinuria in children on nephrotoxic medications. Indeed, TAC leads to afferent glomerular arteriolar vasoconstriction thereby decreasing glomerular filtration pressure. In turn, this alters membrane permeability leading to glomerular proteinuria as measured by albuminuria. Although tubular proteinuria is best assessed by urinary β-2 microglobulin and α-1 microglobulin, both markers of tubular proteinuria and early, sensitive indicators of CNI-induced nephropathy (22), we did not obtain this data in our patients, but aim to do so hereafter. However, in practical terms, we consider proteinuria (10 mg/kg/24 h) to be an early indicator of CNI toxicity and selectively treat all patients with persistent, increased 24-h protein excretion associated with renal hyperfiltration (> 150 mL/min/1.73 m², [23]) or hypertension. In sum, tubular function, as measured by TRP and proteinuria, appears to be relatively spared in our small cohort of patients on TAC, but we take great care in monitoring and minimizing any CNI-nephrotoxicity.
Antihypertensive treatment

Elevated blood pressure is frequently associated with renal impairment. The mechanism of TAC-related hypertension is incompletely elucidated, but it appears first that TAC creates an imbalance of vasoconstrictors and vasodilators contributing to renal and systemic vasoconstriction (4, 8, 24, 25). In adult liver transplant recipients, arterial hypertension is more prevalent in those patients with chronic renal insufficiency post-OLT (17), something not shown to date in children. It has been shown in adults that arterial hypertension during the first year post-OLT often normalizes (9). In our study, the use of antihypertensive medications served as a surrogate marker to estimate frequency of elevated blood pressure. Their use was maximal at three months post-OLT (65.2% patients) but decreased by the end of the first year post-OLT. At two yr, no children needed more than one antihypertensive drug and at three yr only 33% of children needed treatment. Only one of the patients with hypertension had renal insufficiency. The patients requiring long-term antihypertensive therapy are probably a specific subset of patients whose characteristics need to be better understood. There is evidence that hypertension contributes to renal dysfunction in liver transplant recipients (14, 17), but the incidence of hypertension in pediatric liver transplant recipients is not known. It is our opinion that careful monitoring and early treatment of blood pressure abnormalities in pediatric liver transplant recipients is warranted to protect long-term renal function, which is why we treat all patients if blood pressure is greater than 75th percentile for the age, height, and sex.

This study presents several limitations. First, owing to the retrospective nature of the study, some patients’ values are missing. Second, teasing out the role of other renal insults (antibiotics, antivirals, number of rejection episodes warranting steroid use, hypertension) is difficult in this small cohort. Third, a three-yr follow-up is insufficient to understand the long-term implications of CNI exposure on kidney function. It is possible that the improvement in glomerular function one yr after transplant is partly reflective of the reliability of collecting urine in older children, but may also be due to the limitations of the methods used. Finally, this study contributes to the body of literature highlighting the limitations of relying on creatinine-based indices in children with malnutrition (10, 26). In the future, we aim to use more precise methods for the assessment of GFR.

In conclusion, this study shows a reversible impairment of renal function during the first year post-OLT in a small cohort of patients on TAC-based immunosuppression, confirming the findings of others. It suggests that transplanting patients with moderate renal dysfunction is feasible and leads to favorable outcomes. Further, prospective research is required to optimize immunosuppressive protocols to protect long-term renal function in pediatric liver transplant recipients.

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Author contributions

Anastaze Stelle K: Data collection/analyses/interpretation; Belli DC: Concept/design, critical revision of article, approval of manuscript; Parvex P: Data analysis and critical revision of the manuscript; Girardin E: Critical revision of manuscript; Giroud A: Concept/design; Wildhaber B: Critical revision of manuscript; McLin VA: Concept/design, data analysis/interpretation, critical revision of manuscript.

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