Stable graft function after reduction of calcineurin inhibitor dosage in paediatric kidney transplant patients

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Abstract

Background. Chronic calcineurin inhibitor (CNI) toxicity contributes to the development and progression of chronic allograft nephropathy (CAN), which is still the major cause of transplant dysfunction and graft loss. Reduction in dosage of CNI may delay the development of CAN, leading to longer graft survival.

Methods. Therefore, 19 paediatric kidney transplant patients under immunosuppressive therapy with CNI (12/19 ciclosporin A, CSA, 7/19 tacrolimus, Tac), mycophenolat mofetil and some patients on steroids were included in a prospective study. Over a period of 9 months CNI dosage was stepwise reduced from CSA trough levels of 100–150 ng/ml to 50–70 ng/ml and Tac trough levels of 5–8 ng/ml to 2–3 ng/ml, respectively.

Results. Glomerular filtration rate was stabilized in patients after CSA and Tac reduction. One borderline rejection occurred in a patient prior to reduction of Tac. In patients on CSA, one interstitial cellular rejection (BANFF IA) was noted. Reduction of CNI had no significant effects on blood pressure, lipid status and the infection frequency.

Conclusions. In paediatric kidney transplant patients, reduction of CNI down to low trough levels stabilizes renal function. However, the risk of acute rejection episodes may be increased. Therefore, further studies based on protocol biopsies within a randomized trial are warranted.

Keywords: calcineurin inhibitor toxicity; ciclosporin; paediatric renal transplantation; tacrolimus

Introduction

Introduction of calcineurin inhibitors (CNI) and mycophenolate mofetil (MMF) into immunosuppressive therapy significantly improved first year kidney graft survival and reduced the rate of acute rejections [1,2]. In contrast, long-term graft survival did not similarly improve, possibly due to negative long-term effects of CNI on kidney function and structure. It is well known that chronic use of CNI, in particular in high doses, contributes to the development and progression of chronic allograft nephropathy (CAN) [3], which is still the major cause of transplant dysfunction and final graft loss. CAN is clinically characterized by slowly increasing serum creatinine, progressive proteinuria and moderate hypertension [4]. Histological changes, such as glomerulosclerosis, tubular atrophy with interstitial fibrosis and arteriosclerosis, are characteristics of CAN. The pathogenesis of CAN is multifactorial, i.e. immunological and non-immunological risk factors are known. Toxicity of CNI, however, is one of the major non-immunological reasons for the progression of CAN. CNI are known to have acute and chronic toxic effects on the kidney. Acutely vasoconstriction of the afferent arteriole leads to reduction of renal blood flow. Chronic effects are predominantly structural changes of the kidney, such as interstitial fibrosis and thickening as well as hyalinosis of intrarenal arteries [5].

Therefore, treatment strategies aiming to reduce CNI toxicity by lowering the treatment doses and introduction of drugs with different modes of action and without nephrotoxicity are of major importance. In adults, studies with azathioprine and prednisone as additional immunosuppressive therapy to CNI reduction or withdrawal led to increased rates of acute rejections [6]. A combination with other potent immunosuppressive drugs such as MMF is mandatory before CNI can be reduced. As a result, introduction of MMF could reduce the rate of acute rejections after withdrawal of ciclosporin A (CSA) compared with...
azathioprine [7]. Reduction of CSA in the first year after kidney transplantation is also associated with a higher risk of acute rejection. Within the last few years, several studies in adult patients demonstrated a benefit of CSA reduction or withdrawal in patients more than 1 year after transplantation, who were additionally treated with MMF and steroids. It was shown that graft function even ameliorated after CSA reduction. In parallel, hypertension, hyperlipidaemia, glucose metabolism and hyperuricaemia were improved. The rate of acute rejections was not increased in recent studies [8–10].

Therefore, it was the aim of the present prospective study in paediatric recipients of kidney transplants receiving MMF to stepwise reduce CNI dosage down to relatively low trough levels in order to stabilize or even improve kidney function.

Materials and methods

Nineteen paediatric patients were included into the prospective study. Patients’ characteristics are given in Table 1. Immunosuppressive therapy at the time of study enrolment consisted of CSA and MMF in 12 out of 19 patients. Seven patients were treated with MMF and tacrolimus (Tac) and three of them received an additional low dose of prednisone.

The median age of patients at kidney transplantation was 4.8 years (range 1.8–13.7 years) in CSA-treated patients and 9.3 years (range 4.1–13.8 years) in Tac-treated patients. The median duration between transplantation and study enrolment was 2.8 years (range 1.3–7.5 years) in CSA-treated patients and 5.0 years (range 2.3–11.0 years) in Tac-treated patients. Inclusion criteria were as follows: Boys and girls who were younger than 18 years were eligible for the study if they (i) had received a cadaveric or living kidney transplant (1st or 2nd kidney transplantation), (ii) had undergone transplantation 12 months previously, (iii) had been rejection-free for at least 6 months and (iv) had received CSA or Tac for at least 6 months and MMF for at least 3 months (MMF trough level 1.5–4 ng/ml). Exclusion criteria were: (i) glomerular filtration rate (GFR) <40 ml/min/1.73 m², (ii) more than two rejection episodes within the last 12 months, (iii) any steroid-resistant rejection episode in the past medical history, (iv) relapse of the underlying disease, (v) infection with CMV or EBV that required treatment within the last 3 months and (vi) pregnancy or lactation.

Initial immunosuppression after transplantation was azathioprine, CSA and prednisone in five patients and MMF, CSA and prednisone in 14 patients. Initial prednisone treatment was performed according to standard regimen and was continued for at least one year after transplantation. One patient additionally received antithymocyte globulin immediately after transplantation, one patient, daclizumab and another took part in the placebo-controlled basiliximab study for children of the Arbeitsgemeinschaft Pädiatrische Nephrologie (APN). Seven of 19 patients were switched from CSA to Tac for the following reasons: development of CAN (four patients), acute rejection episodes (two patients) and suspected CSA-induced pneumonitis that improved after switch to Tac (one patient).

Before study enrolment, renal biopsy was performed in three of 12 patients under CSA, all of whom had histological signs of chronic CNI toxicity. In patients receiving Tac, renal biopsy was performed in all seven patients, five of whom had histological signs of chronic CNI toxicity. After study enrolment, dosage of CNI was stepwise reduced over a period of 9 months to trough levels of CSA of 50–70 ng/ml and Tac of 2–3 ng/ml (details of reduction procedure are shown in Figure 1). At the following time points, regular study visits were performed: the beginning of the study as well as 3, 6, 9, 12, 15 and 18 months after start of reduction of CNI. The following parameters were determined: serum creatinine, sodium, potassium, phosphate, magnesium, cholesterol, high-density lipoprotein cholesterol and triglycerides. In addition, trough levels of CSA, Tac and MMF were determined. Before reduction of CSA and after the reduction period, CSA levels 2 h after administration of CSA (C2) were determined.

Moreover, the following patient data were recorded on a regular basis: height, weight, blood pressure, CSA dosage, MMF dosage, number and dosage of antihypertensive drugs as well as number and nature of adverse events due to the medication (i.e. infectious adverse events or adverse events due to administered drugs). The patients’ 24 h blood pressure was kept below the 50th percentile according to Soergel et al. [11]. At all time points GFR was calculated using the Schwartz formula (height/creatinine ratio) [12]. As an index of change in GFR over time, i.e. ‘delta-GFR per month’ (in ml/min/1.73 m²/month) was estimated.

Table 1. Characteristics of the study population are shown, including 12 patients treated with CSA and seven patients with Tac

<table>
<thead>
<tr>
<th></th>
<th>Ciclosporin A</th>
<th>Tacrolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (gender F/M)</td>
<td>12 (2/10)</td>
<td>7 (1/6)</td>
</tr>
<tr>
<td>Age at transplantationa</td>
<td>4.8 years (1.8–13.7 years)</td>
<td>9.3 years (4.1–13.8 years)</td>
</tr>
<tr>
<td>Transplantation</td>
<td>12/12 first NTX</td>
<td>6/7 first, 1/7 second NTX</td>
</tr>
<tr>
<td></td>
<td>12/12 cadaver</td>
<td>5/7 cadaver, 2/7 living donor</td>
</tr>
<tr>
<td>Transplant age at study enrolmenta</td>
<td>2.8 years (1.3–7.5 years)</td>
<td>5.0 years (2.3–1.0 years)</td>
</tr>
<tr>
<td>Acute rejections before study enrolment</td>
<td>10/12 without; 2/12 one acute rejection</td>
<td>2/7 without; 2/7 one; 2/7 two; 1/7 three acute rejections</td>
</tr>
<tr>
<td>Biopsy before study enrolment</td>
<td>3/12</td>
<td>7/7</td>
</tr>
<tr>
<td>CNI-toxicity</td>
<td>3/3</td>
<td>5/7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10/12</td>
<td>6/7</td>
</tr>
<tr>
<td>Steroid free immunosuppression</td>
<td>12/12</td>
<td>4/7</td>
</tr>
</tbody>
</table>

aMedian (range).
The area under the time concentration curve (AUC) of CSA was estimated according to the formula of David-Neto et al. [13]: $\text{AUC}_{0-4} = 462 + (2.75 \times C2)$.

During the 2-year recruitment period (January 2002–January 2004) a total of 40 patients were seen in our paediatric nephrology unit after kidney transplantation. Nineteen patients were included into the present study. Twenty patients could not be included for different reasons: In seven patients, kidney transplantation was <1 year at last recruitment time point in January 2004. Six patients were 18 years old in 2002 or in the beginning of 2003. Two patients had recurrent pyelonephritis due to urological malformation; one patient had the 3rd kidney transplantation, one patient was not included because of steroid-resistant acute rejection in past medical history, one patient with ongoing underlying disease (cystinosis) and one patient treated without MMF because of MMF-induced severe diarrhoea. Two patients rejected study enrolment.

Informed consent was obtained from all patients and their parents, respectively. The study protocol was approved by the local ethics committee of the University of Erlangen-Nürnberg.

Statistical analysis

Data are presented as mean±SD for parametrical data and as median (range) for non-parametrical data.

The delta-GFR per month before and after study enrolment was compared with a paired two-tailed t-test. The GFR of the different time points and intervals as well as electrolytes and lipid profile were compared by ANOVA and post hoc t-test.

Table 2. CSA and Tac dosages in milligram per square metre body surface area per day were demonstrated at the different time points of the study, shown as mean±SD

<table>
<thead>
<tr>
<th>-12 months</th>
<th>Study enrolment</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
<th>12 months</th>
<th>18 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA dosage (mg/m²/day)</td>
<td>176.8±58.1</td>
<td>143.9±36.8</td>
<td>124.6±24.0</td>
<td>119.5±29.9</td>
<td>103.1±18.4</td>
<td>105.1±20.6</td>
</tr>
<tr>
<td>Tac dosage (mg/m²/day)</td>
<td>4.70±3.9</td>
<td>3.66±2.5</td>
<td>3.19±1.8</td>
<td>3.10±1.72</td>
<td>2.76±1.7</td>
<td>2.33±1.5</td>
</tr>
</tbody>
</table>
was $0.48 \pm 4.56 \text{ml/min/1.73 m}^2/\text{year}$. The differences in delta-GFR comparing the period of 12 months before study enrolment and the 18 months after study enrolment were not significant ($P = 0.56$, paired $t$-test two-tailed). Overall, eight of 11 CSA patients had a stable or improved renal function during the follow-up period of 18 months. Three of 11 patients had a decrease of GFR of more than 10% in 18 months.

In patients treated with Tac, GFR was stable over the total period of reduction and the following observation time. Comparing the GFR 12 months before and 18 months after study enrolment, there was no significant difference (Figure 2B). We also calculated a ‘delta-GFR per month’ for the different intervals: during the 12 months before study enrolment, the mean loss of GFR was $0.24 \pm 5.76 \text{ml/min/1.73 m}^2/\text{year}$. During the 18 months of follow-up, the mean overall delta-GFR was $1.56 \pm 3.72 \text{ml/min/1.73 m}^2/\text{year}$. The differences in delta-GFR between the period of 12 months before study enrolment and the 18 months after study enrolment were not significant ($P = 0.99$, paired two-tailed $t$-test). Overall five of six Tac patients had a stable or improved renal function during the follow-up period of 18 months, and only one of six patients had a decrease in GFR of more than 10% in 18 months.

Electrolytes (mean ± SD)

CSA patient group. There were no significant differences between study enrolment and the subsequent measurements after CSA reduction in magnesium (i.e. at study enrolment $0.76 \pm 0.06 \text{mmol/l}$ vs $0.78 \pm 0.20 \text{mmol/l}$ 18 months after enrolment; ANOVA, $P = 0.97$), phosphate (i.e. at study enrolment...

Fig. 2. (A) In patients treated with CSA, GFR was stable over the 12 months before study enrolment and the 18 months of follow-up after start of CSA reduction. In the reduction period, CSA was reduced stepwise and after 9 months trough levels of CSA were stable. CSA trough levels are shown with dotted line, GFRs are shown with continuous line. Data are given as mean ± SD. (B) In patients treated with Tac, GFR was stable over the 12 months before study enrolment and the 18 months of follow-up after start of Tac reduction. In the reduction period Tac was reduced stepwise and after 9 months trough levels of Tac were stable. Tac trough levels are shown with dotted line, GFRs are shown with continuous line. Data are given as mean ± SD.
and after study enrolment median was not significant \[\text{systolic blood pressure at study enrolment} \]

CSA reduction. The difference, however, was not significant \[\text{systolic blood pressure at study enrolment} \text{median was} -0.24 \text{ (range} -2.42 \text{ to} +0.56) \text{ and after study enrolment median was} -0.56 \text{ (range} -1.48 \text{ to} +1.38)\].

**Lipid profile (mean ± SD)**

**CSA patient group.** There were no significant differences for cholesterol (i.e. at study enrolment 168 ± 42.4 mg/dl vs 164 ± 23.9 mg/dl 18 months after enrolment; ANOVA, \(P = 0.71\)), high-density lipoprotein cholesterol (i.e. at study enrolment 42.5 ± 8.2 mg/dl vs 45.5 ± 9.9 mg/dl 18 months after enrolment; ANOVA, \(P = 0.48\)) and triglycerides (i.e. at study enrolment 141 ± 65.0 mg/dl vs 124 ± 76.1 mg/dl 18 months after enrolment; ANOVA, \(P = 0.89\)) between study enrolment and the subsequent measurements after CSA reduction.

**Tac patient group.** There were no significant differences for cholesterol (i.e. at study enrolment 144 ± 37.5 mg/dl vs 145 ± 39.7 mg/dl 18 months after enrolment; ANOVA, \(P = 0.998\)), high-density lipoprotein cholesterol (i.e. at study enrolment 44.7 ± 18.1 mg/dl vs 37.7 ± 18.4 mg/dl 18 months after enrolment; ANOVA, \(P = 0.95\)) and triglycerides (i.e. at study enrolment 118 ± 35.4 mg/dl vs 127 ± 42.3 mg/dl 18 months after enrolment; ANOVA, \(P = 0.64\)) between study enrolment and the subsequent measurements after Tac reduction.

**Blood pressure (blood pressure SDS according to de Man et al. [14])**

Systolic and diastolic blood pressure determined by correlation to standard SDS was not significantly different, and the number of antihypertensive drugs was equal in both CSA- and Tac-treated patients (data not shown). Indeed, in patients treated with CSA, a slight decrease in systolic blood pressure was seen after CSA reduction. The difference, however, was not significant \[\text{systolic blood pressure at study enrolment median was} -0.24 \text{ (range} -2.42 \text{ to} +0.56) \text{ and after study enrolment median was} -0.56 \text{ (range} -1.48 \text{ to} +1.38)\].

**MMF dosage and trough level**

**CSA patient group.** MMF trough levels were determined and did not show any difference after reduction of CSA. MMF dosage was not changed in the course of the study. At study enrolment mean dosage was 779 ± 175 mg/m²/day; 18 months after study enrolment mean dosage was 759 ± 208 mg/m²/day. Target trough levels were 1.5–4 ng/ml.

**Tac patient group.** MMF trough levels were determined and did not show any difference after reduction of Tac. MMF dosage was not changed in the course of the study. At study enrolment mean dosage was 482 ± 161 mg/m²/day; 18 months after study enrolment mean dosage was 426 ± 113 mg/m²/day. Target trough levels were 1.5–4 ng/ml.

**Adverse events**

There was no difference between the number of infectious episodes in the reduction period (0–9 months after study enrolment) compared with the period after reduction (9–18 months), whereas the number of severe adverse events due to infections was lower after reduction of CNI. The difference, however, was not significant (data not shown).

**Rejection episodes**

At month 3 of the study, one patient treated with Tac, MMF and low-dose steroids suffered from a borderline rejection. At that time the patient had Tac trough level of 7.1 ng/ml. The maximal increase of creatinine was 4.2 mg/dl (normal creatinine of the patient was 2.0–2.2 mg/dl) and the renal biopsy showed a borderline rejection as well as signs of CNI toxicity. At month 15 of the study, one patient in the CSA group had a biopsy-proven aggressive interstitial rejection episode (BANFF IA) when CSA trough level was only 29 ng/ml after an episode of acute gastroenteritis without any change in CSA dosage. Before this episode, CSA levels were 57–94 ng/ml. In both patients renal function recovered to normal values after pulse therapy with methylprednisolone. The second patient (treated with CSA) was excluded from the study, and in the first patient the study was continued because renal biopsy also showed vascular CNI toxicity. The two cases are summarized in Table 3.

**Study interruption**

The study was interrupted after repeated low trough levels of CSA (29–45 ng/ml) were seen in different patients. The CSA dosage was not changed in these patients, and only in a few patients were low levels associated with acute gastroenteritis. Therefore, the safety of the patients could no longer be guaranteed, and the study was stopped in accordance with the local ethics committee of the University of Erlangen-Nürnberg. The median follow-up of our patients was
24 months (range 15–24 months) whereas several patients only completed 18 months. The main reason for drop out was age exceeding 18 years and lack of information after transmission to an adult centre. Therefore, we analysed the patients up to the time point of 18 months; 11 of 12 CSA patients and six of seven Tac patients completed 18 months after study enrolment.

Discussion

The aim of the present study in paediatric renal transplant patients was to reduce CAN by stepwise reduction of CNI dosage in order to improve graft function as indicated by GFR. In adult studies, reduction of CNI dosage after kidney transplantation led to an increase in GFR [6,9]. Up to now, there are no paediatric studies on isolated reduction of CNI, and only the combination of MMF introduction and simultaneous CSA reduction has been published showing an improvement in kidney function [15,16].

In this study, we can show a constant GFR in 12 paediatric patients after reduction of CSA dosage. In parallel, in seven patients receiving Tac no significant changes of GFR were noted during the follow-up period.

In adult patients, CSA reduction or withdrawal of CSA led to an improvement of the mean GFR [6]. A study of Weir et al. [9] with a large number of adult patients showed stabilization or improvement in 92% of the patients after CSA withdrawal, in 52% after reduction of CSA and in 59% after reduction of Tac. In our patient group during the 18 months of follow-up, GFR was stable or improved in 73% of patients treated with CSA and 83% of patients treated with Tac.

Filler et al. [16] and David-Neto et al. [15] reported on reduction of CSA in eighteen and thirteen paediatric patients, respectively after kidney transplantation. Both studies included patients with progressive loss of graft function and initiated therapy with MMF parallel to reduction of CSA. It was shown that both interventions, at least in combination, could ameliorate renal function [15,16]. The main problem for interpretation is that CSA reduction was started at the same time as MMF therapy was initiated, and there is no possibility of differentiating the various effects, particularly because MMF alone led to an increased kidney graft function by reduction of CAN in children and adults as well [17,18]. In the present study, reduction of CNI led to a stabilization of renal function, i.e. no significant increase of GFR was seen during the follow-up period. Therefore, in both studies, the introduction of MMF seems to have the major beneficial influence on kidney function. Also, stabilization of kidney function would be a great benefit even if it is not possible to improve kidney function after CSA reduction, i.e. if further loss of graft function could be prevented or at least delayed. If there is already chronic structural damage in the kidney, improvement could not be expected, although acute CNI toxicity can be improved by reduction of CNI and improvement of renal flow. Furthermore, it is of note that our paediatric study collective had good renal function before reduction of CNI and improvement of renal flow.

Table 3. Two cases out of 19 patients with rejections following CNI reduction. Both patients were treated with intravenous methylprednisolone over a period of 4 days (400–200–200–100 mg/m²), followed by oral steroids

<table>
<thead>
<tr>
<th>Renal biopsy</th>
<th>Treatment at time of rejection</th>
<th>Creatinine value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Before study enrolment</td>
<td>Tac dosage 1.8 mg/m²/day (trough level 7.1 ng/ml)</td>
<td>(1) 2.2–2.2 mg/dl</td>
</tr>
<tr>
<td>(2) Rejection episode</td>
<td>MMF dosage 0.3 g/m²/day</td>
<td>(2) 4.1 mg/dl</td>
</tr>
<tr>
<td>Patient 1:</td>
<td>Steroid dosage 5 mg/48 h</td>
<td>(3) 2.0–2.5 mg/dl</td>
</tr>
<tr>
<td>(1) Tubular atrophy, interstitial fibrosis</td>
<td>CSA dosage 114 mg/m²/day (trough level 29 ng/ml)</td>
<td>(1) 0.7–0.85 mg/dl</td>
</tr>
<tr>
<td>(2) Mild non aggressive interstitial-cellular rejection, tubular atrophy, progressive interstitial fibrosis, vascular CNI toxicity</td>
<td>MMF dosage 1.1 g/m²/day</td>
<td>(2) 1.32 mg/dl</td>
</tr>
<tr>
<td>Patient 2:</td>
<td>No steroids</td>
<td>(3) 0.85–0.94 mg/dl</td>
</tr>
<tr>
<td>(1) Not performed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2) Aggressive interstitial-cellular rejection (BANFF 1a), ischaemic glomerular changes, progressive tubular atrophy, interstitial fibrosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In heart-transplant patients with progressive loss of renal function due to long-standing extensively high CNI doses, CSA reduction could not reverse renal function [19]. Even in paediatric heart-transplant recipients, late reduction in CSA dosage did not improve renal function [20]. In contrast, CSA nephropathy is likely to be reversible if CSA dosage is reduced early [21]. Therefore, it is evident that if structural lesions had already occurred, CSA reduction can no longer improve kidney function, but further damage by CNI should be reduced. If renal function deteriorated acutely, CNI reduction may ameliorate renal function by diminishing CNI-induced vasoconstriction of the afferent arteriole and subsequently increasing renal blood flow [22].
In addition to reduction or prevention of CNI-induced damage in the kidney, cardiovascular diseases and cardiovascular mortality aggravated by long-term CSA use could be ameliorated with lower doses of CSA. This includes an improvement of lipid profile, blood pressure and uric acid [6,9,23]. In particular, hypertension is evident in CSA-treated patients. In our analysis, neither the change in the number of anti-hypertensive drugs nor the extent of hypertension was noted. In previous studies improvement of hypertension was seen after CSA reduction [6], but in some studies lower blood pressure was noted only after complete withdrawal of CSA [9]. In our prospective analysis a slight decrease of systolic blood pressure was seen after CSA reduction, but there was no significant difference. In Tac-treated patients no effect of reduction on blood pressure was seen, possibly because of the minor effect of Tac on blood pressure per se and the low number of patients. After CSA reduction and in some studies only after withdrawal of CSA, lipid profile was improved, whereas in our study no significant change in cholesterol and triglycerides was seen [6,8,9,23].

After reduction of immunosuppressive therapy the rate of infections is possibly diminished. In our analysis, the number of infectious diseases during and after CSA reduction was not decreased. Serious adverse events due to infectious diseases were lower after CSA reduction, although the number of severe infectious episodes was not significantly decreased. Beside the positive aspects of CNI reduction, the main risks of CNI reduction are acute rejection episodes. The rate of acute rejections was clearly increased after withdrawal of CSA followed by immunosuppressive therapy with azathioprine and steroids [6], while rejection episodes were only slightly increased in patients treated with MMF and steroids [9,10]. In our prospective study, one borderline rejection occurred in a patient treated on Tac prior to reduction of Tac. In patients on CSA, one interstitial-cellular rejection (BANFF IA) was noted during the 18 months of follow-up. However, acute rejection episodes are difficult to assess in our small study population and may well have been triggered by insufficient immunosuppression.

There are different ways to handle the problem of nephrotoxicity of CNI. In addition to reduction or withdrawal of CNI, newer immunosuppressive drugs can be introduced. Sirolimus is a non-nephrotoxic immunosuppressive drug that possibly preserves renal structure and function [24,25]. Various studies showed no significant difference in the outcome of kidney function compared with patients treated with CSA [26,27], but long-term results are still awaited. Furthermore, the corresponding adverse events of sirolimus should be considered, i.e. severe hyperlipidaemia, progressive proteinuria, myelosuppression as well as a higher incidence of post-transplant lymphoproliferative disorders in children.

One limitation of the present study is the lack of control biopsies before reduction of CNI to detect CNI toxicity or subclinical rejections. Also a control biopsy after reduction of CNI should be considered to check the safety of the intervention as well as to evaluate any change in the extent of CNI toxicity. Another potential problem of our study is the relatively small collective of paediatric renal-transplant patients. However, our study is principally designed as a pilot study in preparation for a randomized multicentre study including control biopsies.

In summary, on the basis of our analysis we conclude that in paediatric patients reduction of CNI down to low trough levels maintains renal function after kidney transplantation, while an increased risk of acute rejection episodes cannot be excluded. Therefore, further studies based on protocol renal biopsies within a randomized trial are warranted.

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Conflict of interest statement. None declared.

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