Cyclosporin exposure correlates with 1 year graft function and histological damage in renal transplanted patients

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Abstract

Background. Cyclosporin (CsA) level obtained 2 h after the morning dose (C2) has been shown to accurately predict total CsA exposure and acute rejection (AR) risk, whereas conventional trough levels (C0) do not. The impact of C2 monitoring on long-term kidney graft function, independent from AR risk, is still unclear, however, and it was assessed in the present study.

Methods. We enrolled 39 CsA-treated renal transplant recipients and used 1 year graft function and histological structure as surrogate markers of graft outcome. CsA dose was adjusted according to C2 levels.

Results. In the first 7 days after grafting, 40–51% of patients failed to reach target C2 levels; nevertheless, at 1 year the incidence of AR was only 2.5% and graft and patient survival was 100%. The decrease of serum creatinine (12–6 months) was associated with significantly higher C2 levels over time ($P = 0.0003$) and lower intrapatient variability of CsA relative absorption (CV) ($P = 0.0006$). One year graft biopsy showed chronic tubulointerstitial lesions in 54.5% of patients. Both C2 mean levels and the percentage CV independently predicted the severity of chronic histological lesions ($R = 0.69, P < 0.0001$).

Conclusions. Higher C2 levels, within the proposed target range values, seem to be associated with better renal function and structure.

Keywords: C2 monitoring; chronic allograft nephropathy; cyclosporin; graft function; kidney transplantation

Introduction

Cyclosporin (CsA) has a narrow therapeutic window and dosing is, therefore, dependent on accurate and reliable drug monitoring. The widespread adoption of Neoral®, the microemulsion formulation of CsA, has significantly improved clinical outcomes, due to its greater and more consistent absorption of CsA, improved dose-linearity and reduced inter- and intrapatient variability [1].

Research in renal transplant patients has shown that the area under the time–concentration curve (AUC), based on 12 h pharmacokinetics, strictly reflects drug exposure and is a sensitive predictor for acute rejection (AR) and graft survival at 1 year [2]. Unfortunately, this approach is too inconvenient, costly and difficult to perform on a routine basis.

The measurement of the absorption and exposure of CsA during the first 4 h of the dosing interval (AUC0–4) correlates very closely with full 12-h AUC [1], is a more practical monitoring tool and is very effective in differentiating between patients with normal and impaired absorption of CsA [1]. This 4 h period is associated with a large amount of intraindividual and interpatient variability and is an indicator of the patient’s ability to absorb CsA from the intestine [3]. Furthermore, blood concentrations during the early post-dose period correlate well with the pharmacodynamic effects of calcineurin inhibition and inhibition of interleukin-2 production [4,5]. Most importantly, it has been demonstrated that the CsA level obtained 2 h after the morning dose (C2) correlates most closely with AUC0–4 and can predict the risk of AR, thereby offering a rapid, practical and effective strategy for routine CsA microemulsion monitoring in both the early and later stages post-transplantation [3,6–10]. In contrast, conventional trough level measurements of CsA (C0) correlate poorly with AUC0–4 and do not accurately predict total CsA exposure and rejection risk [2,6]. Therefore, adjustment of Neoral dose based on C2 level has been proposed as
a more effective monitoring strategy than conventional C₀, to optimize the use of the calcineurin antagonist.

The impact of C₂ monitoring on long-term kidney graft function, independent from AR risk, is still undefined, however. Former studies were aimed to identify the optimal cut-off value to be targeted during the early post-operative period to achieve a low rate of AR at 3 months post-graft, whereas the most appropriate C₂ target remains to be defined to maximize Neoral’s immunosuppressive effect and to minimize its toxicity in the longer term after renal transplantation.

In-centre C₀ monitoring of de novo kidney allograft recipients receiving basiliximab, Neoral, mycophenolate mofetil and low-dose steroids has previously resulted in an extremely low rate of AR. Thus, the primary objective of this study was to evaluate the clinical impact of C₂ monitoring on kidney graft outcome, taking 12 month graft function and histological structure as surrogate markers of late graft outcome [11,12], and to explore the possible correlation of renal graft function with C₂ levels.

**Subjects and methods**

**Patients**

Patients who were ≥18 years of age, who were recipients of cadaveric or living-related kidney transplants, who received Neoral on a b.i.d. regimen and who were able to give informed consent were qualified for inclusion in the study. Patients who had a known liver disease, gastrointestinal disease or other disorders that may have altered the absorption or metabolism of CsA; those who were currently receiving another investigational drug; those who were multiorgan recipients or were previously transplanted with any organ; those with PRA >80% at any time-point; and recipients of dual transplant or marginal kidneys or an HLA-identical organ were excluded from the study. The quality of the donor kidney was evaluated by histological examination of pre-transplant biopsy: a histological score of four or more qualified the organ as marginal [13].

Thus, in the period from May 2001 through April 2002, 39 kidney transplant recipients were enrolled at our transplant centre (55.7% of the total number of transplants performed in that period). Both donors and recipients were Caucasians. Their demographics and clinical characteristics are reported in Table 1. The minimum follow-up was 12 months. In all patients, both C₀ and C₂ levels were measured, but CsA dose was adjusted exclusively according to C₂ monitoring. Strict collaboration with inpatient and outpatient nursing staff greatly facilitated timely blood sampling.

Whole blood samples were collected at days 3, 5, 7, 10 and 14 after the introduction of CsA, then weekly up to the end of the third month, thrice a month in the following 3 months and twice from month 7 through month 12, for a total of at least 36 measures for each patient. All measures of CsA blood levels were performed ≥48 h after the last change of dose.

**Immunosuppressive regimen**

All patients received immunoprophylaxis with basiliximab 20 mg intravenous (i.v.) on the day of transplant and 20 mg i.v. on day 4 and maintenance triple-drug immunosuppression consisting of Neoral, mycophenolate mofetil and prednisone.

Treatment with Neoral was commenced at a dose of 12–14 mg/kg given orally in two divided doses, starting 48 h after transplantation. Target therapeutic ranges for C₂ were 1600–2000 ng/ml during the first 4 weeks, 1400–1600 in the second month, 1200–1400 in the third month, 800–1200 during months 4–6, declining to 600–1000 ng/ml during months 7–12 after engraftment [14].

CsA-related nephrotoxicity was defined as 30% increase in serum creatinine (sCr) that was not attributed to any other identifiable cause and that improved with decrease in the Neoral dose.

Mycophenolate mofetil was given at 1 g per os. twice daily, starting from the second day after transplantation and was adjusted according to white blood cell counts or other relevant parameters. All patients were treated with corticosteroids (500 mg methylprednisolone intraoperatively, then 200 mg prednisone daily, tapered to 25 mg by day 8 and to 5 mg by month 3).

**Histological examination**

All grafted kidneys underwent surgical biopsy, performed immediately after graft reperfusion (0 h biopsy). Methods of processing and scoring criteria have been described elsewhere [13].

The diagnosis of AR was always confirmed by percutaneous core needle biopsy, classified according to the Banff criteria [15]. Delayed graft function (DGF) was diagnosed if sCr increased or remained unchanged immediately after graft reperfusion (0 h biopsy). Methods of processing and scoring criteria have been described elsewhere [13].

All recruited patients were asked to undergo protocol biopsy of the kidney graft at ~1 year after transplant. The histopathologist was blinded to any clinical features of the patients and to C₂ and sCr levels. Chronic lesions were scored according to Banff criteria [15], after subtracting for the lesions already present at baseline biopsy, to calculate the

<table>
<thead>
<tr>
<th>Donors</th>
<th>Source</th>
<th>Gender (male/female)</th>
<th>Cause of brain death</th>
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<td>Recipients</td>
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<td>Gender (male/female)</td>
<td>Cold ischaemia time (range)</td>
<td>HLA-MM (hours)</td>
<td></td>
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<td>Cad, cadaveric donor; LRD, living-related donor.</td>
<td>24 Cad/5 LRD</td>
<td>37.2±17.5 (16-66)</td>
<td>14/15</td>
<td>39.2</td>
<td>60.8</td>
<td>78±21</td>
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<td></td>
<td>33/6</td>
<td>Age (years) (range)</td>
<td>40.8±12.1 (18–59)</td>
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Cranial trauma (%) 39.2
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HLA-MM (hours) 3.34±0.6

**Table 1. Clinical features of donors and renal transplant recipients**
C$_2$ levels and chronic renal graft dysfunction

The results of the quantitative variables are expressed as means ± SD and those of the qualitative variables as proportions.

Intrapatient variability of CsA relative absorption [measured as dose- and weight (mg/kg)-corrected C$_2$ (DWC.C2)] [8] was expressed as the coefficient of variation (CV) (months 2–12): %CV = SD of mean DWC.C2/mean DWC.C2. We used a conventional receiver operating characteristic (ROC) curve to analyse %CV values in order to determine the cut-off point that yielded the highest combined sensitivity and specificity with respect to distinguishing patients with an increase of sCr over time from those with a decrease (i.e. an amelioration of renal graft function at the end of follow-up).

For each patient, the mean C$_2$ represented the mean of C$_2$ levels measured in each month (1–12) at the scheduled visits (see above). For the first month, only the measures recorded at days 7, 14, 21 and 28 were considered. For those levels not obtained within the expected time window (120 ± 15 min), values were discarded and, on almost every occasion, patients were re-evaluated within the following 24–48 h.

Differences between quantitative variables were tested by the Mann–Whitney U-test or by repeated measures analysis of variance (ANOVA), as appropriate. The relationship between non-parametric variables was tested by Spearman rank correlation. Stepwise regression analysis was used to evaluate the predictive ability of multiple independent continuous variables. All tests were two-tailed. A P-value of <0.05 was considered statistically significant. The logistic regression model was used to determine the factors significantly related to the deterioration of graft function over time. The significant predictors were next fitted in a multivariate model. The P-value of < 0.05 was used for all analyses.

Results

Patients showed 100% graft and patient survival at 12 months and an extremely low rate of AR (2.5%). DGF occurred in three patients (7.7%). Serum creatinine levels (mg/dl) during 1 year follow-up were 1.49 ± 0.35 at 1 month, 1.47 ± 0.34 at 3 months, 1.42 ± 0.28 at 6 months, 1.37 ± 0.32 at 9 months and 1.32 ± 0.26 at 12 months.

Blood samples for C$_2$ monitoring were obtained within the requisite time window (120 ± 15 min) in 86–93% of patients during the 12 months of follow-up, which apparently demonstrates the feasibility of this monitoring approach, given an adequate organization of nursing staff and information of patients.

None of the patients experienced CsA-related nephrotoxicity with C$_2$ levels within the target range. Two patients had 20% increase of sCr with C$_2$ definitely above 2000 ng/ml.

During the first days after grafting and specifically at days 3–7 after the start of CsA therapy, a sizable percentage of patients failed to reach C$_2$ levels of 1600 ng/ml, in spite of daily Neoral doses of 12–14 mg/kg (Table 2). The percentage of patients below the target range values of C$_2$ remained elevated during the first 3 months, despite frequent dosage adjustments (Table 2).

An observational study on a very large population of adult renal transplants has demonstrated that the change in sCr over the first year strongly predicts long-term renal allograft survival [11]. Thus, we wondered whether CsA exposure, measured as peak blood levels (C$_2$) throughout 12 month follow-up, would affect post-transplant renal graft function, defined as ΔsCr (difference between sCr at 12 months and sCr measured at 6 months). Patients with negative ΔsCr (i.e. an amelioration of sCr levels at 12 months) showed significantly higher levels of C$_2$ over time (Figure 1). Of note, baseline sCr levels were not different between the two groups (at hospital discharge: 1.51 ± 0.32 vs. 1.46 ± 0.39 mg/dl in negative ΔsCr vs. positive ΔsCr patients; P = 0.66). Particularly, during the first 6 months, mean C$_2$ levels above the mean target level (1400 ng/ml) turned out to be associated with the highest decrease of sCr (i.e. the highest negative ΔsCr) at 12 months (Mann–Whitney U-test: Z = 3.36; P = 0.0008).

Patient variability has been advocated to favour both acute and chronic kidney allograft rejection. Therefore, we measured the %CV in each patient and sought for a relationship with the change of sCr over time.

This study showed an inverse association between ΔsCr (12–6 months) and the %CV (Spearman rank correlation).

### Table 2. C$_0$ and C$_2$ levels and CsA relative absorption [measured as dose- and weight (mg/kg)-corrected C$_2$] during 1 year follow-up. At each time-point, the percentage of patients with out-of-range C$_2$ levels is reported.

<table>
<thead>
<tr>
<th>Time</th>
<th>C$_0$ (ng/ml)</th>
<th>C$_2$ (ng/ml)</th>
<th>C$_2$/dose/kg (ng/ml$^{-1}$kg mg$^{-1}$)</th>
<th>Pts above C$_2$ range (%)</th>
<th>Pts below C$_2$ range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>276 ± 69</td>
<td>1597.5 ± 356.6</td>
<td>117.9 ± 46.8</td>
<td>7.7</td>
<td>51.3</td>
</tr>
<tr>
<td>Day 7</td>
<td>349 ± 129</td>
<td>1722.9 ± 355.8</td>
<td>172.7 ± 64.9</td>
<td>17.9</td>
<td>41</td>
</tr>
<tr>
<td>Day 14</td>
<td>324 ± 107</td>
<td>1716 ± 474</td>
<td>201.9 ± 63.5</td>
<td>28.2</td>
<td>35.9</td>
</tr>
<tr>
<td>Day 21</td>
<td>354 ± 90</td>
<td>1783 ± 521</td>
<td>210.3 ± 90.6</td>
<td>28.2</td>
<td>38.4</td>
</tr>
<tr>
<td>Day 28</td>
<td>338 ± 105</td>
<td>1670 ± 418</td>
<td>264.1 ± 77.9</td>
<td>25.6</td>
<td>33.3</td>
</tr>
<tr>
<td>Month 3</td>
<td>283 ± 96</td>
<td>1363 ± 390</td>
<td>294.7 ± 122.4</td>
<td>17.9</td>
<td>30.7</td>
</tr>
<tr>
<td>Month 6</td>
<td>235 ± 68</td>
<td>1071 ± 262</td>
<td>299.4 ± 105.6</td>
<td>12.8</td>
<td>15.4</td>
</tr>
<tr>
<td>Month 9</td>
<td>196 ± 53</td>
<td>952 ± 267</td>
<td>291.8 ± 96.1</td>
<td>15.4</td>
<td>5.1</td>
</tr>
<tr>
<td>Month 12</td>
<td>145 ± 60</td>
<td>860 ± 176</td>
<td>279.1 ± 103.6</td>
<td>12.8</td>
<td>2.5</td>
</tr>
</tbody>
</table>
correlation: $\rho = 0.585; \ P = 0.0003$). ROC analysis revealed an inflection point of plots of %CV vs a positive $\Delta$sCr (i.e. a deterioration of kidney graft function over time) at 19.5% [sensitivity (95% CI): 0.76 (0.50–0.93); specificity (95% CI): 0.77 (0.54–0.92); AUC under ROC curve: 0.815 (95% CI: 0.671–0.959)]. For descriptive purposes, patients were then separated into two groups (CV $\leq 9.5\%$ or $> 19.5\%$); at 12 months, patients with CV $\leq 9.5\%$ (43.6%) showed a significantly better graft function, as measured by both sCr and $\Delta$sCr (Figure 2).

The logistic regression model was used to determine the factors significantly related to a positive $\Delta$sCr (i.e. worsening of graft function). A range of clinical, laboratory and demographic variables, such as arterial hypertension, C0 and C2 levels, %CV, HLA matching with the donor, cold ischaemia time, DGF, age and gender were selected as factors. None of these factors, with the exception of C2 and %CV, showed any significant correlation with the dependent nominal variable. As a matter of fact, the population studied exhibited rather homogeneous values for many of the variables tested (i.e. incidence of hypertension, HLA MM, cold ischaemia time), while some variables (AR, DGF) were negligible and this might help explain the lack of correlation. The significant predictors were next fitted in a multivariate model. Both mean C2 and %CV maintained their relationship with the dependent variable (C2: OR = 0.994, CI = 0.988–1.00; %CV: OR = 1.359, CI = 1.080–1.710; likelihood ratio: 18.107; $P < 0.0001$).

Thirty-three patients (84.6%) accepted to undergo protocol kidney graft biopsy, which was performed 11–13 months (median: 12.2 months) after transplantation. Serum creatinine in biopsied patients was $1.35 \pm 0.30$ mg/dl (non-biopsied patients: $1.28 \pm 0.18$ mg/dl; $P$ not significant). No evidence of borderline changes, suspicious for acute rejection, could be observed. Chronic tubulointerstitial lesions compatible with the diagnosis of chronic allograft nephropathy (CAN) were present in 54.5% of patients. CAN lesions were scored as mild in 36.3% and moderate in 18.2% of patients, with none showing severe lesions. Chronic vascular lesions were present in 45.4% of biopsied patients and were mild in nine patients, moderate in five and severe in one out of 33 patients. The severity of histological lesions was correlated positively with the %CV and negatively with C2 mean levels (Table 3): the higher the CV, and the lower the mean C2, the higher the histological score. Stepwise regression analysis confirmed that both variables independently predicted the severity of chronic histological lesions ($R = 0.69; \ R^2 = 0.475; \ P < 0.0001$). Of note, there was no difference in graft score at implantation between groups (i.e. patients with negative vs those with positive $\Delta$sCr). Finally, donor age failed to correlate with the degree of kidney graft damage ($P = 0.8$), showing a trend, although not significant, towards a correlation with vascular damage ($P = 0.08$).

In contradistinction, CsA trough levels failed to correlate with either 1 year graft function or the severity of histological lesions and definitely underestimated intrapatient variability in CsA exposure (data not shown).

**Discussion**

Emerging evidence over the past few years has shown that there is a robust relationship between Neoral...
absorption profile, measured by either AUC0–4 or C2, and the probability of AR, whereas the relationship between C0 and subsequent AR is weak and fails to reach statistical significance [2,3,6–10]. Adequate exposure to CsA within the first 3–7 days post-transplantation has been advocated to be critically important in preventing subsequent rejection, with C2 threshold ranging from 1500 to 1700 ng/ml [8–10], even in patients with basiliximab immunoprophylaxis [8]. Indeed, Morris et al. [16] reported a 0% rejection rate when C2 exceeded 1200 ng/ml. In sharp contrast, Perico et al. [17] have reported very recently that CsA trough levels measured at day 2 post-transplant would be the strongest predictor of acute graft rejection over a 6 month follow-up period, while C2 levels considered alone would have no predictive values at all; C2 levels of 300–440 ng/ml being associated with the lowest risk of rejection. In the cohort studied here, a sizable percentage of patients were below the target C2 range during the first week after transplantation, 18% being < 1200 ng/ml (and 60% patients had C0 levels of < 300 ng/ml at day 3 after the start of CsA therapy); none of them had AR throughout the follow-up. We suspect that basiliximab immunoprophylaxis might minimize the risk of relative underexposure to CsA in the early post-transplant period, although contrasting evidence exists in the literature [8,9].

Actually, studies designed to explore the impact of C2 monitoring immediately after transplantation on long-term kidney graft function are virtually absent. Mahalati et al. [18] reported that higher early AUC0–4 was associated with lower sCr at 3 months, while Clase et al. [10] found that adequate exposure within the first 3 days post-transplantation is critically important in preventing subsequent rejection, but seemingly does not influence sCr at 6 months. Finally, Pescovitz et al. [9] observed that higher mean C2 levels were not related to higher CsA nephrotoxicity, as expressed by sCr levels at either weeks 4 or 24 post-transplantation [9].

Our results demonstrate that negative ΔsCr (i.e. an amelioration of kidney graft function between 6 and 12 months) is associated with higher C2 levels, within the target range values chosen. Interestingly, C2 levels achieved during the first 6 months after transplant appear to strongly influence graft function at the end of follow-up, which seemingly confirms the critical role of adequate immunosuppression in the early months after engraftment.

Table 3. Histological score at basal biopsy and at 1 year after transplant and correlation between Delta score and mean C2 levels or %CV (n = 33 patients)

<table>
<thead>
<tr>
<th>Glomeruli</th>
<th>Tubuli</th>
<th>Interstitium</th>
<th>Vessels</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal score</td>
<td>0.39±0.49</td>
<td>0.48±0.51</td>
<td>0.67±0.48</td>
<td>0.67±0.64</td>
</tr>
<tr>
<td>Final score (1 year)</td>
<td>0.79±0.58</td>
<td>1.10±0.61</td>
<td>1.40±0.75</td>
<td>1.36±1.00</td>
</tr>
<tr>
<td>Delta score</td>
<td>0.39±0.50</td>
<td>0.62±0.78</td>
<td>0.75±0.86</td>
<td>0.69±0.76</td>
</tr>
<tr>
<td>C2-Delta correlation</td>
<td>R=0.25, P=0.15</td>
<td>R=0.41, P=0.018</td>
<td>R=0.37, P=0.032</td>
<td>R=0.5, P=0.003</td>
</tr>
<tr>
<td>CV-Delta correlation</td>
<td>R=0.43, P=0.012</td>
<td>R=0.55, P=0.0009</td>
<td>R=0.40, P=0.02</td>
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</tbody>
</table>

exposure were predictive of the incidence of acute and chronic rejection in renal transplant recipients. Moreover, data from a prior international multicentre study in de novo renal transplantation, during which kinetics were evaluated from 2 weeks to 3 months post-transplant, have suggested that absorption might stabilize between 1 and 2 months after commencing therapy [20]. We, therefore, measured the %CV of CsA relative absorption between 2 and 12 months in each patient and found that renal transplant recipients with CV >19.5% displayed higher sCr and lower ΔsCr at the end of follow-up.

One year histological alterations have been shown to predict graft survival, even when the graft function is still normal, with the progression of the lesion rather than the intensity of alterations at a single given time-point being the most meaningful predictor [12]. Then, it is critical to identify the clinical risk factors that lead to a high CAN score at 1 year, in order to devise possible intervention trials. In the cohort studied here, the progression of renal lesions during the first year after engraftment was significantly correlated with both mean C2 levels and the %CV of CsA relative absorption. The results point to inadequate CsA exposure as one of the clinical risk factors for CAN and indirectly support the role of immune-mediated mechanisms in the pathogenesis of chronic allograft damage.

In conclusion, higher C2 levels, within the recently proposed target range values [13], seem to be associated with better renal function and structure. Lower C2 threshold values in the early post-transplant period seemingly do not increase the incidence of AR, at least in Caucasian patients receiving basiliximab immunoprophylaxis. Finally, serial measurements of C2 are a simple and practical strategy to reveal the variability of oral absorption of CsA and allow the identification of subjects potentially at higher risk for chronic graft dysfunction. We are aware, however, that the findings presented here were attained retrospectively and in a limited sample of patients and that the above conclusions should be interpreted with caution until results from larger prospective studies are made available.

Conflict of interest statement. None declared.

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