Approaching the Therapeutic Window for Cyclosporine in Kidney Transplantation: A Prospective Study

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Abstract. Neoral dosing is traditionally based on cyclosporine (CyA) trough levels (Cₐ₀). Four-h area under the curve (AUC₀₋₄) for Neoral in the early posttransplantation period was shown previously to have a better correlation to acute rejection (AR) and CyA nephrotoxicity (CyANT), compared with Cₐ₀. An AUC₀₋₄ range of 4400 to 5500 µg/h per L during the first week was associated with the lowest AR and CyANT. This article describes a prospective study to assess the feasibility, safety, and efficacy of dosing Neoral solely by AUC₀₋₄ monitoring, regardless of Cₐ₀, in the first 3 mo after kidney transplantation. Fifty-nine kidney transplant recipients received Neoral-based triple immunosuppression. AUC₀₋₄ was measured on days 3, 5, 7, 10, and 14 and weeks 3, 4, 6, and 8, then monthly. Target AUC₀₋₄ was 4400 to 5500 µg/h per L. Dose was adjusted by percentage difference from target AUC₀₋₄.

Ninety-four percent of AUC were performed on the scheduled day or close to it. No patients had CyANT while AUC₀₋₄ was in target range. Four patients had reversible CyANT with AUC₀₋₄ > 5500. Only 1 of 33 patients (3%) who achieved and maintained AUC₀₋₄ > 4400 by day 3 posttransplantation had AR, whereas 10 of 22 (45%) of those with day 3 to 5 AUC₀₋₄ < 4400 had AR (P = 0.0002). In logistic regression analysis, higher early AUC₀₋₄ was the only significant variable associated with lower serum creatinine at 3 mo. Neoral dose monitoring by AUC₀₋₄ is a potentially valuable tool for optimizing Neoral immunosuppression. Attainment of a target range of 4400 to 5500 µg/h per L for AUC₀₋₄ early after transplantation has been demonstrated to reduce significantly the risk of AR and CyANT.

Cyclosporine (CyA) is the backbone of current immunosuppression protocols in many kidney transplant centers. Therapeutic monitoring of the drug is essential because CyA has a narrow therapeutic window with serious potential side effects. CyA trough blood levels (Cₐ₀) have been used widely to monitor CyA dosing. Significant groups of patients experience acute rejection (AR) or acute CyA nephrotoxicity (CyANT) despite maintaining CyA levels within a “therapeutic range” that tends to be variable and center specific (1,2). The area under the blood CyA concentration versus time curve (AUC) is a better measure of systemic drug exposure than Cₐ₀. Although earlier reports using Sandimmun (Sandoz Pharmaceuticals, Basel, Switzerland) CyA suggested AUC monitoring was associated with better outcomes (3,4), therapeutic monitoring of CyA based on pharmacokinetic studies and AUC has not gained popularity in large part because of the inconvenience and costs associated with multiple sampling and analysis.

A new galenic formulation of CyA, Neoral (Novartis Pharmaceuticals, Basel, Switzerland), has more predictable and consistent pharmacokinetic characteristics than Sandimmune. It was hoped that with Neoral, Cₐ₀ would better reflect true drug exposure, resulting in better immunosuppression with fewer side effects (5–7). Subsequent randomized clinical trials in new kidney transplant patients showed a comparable tolerability and side effect profile for the two CyA formulations and a lower but still significant rate of AR (35 to 45%) (8–10) with Neoral. Better pharmacokinetic characteristics of Neoral, however, allow AUC determination with fewer blood samplings (11–14). A 4-h AUC (AUC₀₋₄), shown to correlate very closely with a full 12-h AUC (r² = 0.94) (11), is a more practical monitoring tool and is very effective in differentiating between patients with normal and impaired absorption of CyA (11). On the basis of this relationship, we analyzed and reported (15) a cohort of 156 de novo kidney transplant recipients who received Neoral-based triple immunosuppression and had an AUC₀₋₄ measured on days 2 to 4 after starting Neoral. In this cohort, the Neoral dose was monitored by Cₐ₀ levels, not AUC₀₋₄. This early AUC₀₋₄ displayed a significant correlation with AR and CyANT during the first 3 mo posttransplantation, whereas Cₐ₀ did not. An AUC₀₋₄ range of 4400 to 5500 µg/h per L was associated with the lowest rate of AR and CyANT (15). Given the demonstrated crucial importance of early exposure to therapeutic levels of CyA as measured by AUC₀₋₄, we conducted this pilot study in which we prospectively monitored and adjusted Neoral doses in de novo renal transplant patients.
by serial AUC$_{0-4}$ determinations rather than by C$_0$. The objective of the study was to assess efficacy, safety, and feasibility of achieving and maintaining therapeutic ranges of CyA as measured by AUC$_{0-4}$ (4400 to 5500 µg/h per L) in the first 3 mo posttransplantation.

**Materials and Methods**

The study population comprised 59 consecutive first kidney transplant recipients who received a transplant between August 1998 and May 1999 at the Queen Elizabeth II Health Sciences Center in Halifax. All patients were followed for a minimum of 3 mo. Collaboration with in-patient and outpatient nursing staff and with the drug monitoring laboratory facilitated timely blood sampling and same-day AUC reporting, without disruption of other normal routines.

Logistic feasibility was measured by the ratio of AUC performed to AUC planned during the first 2 wk. During this time, each patient had five AUC scheduled, compared with only once a week to once a month afterward. AR was the primary efficacy end point. Primary safety end points were 3-mo serum creatinine and episodes of Cy-A NT. Neurotoxicity and hepatotoxicity were secondary safety end points.

**Definitions**

The diagnosis of AR was confirmed by percutaneous core needle biopsy. All patients with >30% rise in serum creatinine that was not due to an identifiable cause, e.g., dehydration, and was confirmed with two consecutive measurements underwent percutaneous needle biopsy. In addition, patients with delayed graft function underwent needle biopsy on days 4 to 7 and weekly thereafter until renal function recovered. Severity of AR episodes was classified according to the Banff criteria (16,17).

CyANT was defined as 30% increase in serum creatinine that was not attributed to any other identifiable cause and that improved with decrease in the Neoral dose. Biopsies performed for renal dysfunction in these patients were free of acute rejection changes. Hepatotoxicity was arbitrarily defined as a 2× increase in aspartate aminotransferase and/or alanine aminotransferase above the normal values or any elevation in direct or indirect bilirubins. Neurotoxicity was defined as seizures, severe headache, or moderate-severe tremors. Delayed graft function (DGF) was defined as lack of >10% spontaneous drop in serum creatinine by the third postoperative day regardless of the need for dialysis. All CyA blood concentration values refer to whole-blood concentrations, determined by a monoclonal, parent compound-specific RIA test (Incstar Cyclo-Trac whole blood RIA kit, Stillwater, MN).

**Immunosuppression**

None of the patients received antilymphocyte antibody treatment. Recipients of HLA-identical living related transplants (4 patients) were treated by prednisone (Pred) and Neoral only. The other 55 patients received Pred, Neoral, and a third immunosuppressive drug according to one of the following protocols: (1) Pred, Neoral, mycophenolate mofetil (MMF; 35 patients [59%]); (2) Pred, Neoral, and either SDZ RAD (40-O-[2-hydroxyethyl]-rapamycin) or MMF (as part of a randomized, double-blind study; 12 patients [20%]); or (3) Pred, Neoral, rapamycin (as a part of open-label, multicenter study; 8 patients [14%]).

In all patients, CyA was initiated in the recovery room immediately after transplantation by continuous intravenous infusion at a dose of 3 mg/kg per d, which was maintained until the next Neoral dosing time or until they were deemed able to take oral medication (usually 8 to 16 h). Neoral was started at 9 to 14 mg/kg per d in two divided doses. We progressively increased the starting dose in an effort to increase the proportion of patients who exceeded the 4400 µg/h per L AUC$_{0-4}$ target threshold within the first 5 d posttransplantation. AUC$_{0-4}$ was performed on days 3, 5, 7, 10, and 14 and at week 3, 4, 6, 8, and 12. Blood for CyA levels was drawn before (C$_0$) and at 1, 2, 3, and 4 h after the Neoral morning dose (C$_1$, C$_2$, C$_3$, and C$_4$, respectively). AUC$_{0-4}$ was determined by the following regression formula obtained from our retrospective study database (15), using only C$_1$, C$_2$, and C$_4$: AUC$_{0-4}$ = 256 + C$_1$ + 0.9 × C$_2$ + 1.4 × C$_4$. C$_0$ and C$_4$ values were obtained and stored for later calculation of actual AUC$_{0-4}$. The Neoral dose was adjusted to achieve an AUC$_{0-4}$ target range of 4400 to 5500 µg/h per L (15), regardless of C$_0$. Assuming an almost linear relationship between dose and systemic exposure for Neoral within the same patient, dose adjustments were made by multiplying the ratio of mid-range target AUC$_{0-4}$ (5000 µg/h per L) to patient’s AUC$_{0-4}$ by the previous Neoral dose to obtain the new dose (New dose = 5000/current AUC$_{0-4}$ × previous dose).

Methylprednisolone 500 mg intravenously was given intraoperatively followed by Pred 1 mg/kg per d orally and tapered by 5 mg every other day to 20 mg/d for the first month, 15 mg/d for the second month, and 10 mg/d for the third month. MMF 1 g orally twice a day was started as soon as oral medication could be tolerated and adjusted to maintain white blood cells >4000/mm$^3$. Patients who were receiving SDZ RAD/MMF were part of a randomized, double-blind study and were assigned to receive either MMF 1 g orally twice a day, SDZ RAD 0.75 mg orally twice a day, or SDZ RAD 1.5 mg orally twice a day. Rapamycin was given as a 6-mg loading dose on postoperative day 1 followed by rapamycin 2 mg/d orally and adjusted to keep rapamycin trough blood levels above 5 ng/ml.

**Statistical Analyses**

A $t$ test was used to compare means of continuous numeric values. Stepwise logistic regression analysis was done to explore the relation of source of transplant, HLA mismatch, type of immunosuppression, DGF, C$_0$, AUC$_{0-4}$, and Neoral dose to incidence of AR and renal function at 3 mo. Fisher’s exact test was used to compare incidence of AR between different groups. In all statistical analyses, $P < 0.05$ was considered significant. Statistical calculations were performed with SAS/STAT (SAS institute Inc., Cary, NC).

**Results**

Table 1 shows the characteristics of the patients in the study. The only unusual finding for our center is the unexpectedly

| Table 1. Demographic characteristics of patients studied$^a$ |
|-------------|--------|
| Mean age (yr) | 44 ± 11 |
| Male         | 30/59 (51%) |
| LR           | 33/59 (56%) |
| HLA identical| 4 (7%) |
| non-HLA identical | 29 (49%) |
| Cadaveric    | 26/59 (44%) |
| Delayed graft function | 8/26 (31%) |
| Median HLA mismatches | 3 |
| PRA > 30%    | 6/59 (10%) |

$^a$ LR, living related kidney transplant; PRA, panel reactive antibody.
high percentage of living related kidney transplants, which was due to an unusual paucity of cadaver kidneys during the study period.

**Logistic Feasibility**

Of 295 planned AUC for 59 patients within the first 2 wk, 260 (88%) were performed on the scheduled days. An additional 16 (5%) AUC were obtained within 4 d of the scheduled AUC.

**Pharmacokinetic Analysis**

A total of 489 AUC\(_0-4\) were performed. AUC\(_0-4\) calculated by the regression formula based on C\(_1\), C\(_2\), and C\(_3\) showed excellent correlation with the actual AUC\(_0-4\) (r\(^2\) = 0.99). C\(_0\) correlated poorly with AUC\(_0-4\) (r\(^2\) = 0.22), as did the weight-adjusted Neoral dose (r\(^2\) = 0.08). The single sampling point concentration that correlated best with AUC\(_0-4\) was C\(_2\) (r\(^2\) = 0.76).

**Clinical Parameters**

**Efficacy.** Four recipients of HLA-identical living donor kidney recipients were deliberately excluded from the acute rejection efficacy analysis, leaving 55 patients for analyses regarding AR. In 33 of 55 recipients (60%), AUC\(_0-4\) >4400 \(\mu\)g/h per L was achieved on postoperative day 3 and maintained afterward (group 1). In 22 of 55 recipients (40%), AUC\(_0-4\) on day 3 and/or day 5 (AUC\(_0-4\)) was <4400 \(\mu\)g/h per L (group 2). Only 1 patient (3%) in group 1 versus 10 patients (45%) in group 2 had AR (P = 0.0002). Virtually all AR episodes occurred early, within 26 d of transplantation (Figure 1). The only patient in group 1 who had AR was a highly sensitized (panel reactive antibody, 60%) recipient with severe DGF. Protocol biopsy on day 6, while the graft was still not functioning, showed vascular rejection. In group 2, 10 patients had 12 episodes of AR. Eight of them had AR within 20 d posttransplantation. Two patients had AR on days 26 and 87, respectively, when their Neoral dose was decreased because of assumed neurotoxicity (severe tremors) and nephrotoxicity, despite AUC\(_0-4\) in the low target range. Reducing the Neoral dose led to AUC\(_0-4\) values below target levels, which was followed by AR within 14 d, without an interval fall in serum creatinine. Two of these 10 patients had recurrent rejection on days 40 and 54, respectively, both with AUC\(_0-4\) < 4400 \(\mu\)g/h per L. The Neoral dose had been decreased because of severe tremors and assumed nephrotoxicity, but again, the Neoral dose reduction did not lead to a reduction in serum creatinine.

Stepwise logistic regression analysis of variables that affect AR showed that only AUC\(_0-4\) (P = 0.0001) and DGF (P = 0.04) were significant predictors of AR. Age, gender, C\(_0\), weight-adjusted Neoral dose, HLA mismatch, source of transplantation (cadaver versus living), and type of third immunosuppressive drug were not significant.

Figures 2, 3, and 4 show mean serum creatinine, AUC, and weight-adjusted Neoral dose, respectively, in both group 1 and group 2 patients during the first 3 mo after transplantation. Group 1 patients had lower mean serum creatinine levels throughout (Figure 2), despite higher mean AUC\(_0-4\) for most of the 3 mo (Figure 3). The influence of early AUC\(_0-4\) on AR and 3-mo serum creatinine was seen in both cadaveric and live donor kidney recipients (Table 2), but because of the small number of patients in the cadaveric group, the difference did not reach statistical significance despite a strong trend. The dose of Neoral required to maintain target AUC\(_0-4\) diminished over time to 4.5 \pm 1.3 mg/kg per d in group 1 patients and to 5.1 \pm 1.4 mg/kg per d in group 2 patients at 3 mo posttransplantation (P = 0.29; Figure 4). The dose of Neoral in 156 historic patients monitored by C\(_0\) in our center was 4.6 \pm 1.6 mg/kg per d at 3 mo posttransplantation.

**Safety.** Nephrotoxicity. None of the patients experienced CyANT with AUC\(_0-4\) < 5500 \(\mu\)g/h per L. Four patients had episodes of CyANT while AUC\(_0-4\) was in the range of 6200 to 8300 Journal of the American Society of Nephrology J Am Soc Nephrol 12: 828–833, 2001
In all four patients, CyANT was reversed by appropriate reduction in the Neoral dose. Multiple regression analysis showed that AUC 0-4 and DGF were the only two independent variables measured that affected serum creatinine at 3 mo. Higher early AUC 0-4 was associated with lower serum creatinine at 3 mo (P < 0.001). Presence of DGF was associated with higher serum creatinine at 3 mo (P < 0.02). Source of transplantation, C₀, weight-adjusted Neoral dose, recipient’s diabetes mellitus, HLA mismatch, and type of third immunosuppressive drug were not significant.

Hepatotoxicity. Twenty-two patients (37%) had transient elevations of aminotransferase, alanine aminotransferase, and/or bilirubin. All patients were asymptomatic. None of the patients had the Neoral dose reduced specifically because of elevated liver enzymes. By adjusting the Neoral dose according to AUC₀-₄, however, 20 of the 22 patients had normal liver enzymes at the end of the first month and another by the end of the second month. One patient, although completely asymptomatic, had persistently high bilirubin levels.

Neurotoxicity. None of the patients had seizures or reported severe headaches. Five patients (8%) developed moderate to severe tremors after transplantation. In one patient, tremors resolved spontaneously despite increasing Neoral doses. Three patients had tremors associated with AUC₀-₄ ≥ 5500 μg/h per L, and all improved on achieving target AUC₀-₄ range with decreasing Neoral doses. Only one patient (1.7%) had persistent tremors, even with AUC₀-₄ in the low target range.

Discussion

C₀ is used widely for monitoring Neoral dosing, although it correlates poorly with AR and CyANT (1,15). Despite improved pharmacokinetic characteristics of Neoral, with current C₀-based dosing and monitoring regimens, AR occurs in almost one third of kidney transplant recipients (8–10). With effective treatment of AR, early graft loss from AR is uncommon. However, AR is still an important predictor of chronic rejection and long-term graft survival (18–20).

Using the original Sandimmune CyA preparation, CyA exposure measured by AUC had been reported to affect AR rate and/or graft survival in kidney transplant recipients (3,4). Lindholm and Kahan (3) dosed CyA-Sandimmune by serial AUC monitoring in 160 kidney transplant recipients and showed that average CyA blood concentration of <400 ng/ml on the first posttransplant pharmacokinetic study, usually on postoperative day 7, was associated with higher AR rate and poorer graft survival. Only approximately one third of patients achieved the targeted AUC levels, and even in this group the 1-yr AR rate was 34%. No correlation was found between pharmacokinetic parameters and CyANT. In an extension of that study, Senel et al. (4) reported that an average CyA blood concentration >550 ng/ml on day 7 after renal transplantation was associated with higher graft survival for up to 6 yr posttransplantation, although it did not influence the incidence of acute rejection. C₀ did not correlate well with graft or rejection-free survival.

Despite an abundance of information in the literature regarding correlation between limited sampling AUC and AUC₀-₁₂ for Neoral, there are very limited data on the influence of AUC₀-₁₂ or of any limited sampling strategy on the incidence of AR in kidney transplant recipients. Also, we were unable to find any reports that compared the differential influence of AUC₀-₄ and AUC₀-₁₂ on clinical events posttransplantation.

On the basis of excellent correlation established between AUC₀-₄ and AUC₀-₁₂ in stable kidney transplant recipients (11) and also because it provides an accurate estimate of CyA bioavailability from the Neoral formulation and was demonstrated to be a useful tool for the determination of CyA absorption characteristics in a broad range of renal transplant recipients (11), our group recently reported a retrospective study of 156 first kidney transplant recipients who received Neoral-based triple immunosuppression and who were monitored by C₀ but had AUC₀-₄ measured during the first posttransplantation week. We demonstrated that achieving an AUC₀-₄ range of 4400 to 5500 μg/h per L as early as days 2 to
measured by AUC\(_{0-4}\) had a very significant inverse relationship with 3-mo serum creatinine. This effect might be related to prevention of subclinical immunologic injury to the graft with proper CyA exposure (21,22). The absence of nephrotoxicity may also be related in part to rapid and appropriately rational reduction of the Neoral dosage to prevent prolonged overexposure to CyA. This is possible with AUC monitoring but not with C\(_0\) monitoring, because the latter does not reflect accurately true drug exposure, and low or “normal” C\(_0\) levels may actually be associated with high exposure to CyA. This may help explain the anachronistic findings of nephrotoxicity with “low” C\(_0\) and excellent renal function with “high” C\(_0\). It is also interesting that at the end of 3 mo, the mean Neoral dose in mg/kg in patients who were monitored by AUC\(_{0-4}\) was similar to the mean Neoral dose in our historic patients who were monitored by C\(_0\). Although the mean dose was similar, the distribution of dosage was more appropriately allocated in AUC-monitored patients because AUC monitoring allows for more rational adjustment of the Neoral dose to maintain optimal CyA exposure. In addition, with AUC monitoring, clinical hepatotoxicity was not seen in our 59 patients. Elevated liver enzymes were seen in 37% of patients, but it was asymptomatic in all and normalized with Neoral dose adjustments designed to maintain CyA exposure within the target range. Similarly, neurotoxicity was not a clinical problem when CyA exposure was maintained within the target AUC range.

Our experience also suggests that rapidly achieving and maintaining AUC\(_{0-4}\) within the 4400 to 5500 µg/h per L range may effectively prevent AR. In this group, only one highly sensitized patient with severe DGF had early vascular AR. Prevention of this type of AR arguably might not be possible with any currently available oral immunosuppressive agents, all of which act by inhibiting T-cell activation or function in some way. The poor correlation between C\(_0\) and AUC\(_{0-4}\) may help to explain the occurrence of AR with “high” or target C\(_0\) levels and its absence in many patients with “low” C\(_0\). Interestingly, four patients developed AR when their Neoral dose was decreased because of assumed toxicity despite an AUC\(_{0-4}\) at the low end of the target range. This decrease in dose, attributable to early inexperience with AUC\(_{0-4}\) monitoring, resulted in AUC\(_{0-4}\) <4400 µg/h per L. The subsequent AR occurred without any previous reduction in serum creatinine, suggesting that CyANT had not been present before dose monitoring.

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Table 2. Acute rejection and 3-mo serum creatinine in cadaveric and living donor kidney transplant recipients in relation to early CyA exposure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cadaveric Donor (N = 26)</th>
<th>Living Donor (N = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First 5-D</td>
<td>First 5-D</td>
</tr>
<tr>
<td></td>
<td>AUC(_{0-4}) &gt;4400 µg/h</td>
<td>AUC(_{0-4}) &lt;4400 µg/h</td>
</tr>
<tr>
<td></td>
<td>per L</td>
<td>per L</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>1/12 (8%)***</td>
<td>5/14 (36%)***</td>
</tr>
<tr>
<td>3-Mo serum creatinine</td>
<td>146 ± 59****</td>
<td>172 ± 44****</td>
</tr>
</tbody>
</table>

* HLA-identical living donor kidney transplant recipients were excluded. *, \(P = 0.0005\); **, \(P = 0.04\); ***, \(P = 0.07\) Fisher’s exact test; ****, \(P = 0.13\), two-tailed \(t\) test.
reduction. All four of these patients were in group 2, with early subthreshold exposure to CyA during the first 5 postoperative days. This experience emphasizes the importance of not only rapidly reaching adequate levels of CyA exposure as measured by AUC0-4 but also maintaining it, especially in patients who may have experienced early donor-specific T-cell activation as a result of inadequate early exposure to CyA.

This study shows for the first time that with Neoral, therapeutic drug monitoring by AUC0-4 is feasible; safe in terms of renal, hepatic, and neurologic function; and efficacious in therapeutic drug monitoring by AUC0-4 but also maintaining proper CyA drug exposure may essentially eliminate AR and CyANT. If confirmed by subsequent larger experience, these findings may have a significant impact on our understanding and management of CyA immunosuppression in clinical renal transplantation.

References