Effect of Cyclosporine on the Rate of Renal Function Recovery After Renal Transplantation

Francis Dumler
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Francis Dumler, MD†

To assess the effect of cyclosporine therapy on the rate of renal function recovery after renal transplantation, patients with no clinical evidence of rejection and who were treated with either cyclosporine or azathioprine in addition to steroid therapy were studied (n = 74). Of the patients with immediate renal function (n = 57), those receiving organs from living, related donors had a faster recovery rate of glomerular filtration than patients with cadaveric grafts (azathioprine, 15 ± 2 versus 7 ± 1 mL/min/day, P = 0.0001; cyclosporine, 14 ± 3 versus 6 ± 1 mL/min/day, P = 0.001). Recipients of cadaveric grafts with delayed renal function (n = 17) had a decreased recovery rate of allograft function when treated with cyclosporine as compared to those treated with azathioprine (4 ± 2 versus 6 ± 1 mL/min/day, respectively; P = 0.026). Patients on azathioprine achieved better renal function (P = 0.01) than those on cyclosporine (recipients of organs from living, related donors, 59 ± 5 versus 52 ± 3 mL/min; recipients of cadaveric grafts, 52 ± 5 versus 40 ± 2 mL/min). Thus, even in this early period, cadaveric-graft recipients treated with cyclosporine demonstrate an apparent reduction in creatinine clearance when compared to patients treated with azathioprine. (Henry Ford Hosp Med J 1989;37:24-7)

Use of cyclosporine has resulted in significant improvements in allograft survival (1-3). However, nephrotoxicity is almost a universal finding in cyclosporine-treated patients, ranging from minor reversible decreases in renal function to chronic nephropathy and severe renal failure (4-7). The pathogenesis of acute and chronic cyclosporine-induced nephrotoxicity is not well defined. However, in experimental animals acute reductions in single nephron glomerular filtration rate result from reductions in single nephron plasma flow and ultrafiltration coefficient associated with simultaneous increases in afferent and efferent arteriolar resistance (8). Cyclosporine also may worsen renal ischemic injury and contribute to immediate post-transplant acute renal failure (9-11). Thus, it is important to define the effect of cyclosporine treatment on the immediate rate of renal function recovery in patients undergoing renal transplantation.

Materials and Methods

Patients receiving their first renal transplant between July 1, 1982, and July 1, 1986 (n = 140) were considered eligible for evaluation. However, only patients with no clinical evidence of rejection during the time required to achieve a stable serum creatinine concentration were entered into the study (n = 74). All patients were treated with methylprednisolone (250 mg/day intravenously for three days) followed by oral prednisolone (0.5 mg/kg/day). All cadaveric renal transplant recipients received three to five doses (17.5 to 25 mg/kg intravenously) of Minnesota antilymphoblast globulin starting on postoperative day 3. All patients received a preoperative dose of azathioprine (2 mg/kg). Patients with immediate graft function, defined as urine output > 1 L/day with a concomitant fall in serum creatinine concentration without dialysis, were either started on azathioprine (2 mg/kg/day) or cyclosporine-A (4 mg/kg/day intravenously) with conversion to oral doses (15 mg/kg/day for cadaveric-graft recipients and 10 mg/kg/day for recipients of organs from living, related donors) by postoperative day 3. In recipients with delayed renal function, azathioprine was continued until allograft function was established. Cyclosporine doses were then adjusted to maintain serum trough levels of 150 to 200 ng/mL for cadaveric-graft recipients and 100 to 150 ng/mL for recipients of organs from living, related donors using a polyclonal antibody radioimmunoassay (2).

Serum creatinine concentrations were measured pretransplant and daily at 24-hour intervals. All values were corrected to the established posttransplant dry weight. Creatinine clearances were estimated daily by single-pool kinetic modeling as described previously (12,13). The creatinine generation rates used for modeling were calculated as the average of values obtained by three separate methods (14-16). To validate this method in...

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renal transplant recipients, a subset of nine patients had 15 separate creatinine clearances calculated simultaneously by single-pool kinetic modeling (12,13) and by standard clearance techniques during 24-hour periods. The rate of increase in renal function was calculated as the slope of the linear regression defining the relationship between creatinine clearance values and days post initiation of renal allograft function.

Unless otherwise indicated, all results are expressed as mean ± SEM. Differences between groups were evaluated by one-way analysis of variance and a posteriori Student t test for non-paired samples when necessary.

Results

Standard creatinine clearance measurements were carried out in 15 independent instances in nine patients. A significant correlation was found between measured and estimated creatinine clearances (Figure) for values ranging between 1 and 48 mL/min (R = 0.959; P < 0.0001; coefficient of variation = 8.26%).

Pertinent demographic and clinical characteristics of the patients included in this study are shown in Table 1. Although the number of cadaveric-allograft recipients treated with azathioprine (n = 24) and cyclosporine (n = 32) was similar, the majority of patients receiving a kidney from a living, related donor were treated with azathioprine (n = 14) as opposed to cyclosporine (n = 4). For all subsequent analyses, patients were allocated to one of four groups according to the type of immunosuppression and organ donor (Tables 2 and 3). Since age and weight are important factors determining endogenous creatinine generation, these parameters were assessed separately in the patient groups. Although cyclosporine-treated patients were older than those on azathioprine, no differences existed in body weight between treatment groups (Tables 2 and 3).

In patients with immediate allograft function, analysis of variance demonstrated a significant difference (F = 5.261; P = 0.003) in the rate of renal function recovery between patient groups (Table 2). However, this result was entirely accounted for by the higher rates in recipients of organs from living, related donors when compared to recipients of cadaveric grafts in both treatment groups (azathioprine, 15 ± 2 versus 7 ± 1 mL/min/day, P = 0.0001; cyclosporine, 14 ± 3 versus 6 ± 1 mL/min/day, P = 0.001). The immunosuppressive regimen used had no impact on the rate of renal function recovery when donor type was taken into account. Similar results were noted for the days required to achieve stable renal function (Table 2).

Although recipients of cadaveric grafts and of organs from living, related donors who were treated with cyclosporine had higher serum creatinine concentrations than those on azathioprine, differences did not reach statistical significance. Creatinine clearance estimates were different between groups (F = 5.261; P = 0.003), with cyclosporine-treated recipients of cadaveric grafts having significantly lower creatinine clearances (P = 0.012) than similar recipients treated with azathioprine (Table 2).

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Azathioprine</th>
<th>Cyclosporine-A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR (n = 17)</td>
<td>C (n = 22)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32 ± 3</td>
<td>43 ± 4</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>58 ± 3</td>
<td>45 ± 5*</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)*</td>
<td>1.1 ± 0.1</td>
<td>1.3 ± 0.2</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)*</td>
<td>59 ± 5</td>
<td>52 ± 3</td>
</tr>
<tr>
<td>Rate of increase in clearance</td>
<td>15 ± 2</td>
<td>14 ± 3</td>
</tr>
<tr>
<td>Days to stable creatinine</td>
<td>5 ± 1</td>
<td>8 ± 1*</td>
</tr>
</tbody>
</table>

*Values at the time when renal allograft function had stabilized.
†P = 0.03 when compared to the azathioprine groups.
‡P = 0.011 when compared to the azathioprine, living, related group.
§P = 0.012 when compared to the cyclosporine, living, related group.
∥P = 0.0001 when compared to the cyclosporine, living, related group.
††P = 0.0001 when compared to the cyclosporine, living, related group.
LR = living, related; C = cadaveric.

Table 2

<table>
<thead>
<tr>
<th>Effect of Cyclosporine on the Recovery of Renal Allograft Function in Patients with Immediate Renal Allograft Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Arithmetic parameters</td>
</tr>
<tr>
<td>Cyclosporine dose* (mg/kg/day)</td>
</tr>
</tbody>
</table>

Figure—Relationship between measured 24-hour creatinine clearance values and those estimated by kinetic modeling in nine renal transplant recipients (R = 0.959; P < 0.0001). See text for description of method used.
Table 3
Effect of Cyclosporine on the Recovery of Delayed Cadaveric Renal Allograft Function in the Immediate Posttransplantation Period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Azathioprine (n = 7)</th>
<th>Cyclosporine-A (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39 ± 4</td>
<td>48 ± 4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55 ± 5</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)*</td>
<td>1.1 ± 0.1</td>
<td>1.6 ± 1†</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)*</td>
<td>55 ± 6</td>
<td>35 ± 3‡</td>
</tr>
<tr>
<td>Rate of increase in creatinine clearance (mL/min/day)*</td>
<td>6 ± 1</td>
<td>4 ± 1§</td>
</tr>
</tbody>
</table>

*Values at the time when renal allograft function had stabilized.
†P = 0.041 when compared to the azathioprine group.
‡P = 0.005 when compared to the azathioprine group.
§P = 0.026 when compared to the azathioprine group.

All patients with delayed allograft function were recipients of cadaveric kidneys. Cyclosporine-treated patients had significantly lower rates of renal function recovery (P = 0.026) and lower creatinine clearance values (P = 0.005) than azathioprine-treated patients (Table 3). No consistent differences in preservation techniques, time from harvest to transplantation, or in the age of donors were noted between cyclosporine- and azathioprine-treated recipients of cadaveric grafts.

Because the early stages of type 1 diabetes mellitus are characterized by increased glomerular filtration rates, the effect of diabetes on the rate of renal function recovery was assessed in a subset of type 1 diabetic patients (n = 7) treated with cyclosporine who had received a cadaveric renal allograft. The rate of renal function recovery was higher in diabetic patients (6.8 ± 2.2 mL/min/day) when compared to control patients (4.2 ± 1.3 mL/min/day) but did not reach statistical significance (P = 0.069). No differences were noted in the number of days required to achieve steady renal function (8.5 ± 1.7 and 7.7 ± 1.9 days for control and diabetic patients, respectively; P = not significant). Creatinine clearance values were also similar in both groups (39 ± 4 versus 41 ± 3 mL/min for control and diabetic patients, respectively; P = not significant).

Discussion

Cyclosporine is an important addition to the immunosuppressive regimens used in renal transplantation and has resulted in significant improvements in graft survival (1-3). However, cyclosporine-induced nephrotoxicity, both short- and long-term, is an important side effect that warrants close observation (4-7). Researchers have also suggested that cyclosporine may aggravate ischemic renal injury (9-11). The purpose of this study was to determine the effect of cyclosporine therapy in the early post renal transplantation period on the rate of renal function recovery in the absence of clinical rejection. In this way the direct effect of cyclosporine on immediate and delayed renal allograft function could be better evaluated clinically.

Assessment of renal function by estimation of creatinine clearance using single-pool creatinine kinetics allows the daily assessment of renal function without the difficulties inherent in daily urine collections in a routine clinical setting. Although a close correlation was observed between actual creatinine clearance measurements and those estimated by kinetic modeling (Figure), it could be argued that the calculated values are not accurate. However, the coefficient of variation between measured and estimated values was 8.26%—a value acceptable for clinical practice. In addition, the purpose of this study was not to define the absolute rates of renal function recovery but to compare these rates in relation to treatment and donor type. Any deviation of the estimated clearance value when compared to actual measurements would be systematic and equally applicable to all groups.

As expected, the rate of renal function recovery was better in recipients of organs from living, related donors compared to recipients of cadaveric grafts (Table 2). These findings were independent of the type of immunosuppressive regimen used (Table 2). The number of days to a stable creatinine clearance was also less in those who received organs from living, related donors when compared to cadaveric-graft recipients (Table 2). However, even in this early posttransplantation period, reduced renal function was apparent in cadaveric-graft recipients treated with cyclosporine compared to those treated with azathioprine (Table 2). This effect occurred at low serum cyclosporine trough levels (150 to 200 ng/mL) which are known to result in better preservation of renal function than protocols aiming for higher levels (2). Although others have addressed the issue of the effect of cyclosporine on early graft function (17-19), no data were provided on the rate of renal function recovery. These reports have dealt mostly with the prevalence of acute tubular necrosis posttransplantation and its resolution. The present study confirms that cyclosporine therapy decreases the rate of recovery in patients with delayed allograft function as well as provides a quantitative measure of such an effect (Table 3). Thus, posttransplant acute tubular necrosis is necessary to demonstrate the negative effect of cyclosporine on the rate of renal function recovery. These results suggest that renal vasoconstriction (a cyclosporine effect) and/or tubular damage (whether or not related to cyclosporine) may result in decreased graft function in the early post renal transplant period.

Although creatinine clearance measurements demonstrated significant differences between azathioprine- and cyclosporine-treated patients with immediate renal allograft function, serum creatinine values did not reach statistical significance. Serum creatinine concentration is a function of lean body mass, and its elimination is mainly by glomerular filtration rate. Thus, when comparing individuals with differing lean body mass, creatinine clearance is a more accurate comparative measurement of renal function than serum creatinine concentration.

Since the early stages of type 1, insulin-dependent diabetes mellitus are characterized by hyperfiltration (20,21), the rate of improvement in renal function was compared in cyclosporine-treated type 1 diabetic and nondiabetic patients who had received a cadaveric allograft. Although the recovery rate was 1.6 times greater in type 1 diabetic patients than in nondiabetic patients, the results were not statistically significant. However, because of the need to stratify by donor type and treatment regimen, this negative finding may be related more to sample size rather than to lack of a biological effect. Alternatively, the use of cyclosporine may abolish diabetic-induced hyperfiltration.
Cyclosporine treatment has no effect on the recovery rate of renal allograft function in the absence of clinical rejection and posttransplant acute tubular necrosis. In patients with delayed allograft function, cyclosporine treatment decreases the rate of renal function recovery. However, even in this early postoperative period, patients receiving cyclosporine achieve a lower level of renal function than those treated with azathioprine.

References