Conversion of Cyclosporine to Sirolimus Before 12 Months is Associated With Marked Improvement in Renal Function and Low Proteinuria in a South African Renal Transplant Population.

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Abstract

Objectives: Avoidance of calcineurin inhibitor-associated nephrotoxicity has recently gained focus. To assess the impact of the conversion to sirolimus, we performed a retrospective audit on renal transplant patients switched to sirolimus at the Inkosi Albert Luthuli Central Hospital (South Africa) from 2003 until June 2007.

Materials and Methods: Medical records of transplant recipients were analyzed. Twenty-four–hour urine protein excretion and estimated glomerular filtration rates before initiation of sirolimus (baseline), and at their last clinic visit, were compared. Patients were then subcategorized according to their specific indications for switching to sirolimus.

Results: Thirty patients were included. Average follow-up was 25 months. Indications for use of sirolimus were group 1 (cyclosporine-induced biochemical toxicity, n=6); group 2 (chronic allograft nephropathy, n=6); group 3 (severe gum hypertrophy, n=9); group 4 (posttransplant diabetes, n=4); group 5 (calcineurin-inhibitor–induced histologic nephrotoxicity, n=2); and group 6 (calcineurin inhibitor associated malignancy, n=3). Average urine protein excretion rate and estimated glomerular filtration rate before starting sirolimus were 0.44 ± 0.08 g/24 h and 50.1 ± 3.1 mL/min respectively, compared to 0.94 ± 0.2 g/24 h and 52.1 ± 4.8 mL/min, at an average follow-up of 25 months. On subgroup analysis, estimated glomerular filtration rate was increased/unchanged in groups 1 (47.3 vs 51.16 mL/min) and 4 (60.0 vs 60.0 mL/min) when compared to baseline, but decreased in groups 2 (47 vs 27.6 mL/min), 3 (51.3 vs 42.2 mL/min), 5 (54.0 vs 29.5 mL/min), and 6 (60.0 vs 56.5 mL/min). Combining the latter 2 groups, most patients (80%) received sirolimus within 1 year of transplant, whereas only 2 patients in the former groups (10%) received the drug within 1 year of transplant.

Conclusions: Overall, sirolimus therapy was associated with improved estimated glomerular filtration rate, and also an increase in urine protein excretion rates. Maximum benefit was achieved when patients were switched to sirolimus within the first transplant year.

Key words: mTOR inhibitor, Kidney transplant, Estimated glomerular filtration rate

Introduction

After more than 2 decades of calcineurin-based immunosuppression for transplant, the limitations of calcineurin inhibitors are more and more apparent. Calcineurin inhibitor use in transplants has improved graft survival from 50% to 80% after 5 years. However, the long-term graft survival after 10 years is compromised by calcineurin nephrotoxicity; hence, the need to seek an alternative treatment.

Sirolimus, an mTOR inhibitor, offers that opportunity. We switched several of our patients to sirolimus. Recent studies have revealed an improvement in renal function after a switch from
calcineurin inhibitors to sirolimus (1, 2). However, de novo use of sirolimus in new transplants has been associated with an increased incidence of acute rejection (3).

In this retrospective study, we aimed to assess the efficacy and complications related to the use of sirolimus in renal transplant patients at the Inkosi Albert Luthuli Central Hospital. Sirolimus was introduced as a switch systematically after 3 months, or after a diagnosis of calcineurin-associated nephropathy, or other indications including posttransplant diabetes mellitus and malignancy.

Sirolimus was first introduced as an alternate immunosuppressant in renal transplant. It was shown to be effective and nonnephrotoxic, when compared with cyclosporine in the context of either azathioprine or mycophenolate mofetil (3, 4). A short while later, both sirolimus and everolimus were associated with an increase in calcineurin-inhibitor nephrotoxicity due to the inhibition of p-glycoprotein, leading to intrarenal accumulation of cyclosporine (2, 5, 6).

In a hemodynamic study, Dieckman and associates reported that cyclosporine withdrawal is associated with afferent arteriolar vasodilatation and an increase in glomerular hydrostatic pressure, leading to hyperfiltration that may result in glomerular proteinuria (5). Currently, experimental and clinical evidence reveals that hyperlipidemia may be associated with the induction or progression of proteinuria (7, 8). Sirolimus-induced hyperlipidemia may be causative. Rapamycin causes cell cycle arrest; not only in B lymphocytes and T lymphocytes (preventing acute rejection), but also in endothelial mesangial tubular cells (9, 10). Evidence also exists that in renal tissue injury, sirolimus may inhibit tubular cell proliferation and promote their apoptosis (11). This indicates a possible tubular origin for the proteinuria as well.

Materials and Methods

Patients

Medical records from all renal allograft recipients receiving sirolimus-based immunosuppression, treated from December 2002 to June 2007, were included and reviewed. There were 22 men and 8 women; 8 patients were black, 16 were Indians, 5 were white, and 1 was colored (mixed race). In a further analysis, patients were subcategorized based on (1) specific indication for conversion to sirolimus-based therapy; (2) duration of prior calcineurin inhibitor exposure; and (3) data on the use of angiotensin-converting enzyme inhibitor and angiotensin receptor blockers were collected.

Methods

This is a retrospective analysis of renal function and proteinuria of renal transplant patients attending the Inkosi Albert Luthuli Central Hospital in Durban, South Africa.

Assessment of the evolution of renal function

Serum creatinine was measured with a well-established method the alkaline picrate method, using a Siemens machine (Siemens, Erlangen, Germany) (12). The estimated glomerular filtration rates were calculated using the Modification of Diet in Renal Disease study equation and recorded (13). Assessment was done before and after conversion to sirolimus and at the last clinic visit within the study period.

Assessment of protein excretion

Twenty-four hour urine was collected, and protein concentration was measured using the dye-binding method Advia Siemens (Siemens, Erlangen, Germany) as previously described (14). The total 24-hour protein excretion was recorded and analyzed according to patient groups.

Statistical analysis

Graphpad Instat 3 software (San Diego, CA, USA) was used to make the calculations, and to compare results of various groups of patients. Values before and after conversion were compared using a Wilcoxon signed rank test. For unpaired data, the Mann-Whitney U test was used. Values for \( P < .05 \) were considered to be statistically significant.

Results

Overall results

Thirty-three patients received sirolimus during the study period. Three patients were excluded because of drug discontinuation, 1 for a rapid decline in renal function, 1 for interstitial lung disease, and 1 for severe electrolyte disturbances that resolved after discontinuation of sirolimus. Thirty patients were included. The mean follow-up was 25.4 ± 2.7 months.
The distribution of patients according to kidney source was 17 living-related kidney transplants, 10 deceased-donor transplants, and 3 living-unrelated donor transplants. The average duration of calcineurin inhibitor exposure was 47.7 ± 8.3 months (cyclosporine, n=26; tacrolimus, n=4).

**Indications for conversion to sirolimus**

Table 1 summarizes the indications for conversion to sirolimus. At the start of the study, 26/30 patients were on ACE-I therapy. The indications for ACE inhibitors were hypertension, proteinuria, or both.

For estimated glomerular filtration rate, the overall estimated glomerular filtration rate increased over the study period from 50.1 ± 3.1 (baseline) to 52.1 ± 4.8 mL/min (study end) \((P = .51, \text{NS})\). They included 17/30 patients who had an increase in estimated glomerular filtration rate, while 13/30 had a decrease in estimated glomerular filtration rate (Figure 1).

For 24-hour urine protein excretion, overall, the total proteinuria was 0.44 ± 0.08 g/24 h at baseline. At 13.4 months, total proteinuria was 0.56 ± 0.1 g/24 h \((P = .39, \text{NS})\), while at 25.4 months, it rose to 0.94 ± 0.2 g/24 h \((P = .02)\) (Figure 1).

**Subgroup analysis**

The most-favorable response to sirolimus conversion was obtained in groups of patients transferred because of cyclosporine biochemical toxicity or tacrolimus-induced posttransplant diabetes mellitus. On combining groups 1 and 4 above, 80% of patients \((n=10)\) were converted 1 year after the transplant \((\text{ie, < 1 year of calcineurin inhibitor exposure})\) (Table 1).

In groups 2, 3, 5, and 6, only 20% \((n=20)\) were converted within 1 year of calcineurin inhibitor exposure (Table 1). All patients that converted before 12 months of calcineurin inhibitor exposure were compared to patients on calcineurin inhibitors for more than 12 months of treatment (Table 2). Thirteen patients before 12 months \((27.3 ± 4.6 \text{ months of sirolimus treatment})\), 17 patients converted after 12 months \((23.9 ± 3.4 \text{ months of sirolimus treatment}); \text{that is, no significant change in 24-h urine protein excretion or estimated glomerular filtration rate (Table 2; Figures 1, 2).}

**Effect of baseline proteinuria**

In 2005, with the data on the proteinuric effects of sirolimus expanding, it was suggested that the drug not be used in patients with baseline proteinuria greater than 800 mg/d. The evolution in patients with baseline proteinuria less than 800 mg/day \((n=24)\) was compared with that of patients with a

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**Table 1. Summary of protein excretion and estimated glomerular filtration rate according to patient group.**

<table>
<thead>
<tr>
<th>Subgroup (n)</th>
<th>CNI duration (mo)</th>
<th>TP (baseline) g/d</th>
<th>TP (end) g/d</th>
<th>eGFR (baseline) mL/min</th>
<th>eGFR (end) mL/min</th>
<th>SRL duration (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CNI biotoxicity (6)</td>
<td>34.6</td>
<td>0.20</td>
<td>0.26</td>
<td>44.5</td>
<td>56.7</td>
<td>19</td>
</tr>
<tr>
<td>2. CAN (6)</td>
<td>52.1</td>
<td>0.59</td>
<td>1.44</td>
<td>39.5</td>
<td>29.8</td>
<td>25.8</td>
</tr>
<tr>
<td>3. Gum H (9)</td>
<td>60.3</td>
<td>0.56</td>
<td>1.55</td>
<td>49.1</td>
<td>48.1</td>
<td>25.3</td>
</tr>
<tr>
<td>4. PTDM (4)</td>
<td>4.5</td>
<td>0.43</td>
<td>0.21</td>
<td>78.5</td>
<td>91.8</td>
<td>34.2</td>
</tr>
<tr>
<td>5. CSA (2) HistoTox</td>
<td>5.5</td>
<td>0.14</td>
<td>0.77</td>
<td>39.5</td>
<td>29.5</td>
<td>43.5</td>
</tr>
<tr>
<td>6. PT Malig (3)</td>
<td>112.6</td>
<td>0.44</td>
<td>0.53</td>
<td>55.0</td>
<td>62.0</td>
<td>13.6</td>
</tr>
</tbody>
</table>

**Abbreviations:** CNI, calcineurin inhibitor; CAN, chronic allograft nephropathy; CSA Histo Tox, cyclosporine histology proven toxicity; Gum H, gum hypertrophy; PTDM, posttransplant diabetes mellitus; PT Malig, posttransplant malignancy; SRL, sirolimus.

**Table 2. Comparison of protein excretion and estimated glomerular filtration rate according to timing of conversion to sirolimus.**

<table>
<thead>
<tr>
<th>Conversion</th>
<th>Conversion</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>before 12/12</td>
<td>after 12/12</td>
<td></td>
</tr>
<tr>
<td>Baseline (mean TP)</td>
<td>0.37 ± 0.1 g/24 h</td>
<td>0.49 ± 0.1 g/24 h</td>
</tr>
<tr>
<td>End (mean TP)</td>
<td>0.38 ± 0.08 g/24 h</td>
<td>1.37 ± 0.35 g/24 h</td>
</tr>
<tr>
<td>(increment) Baseline (mean eGFR)</td>
<td>55.0 ± 5.9 mL/min</td>
<td>46.4 ± 3.1 mL/min</td>
</tr>
<tr>
<td>End (mean eGFR)</td>
<td>63.2 ± 7.6 mL/min</td>
<td>43.6 ± 5.7 mL/min</td>
</tr>
</tbody>
</table>

**Figure 1. Urine protein excretion and estimated glomerular filtration rate in patients switched to sirolimus at 12 months before transplant.**

**Figure 2. Urine protein excretion and estimated glomerular filtration rate in patients switched to sirolimus 12 months after baseline.**
baseline proteinuria greater than 800 mg/d (Figure 3). Calcineurin inhibitor exposure was 12/30 patients with baseline urine protein excretion less than 800 mg/d. This was converted to 12 months before calcineurin inhibitor exposure showed a beneficial effect (Figure 2).

Discussion

Overall, sirolimus treatment was associated with an improvement in estimated glomerular filtration rate and a significant increase in urine protein excretion rates. This is consistent with the findings in larger prospective studies above (15, 16, 17). Conversion before 12 months to calcineurin inhibitor treatment was associated with a stabilization of renal function. Even conversion in patients with low baseline proteinuria (< 800 mg/d) was associated with a significant increase in urine protein excretion at the study end. The best outcome was seen in patients with a low baseline urine protein excretion (< 800 mg/d) who were converted before 12 months of calcineurin inhibitor therapy.

Recently, data on de novo appearance or worsening of pre-existing proteinuria in patients converted to sirolimus-based therapy has accumulated (5, 9, 15). Morelon and associates reported 50 patients who were switched to sirolimus, mainly for calcineurin-associated nephropathy (CAN), 32/50 had improved renal function (18). But 32/50 had new onset of proteinuria, with 18/32 having nephrotic range proteinuria (15).

Only 6 responded to ACE-I Rx. Bumbea and associates converted 43 patients to sirolimus, overall stabilization of renal function was achieved after 2 years (1). One-third of patients acquired de novo proteinuria (> 1 g/d), with 5 in that nephrotic range.

Patients with baseline proteinuria (< 800 mg/d) had a value of 90% in predicting a successful response when switching patients to sirolimus (2). However, the exact origin of the proteinuria is still unknown.

Schena and associates, in a recent publication on the CONVERT trial, reported that conversion from calcineurin inhibitor to sirolimus was most beneficial when the glomerular filtration rate was more than 40 mL/min (19). We have recorded a similar observation in our study. Patients who switched for calcineurin inhibitors to sirolimus with estimated glomerular filtration rate below 40 mL/min, recorded a marked deterioration of their renal function, while those with a higher estimated glomerular filtration rate had improved or marginal decrease in estimated glomerular filtration rate.

Calcineurin-associated nephropathy is a major cause of long-term renal allograft loss. Long-term calcineurin inhibitor exposure is one of the most significant predisposing factors. Histologic changes in calcineurin-inhibitor–induced nephrotoxicity may be observed as early as 3 months after the transplant. The average duration of calcineurin inhibitor prescription before conversion in the study population was approximately 48 months. Although only 8 patients underwent biopsy showing evidence of CAN/calcineurin inhibitor toxicity; 48 months may very well be sufficient time for subclinical calcineurin-inhibitor–induced graft injury to develop.

Conversion to sirolimus with a background of prolonged calcineurin inhibitor exposure and possible graft injury may thus induce/contribute to proteinuria. Timing of conversion may be a more significant predictor than baseline proteinuria in determining a positive outcome to sirolimus-based therapy.

References


