

## BENEFICIAL EFFECT OF LOW DOSE CYCLOSPORINE WITH MMF (MYCOPHENOLATE MOFETIL) IN RENAL ALLOGRAFT RECIPIENTS

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### ABSTRACT

**Background:** Calcineurin inhibitors (CNI) have significantly reduced the incidence of acute rejection. Nephrotoxicity however may contribute to long-term allograft dysfunction. Mycophenolate mofetil (MMF) may allow cyclosporine (CsA) dose reduction without increasing the risk of rejection.

**Methods:** In seventy-eight living unrelated kidney transplant patients with renal dysfunction, we studied the effect of CsA dose reduction in association with MMF on renal function and cardiovascular risk profile.

**Results:** We reduced the cyclosporine dose from mean  $3.5 \pm 0.94$  mg/kg/d to  $2 \pm 0.51$  mg/kg/d,  $p < 0.0001$ . Mean follow up duration was  $22.99 \pm 8.98$  weeks. The reduction of CsA was associated with decrement of median serum creatinine from  $1.7 \pm 0.99$  mg/dL to  $1.3 \pm 0.52$  mg/dL,  $p < 0.0001$ . We found improvement in lipid profile, mean cholesterol level from  $212.73 \pm 41.72$  to  $199.69 \pm 37.33$  mg/dL,  $p < 0.002$  and also with triglyceride from  $195.28 \pm 92.21$  to  $167.64 \pm 60.82$  mg/dL,  $p < 0.005$ . No rejection episodes occurred, and an improvement in systolic and diastolic pressure was observed from  $131.41 \pm 21.26$  to  $127.83 \pm 17.53$  mm/Hg,  $p < 0.01$  and from  $82.82 \pm 13.15$  to  $78.88 \pm 8.3$  mmHg,  $p < 0.03$  respectively. No significant difference in plasma uric acid level was observed after CsA reduction,  $p < 0.06$ .

**Conclusion:** This study suggests that CsA reduction is safe and is not associated with an increased risk of acute rejection. It also has the potential to improve allograft function and appears to reduce cardiovascular risk factors such as hypertension and hyperlipidemia.

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**Keywords:** Cyclosporine-Mycophenolate Mofetil-Graft survival-Chronic Nephropathy- Hyperlipidemia.

### INTRODUCTION

Calcineurin inhibitors (CNI) have significantly re-

duced the incidence of acute rejection. Nephrotoxicity however may contribute to long-term allograft dysfunction. The nephrotoxicity of calcineurin inhibitors is an important factor in the pathogenesis of chronic allograft nephropathy. Furthermore, CNI have adverse cardiovascular side effects that may contribute to morbidity and mortality in renal allograft recipients.<sup>1,2</sup> Thus, CNI, de-

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spite their unquestioned efficacy in improving short-term survival following organ transplantation, have the potential to adversely affect long-term outcomes. In general, the nephrotoxicity of calcineurin inhibitors can be classified as acute, functional and dose dependent in renal plasma flow (RPF) and glomerular filtration rate (GFR) or chronic structural changes and dose independent interstitial fibrosis.<sup>3</sup> Cyclosporine (CsA)-associated renal fibrosis has been related to the overproduction of transforming growth factor (TGF- $\beta$ 1), a fibrogenic cytokine. Mycophenolate mofetil (MMF) may allow CsA reduction without increasing the risk of rejection.

Mortality and morbidity due to cardiovascular problems and chronic renal graft dysfunction remain high.<sup>4</sup> This is probably related to hypertension, renal dysfunction, hyperuricemia and dyslipidemia. All of which are aggravated by CsA. MMF is a potent and specific inhibitor of purine biosynthesis and hence, T and B lymphocyte proliferation. There is some evidence that MMF in combination with a reduced dose of cyclosporine is an effective regimen for the treatment of established chronic allograft nephropathy.<sup>5</sup>

We therefore studied the effect of CsA dose reduction with MMF on renal function, blood pressure, lipid profile and anti-rejection efficacy in patients with slow deterioration of allograft function.

### PATIENTS AND METHODS

This study was a single center, prospective clinical trial. Adult renal transplant recipients who underwent first or second living unrelated kidney transplant were regularly monitored. Inclusion criteria included patients with slow deterioration of allograft rejection, based on clinical symptoms, signs and laboratory abnormalities (serum creatinine). They were maintained on a conventional triple-immunosuppressive regimen (CsA, MMF, and prednisolone).

Blood samples were used to measure creatinine, triglycerides, cholesterol, and uric acid, before and after CsA reduction.

Another follow up was measurement of blood pressure. All results are expressed as mean $\pm$ standard deviation (SD). Statistical analysis was performed using the Student's t-test for paired data and the relationship between variables was analyzed using linear regression analysis. A  $p$  value $<$ 0.05 was considered significant.

### RESULTS

A total of 78 patients were enrolled in the study, 46 (59%) men and 32 (41%) women. Mean age was 36.29 $\pm$ 13.24 years. We reduced the cyclosporine dose

(from mean 3.5 $\pm$ 0.94 mg/kg/day to 2 $\pm$ 0.5 mg/kg/day,  $p$  $<$ 0.0001). Mean follow up duration was 22.93 $\pm$ 8.98 weeks. The reduction of CsA was associated with a decrement of median serum creatinine levels (from 1.7 $\pm$ 0.99 (1.4-7.9) mg/dL to 1.3 $\pm$ 0.52 (0.6-5.3) mg/dL,  $p$  $<$ 0.0001). We found improvement in lipid profile in all patients.

There was a significant decrease in serum cholesterol concentration (from 212.73 $\pm$ 41.72 to 199.69 $\pm$ 37.33 mg/dL,  $p$  $<$ 0.002), and also with triglyceride (from 195.28 $\pm$ 92.21 to 167.64 $\pm$ 60.82 mg/dL,  $p$  $<$ 0.003). No rejection episodes occurred, and an improvement in systolic and diastolic pressure was observed (from 131.41 $\pm$ 21 to 127.83 $\pm$ 17.53 mmHg,  $p$  $<$ 0.01, and from 82.82 $\pm$ 13.15 to 78.88 $\pm$ 83 mm/Hg,  $p$  $<$ 0.03, respectively).

No significant difference in plasma uric acid level was observed after CsA reduction ( $p$  $<$ 0.06) (Table I).

### DISCUSSION

The result of this short-term prospective study suggests that the addition of MMF allows a reduction of CsA without increasing the incidence of acute rejection. This is supported by the following observation, that low exposure of CsA in association with MMF leads to similar inhibition of calcineurin activity and cytokine production. Our finding suggests that very low dose CsA associated with MMF may attenuate nephrotoxicity without entailing a risk of under-immunosuppression.<sup>6</sup>

CsA reduction was followed by only one episode of acute reversible rejection in the study of Moarad et al. two years after CsA reduction.<sup>7</sup>

In the study of Almondet, long-term CsA dose under 4 mg/kg/day was shown to be a risk factor for chronic rejection. Some evidence suggests that a decrease in or withdrawal of CNI therapy may ameliorate progressive renal dysfunction. In the study of Matthew et al, long term CsA reduction or discontinuation was deemed necessary to slow the rate of loss of renal function in patients with deterioration of renal function. This intervention is safe, well tolerated and associated with a minimal incidence of acute rejection.<sup>8</sup> In stable patients more than one year post transplant who receive CsA, prednisone and MMF, a strategy consisting of 50% CsA reduction is safe, has the potential to improve short-term allograft function and appears to reduce cardiovascular risk factors such as hypertension and hyperlipidemia.<sup>9</sup>

In our population no episode of acute rejection or chronic rejection developed after CsA reduction. In addition to the improvement in renal function, change in a number of other laboratory parameters was also observed. Total cholesterol and triglyceride levels were significantly reduced, consistent with the known hyperlipidemic effect of CsA. There was a trend toward lower

**Table I.** Clinical parameters before and after CsA reduction.

	Before CsA reduction	After CsA reduction
Mean CsA dose (mg/kg/d)	3.5± 0.94	2± 0.51
Median serum creatinine (mg/dL)	1.7± 0.99	1.3± 0.52
Mean triglyceride (mg/dL)	195.28± 92.21	167.64± 66.82
Mean cholesterol (mg/dL)	212.73± 41.72	199.69± 37.33
Mean systolic pressure (mmHg)	131.41± 21.62	126.65± 13.64
Mean diastolic pressure (mmHg)	82.82 ±13.15	79.88± 8.3
Mean uric acid (mg/dL)	6.81± 1.63	6.49± 1.52

blood pressure.

CsA reduction in patients with a stable renal function is accompanied by a decrease in systolic blood pressure, improvement of lipid profile and hyperuricemia.<sup>10</sup> Total CsA withdrawal is associated with improved renal function and reduced systolic and diastolic blood pressure, but no significant improvement in cholesterol and triglyceride levels.<sup>11</sup> In Ducloux's study with a mean follow up of 12±2 months, CsA withdrawal with a concomitant switch from AZA to MMF seemed to be safe and allows a substantial improvement in renal function, hypertension and hyperlipidemia.<sup>12</sup> Reduced uric acid excretion can occur after renal transplantation, leading to hyperuricemia. This problem is common with cyclosporine. The lower GFR induced by cyclosporine probably plays a contributing role in uric acid retention, but tubular damage may also be important by impairing urate secretion. The CsA withdrawal studies of Schnuelle et al. showed that uric acid levels decreased with withdrawal or dosage reduction of CsA.<sup>13</sup> In our study, there was no significant decrease of uric acid after CsA reduction. In summary, our study found that reduction in CsA dosage, with the concomitant use of MMF, was not only safe but also improved renal allograft function, hyperlipidemia, and systolic and diastolic blood pressure. However, larger clinical trials with longer follow up may be needed to further evaluate the effect of CsA reduction.

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