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# Early or delayed onset of cyclosporine by sequential immunosuppression?

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**Abstract.** In a prospective randomized trial, 57 renal transplant patients (group A) received a sequential course of 14 days conventional immunosuppression (anti-lymphocyte globulin (ALG), azathioprine and steroids) and cyclosporine and steroids thereafter, while 57 patients (group B) received the conventional immunosuppression for 2 days followed by cyclosporine and steroids. In group A, ALG was tolerated for a mean of 7.8 days while, in group B, conventional therapy had to be changed to cyclosporine therapy after a mean of 2.1 days due to ALG intolerance. Patient survival rates 1 and 2 years after transplantation were 95% and 92% in group A and 96% and 92% in group B, and graft survival rates were 79% and 79% in group A and 89% and 82% in group B. In group A, the dialysis frequency in the second, third and fourth weeks after transplantation was significantly higher than in group B. Serum creatinine 1 year post-transplant showed no significant difference between the two groups.

**Key words:** Renal transplantation – Cyclosporine – Immunosuppressive therapy – Anti-lymphocyte globulin intolerance

It was the purpose of this study to define the most favourable moment for a change from conventional immunosuppression to cyclosporine therapy.

## Patients and methods

A total of 114 patients receiving primary cadaver renal transplants were included in a prospective study. The patients were randomly divided into two groups and none was excluded from the study. The patients in group A ($n = 57$) received conventional immunosuppression consisting of azathioprine, steroids and ALG for 14 days after transplantation. Subsequently azathioprine and ALG were replaced with cyclosporine. The patients in group B ($n = 57$) received azathioprine, steroids and ALG for only 2 days post-transplant. Thereafter cyclosporine was given instead of ALG and azathioprine.

When ALG intolerance or fever exceeding 39 °C occurred the conventional treatment was replaced with cyclosporine.

### *Treatments*

*ALG therapy.* ALG (anti-lymphocyte globulin, Institut Mérieux) was administered at 5 ml/10-kg body weight, maximum 30 ml/day, by a central venous line using continuous mechanical infusion.

*Steroid therapy.* All patients received 250 mg prednisolone on the first day post-transplant. The dosage was tapered daily in increments of 25 mg to 100 mg, and then every other day in increments of 5 mg, until a permanent dose of 5–10 mg per day was achieved. In cases of graft rejection, a daily dose of 0.5 g methylprednisolone was given 3–5 times.

*Azathioprine therapy.* A maximum of 3 mg/kg body weight per day was administered while white blood cell counts and platelet counts were monitored. A white blood cell count of less than 3000, and a platelet count of less than 80000/mm$^3$ were considered the lower limits.

*Cyclosporine therapy.* Cyclosporine was initiated at 8–10 mg/kg body weight per day in two doses to achieve whole-blood trough levels of 300 ng/ml assessed by radioimmunoassay (RIA). Cyclosporine was tapered in increments of 1 mg/kg per day when the whole-blood trough levels were exceeded 300 ng/ml.

*Perioperative antibiotic prophylaxis.* All patients received a perioperative dose of 1.5 g cefuroxime.

### *Statistical analysis*

The cumulative patient and transplant survivals were analysed using the Kaplan-Meier method. Frequencies of dialysis, rejection episodes and kidney function were analysed by linear regression.

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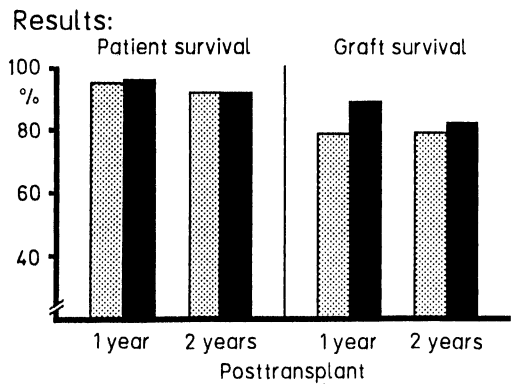


**Fig. 1.** Patient and transplant survival after early or delayed onset of cyclosporine by sequential immunosuppression. ▨, group A; ■, group B

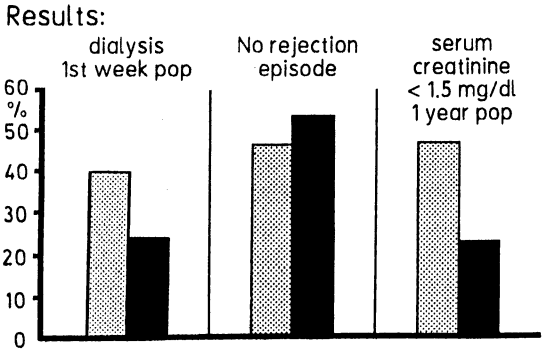


**Fig. 2.** Frequencies of dialysis, rejection episodes and kidney function in relation to early or delayed onset of cyclosporine by sequential immunosuppression. ▨, group A; ■ group B

## Results

Donor data and recipient data did not differ significantly between the two groups with regard to donor age, kidney function and preservation time. All kidneys were stored hypothermicly in Euro-Collins solution. The recipient age and the time between onset of dialysis and transplantation were not significantly different between the two groups, and the HLA-DR histocompatibilities were comparable between the groups.

### *Patients and transplant survival*

Patient survival rates (Fig. 1) 1 and 2 years after transplantation were 95 % and 92 % in group A, and 96 % and 92 % in group B. The graft survival rates in group A were 79 % and 79 %, and in group B 89 % and 82 %. In group A the dialysis frequency (Fig. 2) in the second, third and fourth week postoperatively was significantly higher than in group B.

### *ALG treatment*

The mean time of ALG administration in group B was 2.1 days, but was 7.8 days in group A.

## Discussion

In the present study, we sought to determine whether the nephrotoxic side effects of cyclosporine could be avoided by delaying its use in the early post-transplant period. Conventional immunosuppression was applied immediately after transplantation, assuming that in this phase the kidney, having been subjected to cold and warm ischaemia, is especially susceptible to the nephrotoxicity of cyclosporine.

Early conventional immunosuppression and early preceding cyclosporine therapy gave excellent results. Our findings confirm that an early beginning of cyclosporine therapy showed good results.

## Conclusion

Patient survival, graft survival, kidney function and rejection episodes showed no significant differences between the two groups. However, the frequency of dialysis was significantly lower in group B. A delayed onset of cyclosporine therapy showed no better results than early cyclosporine therapy.