THE USE OF CYCLOSPORINE ONLY IN CADAVERIC
RENAL TRANSPLANT RECIPIENTS: CONVERSION TO
PREDNISOLONE AND AZATHIOPRINE AFTER
FOUR MONTHS

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Summary

After conversion from cyclosporine (Cys) only to prednisolone and azathioprine four months after cadaveric renal transplantation, effective renal plasma flow (ERPF), glomerular filtration rate (GFR) and filtration fraction (FF) all improve. However, this improvement is not uniform. GFR and FF improve in all patients after one week of combined Cys and prednisolone treatment. ERPF improves under the same circumstances only in recipients without previous rejection episodes. After discontinuation of Cys and addition of azathioprine ERPF improves further in all patients. These findings suggest the presence of a low grade rejection, together with Cys nephrotoxicity. The conversion procedure seems to be safe at least during a follow-up period of 9–14 months.

Introduction

The results of cadaveric renal transplantation are improved by the use of Cys as the only immunosuppressive agent. However, renal function was worse in these cadaveric renal transplant patients than in conventionally treated cadaveric renal transplant patients [1,2]. Elective conversion three months after grafting from Cys to prednisolone and azathioprine was followed by improvement in renal function without serious side-effects [3]. In an attempt to improve renal function, elective conversion four months after transplantation was carried out in our cadaveric renal transplant patients. The improvement in renal function was monitored by serial determinations of ERPF and GFR before, during and after conversion.

Patients and methods

Forty-four cadaver renal transplant patients were treated with Cys alone during the first four months after grafting. Rejection episodes were diagnosed on clinical grounds such as tenderness and enlargement of the graft, serial ultrasonographic
studies and a rise in serum creatinine levels for more than two days despite a decrease in the Cys doses. In addition one to three percutaneous renal biopsies were done in 31 of 44 cadaveric renal transplant patients. Rejection episodes were treated with 3 x 1g of Solu-Medrol intravenously per rejection episode on three consecutive days. If more than three rejection episodes occurred, cadaver renal transplant patients were converted to prednisolone and azathioprine. Otherwise, patients were treated with Cys only for four months post-operatively.

Elective conversion was carried out by adding 20mg prednisolone daily to the Cys therapy over one week. Thereafter Cys was replaced by azathioprine, 1.5mg/kg body weight, while 20mg of prednisolone was continued.

ERPF and GFR were determined by continuous simultaneous infusion of $^{131}$I-hippurate and $^{125}$I-thalamate, respectively. Each investigation was carried out over a period of six hours. After an equilibration period of two hours urine and blood samples were collected twice over the remaining two periods of two hours [4]. FF was calculated by GFR : ERPF.

ERPF and GFR were measured one month and just before administration of prednisolone to Cys, after one week of prednisolone together with Cys, one week after cessation of Cys and finally, six weeks later on the same dose of prednisolone and azathioprine.

**Results**

Twenty-one of 44 cadaver renal transplant patients were converted from Cys to prednisolone and azathioprine before the fourth post-operative month because of more than three rejection episodes (n=16), technical problems or prolonged post-operative oliguria (n=5). Four of 44 cadaver renal transplant patients were kept on permanent Cys therapy. Finally, one patient was successfully converted after four months without ERPF and GFR determinations. His renal function measured by serum creatinine concentrations and creatinine clearances improved.

The course of the ERPF and GFR in the remaining 18 cadaver renal transplant patients during and after conversion from Cys to prednisolone and azathioprine four months after grafting is shown in Figures 1a and 1b. Six of 18 cadaver renal transplant patients, shown in the upper curves had no rejection episodes, while 12 of 18 cadaver renal transplant patients (lower curves) had one to three rejection episodes. During the last month before conversion ERPF and GFR remained stable in both groups. Also before conversion ERPF and GFR were the same in cadaver renal transplant patients with or without rejection episodes. After one week of 20mg prednisolone together with Cys, GFR improved in both groups of cadaveric renal transplant patients (p<0.05 and p<0.02, respectively). ERPF, however, improved only in cadaveric renal transplant patients without rejection episodes (p<0.05). One week after replacement of Cys by azathioprine, a further rise in GFR was observed in all cadaveric renal transplant patients. In contrast to the previous period a rise of ERPF was observed in all patients. At one week after replacement of Cys by prednisolone and azathioprine the mean ERPF and GFR were again the same in cadaver renal transplant patients with or without rejection episodes.
Figure 1a. The course of ERPF before, during and after conversion from Cys to prednisolone and azathioprine four months post-transplantation. Top curve: six patients without previous rejection episodes. Bottom curve: 12 patients with one to three rejection episodes.
Figure 1b. The course of GFR before, during and after conversion from Cys to prednisolone and azathioprine four months post-transplantation. Top curve: six patients without previous rejection episodes. Bottom curve: 12 patients with one to three rejection episodes.
In Figure 2 our data are expressed as percentage change of ERPF, GFR and FF over every period during conversion. The data concerning ERPF and GFR are the same as mentioned above, but a rise of FF is also observed in all cadaver renal transplant patients during steroid treatment together with Cys.

No kidneys were lost after elective conversion during the observation period of 9–14 months. Only one patient developed an acute rejection, reversible with oral prednisolone. No other complications occurred. A total of four of 44 patients lost their kidneys due to rejection or technical complications. The overall patient survival was 100 per cent.
Discussion

One week after adding 20mg of prednisolone to Cys four months after cadaveric renal transplantation we observed a significant rise in GFR and FF in all cadaver renal transplant patients, together with a rise in ERPF in cadaver renal transplant patients without previous rejection episodes. This finding suggests the presence of a subclinical, steroid sensitive rejection. In particular the rise in the FF during this period is in accordance with our earlier observation that a low FF points to an impending rejection [5]. The fact that ERPF, GFR and FF were stable during the last month before conversion makes spontaneous improvement unlikely. On the other hand it is also possible that steroids counteract Cys nephrotoxicity. Cessation of Cys led to a further increase of ERPF and GFR in all cadaver renal transplant patients as a possible sign of resolving Cys nephrotoxicity. Studies in experimental animals and in heart transplant patients on long-term Cys therapy have shown morphological and functional proximal tubular abnormalities [6–8]. $^{131}$I-hippurate is mainly excreted by the proximal tubules. Therefore, our observation that ERPF is depressed during Cys treatment can at least be partially explained by these morphological findings. Unfortunately, we did not measure $^{131}$I-hippurate excretion. The difference in the recovery of the ERPF between cadaver renal transplant patients with or without rejection episodes is difficult to understand. An explanation could be a different degree of Cys nephrotoxicity in the two groups of cadaver renal transplant patients. The clinical results in terms of graft and patient survival after elective conversion are satisfactory without significant clinical complications.

References

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8 Moran M, Newton L, Perlooth M et al. Kidney Int 1984; 25: 1