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# Cyclosporin A (CsA) and azathioprine (AZA) combination in renal allografts with CsA nephrotoxicity

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Cyclosporin A (CsA) is a potent immunosuppressive drug whose effect is well known in the organ transplantation field. Treatment with CsA reduces the incidence of rejection and improves graft survival after renal transplantation (RT). However, to set against the clear advantages of CsA, a most important problem is nephrotoxicity [1, 3]. Scientists are therefore seeking new non-nephrotoxic Cs derivatives, but the search has not yet borne fruit.

Teams working in organ transplantation attempt to avoid nephrotoxicity by switching to conventional treatment with azathioprine (AZA), starting 1, 3 or 6 months after transplantation [8, 11]. Conversion from CsA to AZA has not always been successful due to the high incidence of rejection [4]. AZA has also been started immediately after transplantation in combination with CsA at low doses [5], and in some instances no CsA is administered when oliguric acute tubular necrosis is present [10].

In a previous report [2], we presented the short-term results of the treatment with a CsA–AZA combination, reducing the CsA dose and giving a moderate dose of AZA in 21 transplanted patients not achieving acceptable graft function. In the present study we analysed the long-term results in a group of patients whose kidney biopsy examination results were compatible with CsA nephrotoxicity.

**Key words:** Renal transplantation – Nephrotoxicity – Cyclosporin toxicity

## Material and methods

Between March 1984 and March 1990, 377 patients who had received a RT in our hospital were treated with CsA–prednisone (PNS) or CsA–antilymphocyte globulin–PNS (CsA–ALG–PNS). The first group of patients received oral CsA 14 mg/kg per day, tapered according to whole blood levels (polyclonal RIA, $n = 300$–800 ng/ml) and PNS 0.25 mg/kg per day. The second group of patients received oral CsA 8 mg/kg per day, tapered according to blood levels, a maximum of six alternate-day doses of 10 mg/kg per day horse ALG, or less if CsA levels were higher than 400 ng/ml, and PNS 0.25 mg/kg per day. Acute rejection (AR) episodes were treated in the first group with three boluses of endovenous methyl-PNS, 0.5 g/day, and with oral PNS, 3 mg/kg per day tapered to 1 mg/kg per day in 1 week and to 0.25 mg/kg per day in 1 month, in the second group.

In 44 of these 377 patients (11.6%), graft function did not achieve an optimal level, with plasma creatinine remaining over 250 µmol/l in a period of 1 to 24 months after RT, in spite of normal CsA blood levels. Because of this, we decreased the CsA dose and added azathioprine (1.01 ± 0.18 mg/kg per day). All the patients received oral co-trimoxazole (one tablet 480 mg every 12 h) when AZA was started, maintaining this treatment during a 3 month period.

Renal percutaneous biopsies were examined by optic, electronic and immunofluorescence microscopy, according to usual techniques. Statistical analyses were performed using the Wilcoxon test.

## Results

We studied 44 patients, 28 male and 26 female, mean age 34 ± 12 years. All but one received a cadaver kidney, and two patients underwent a second transplantation. There were no significant differences in age, cold and warm ischaemia time or HLA matching (AB matches 1.5 ± 1.3, DR matches 1.2 ± 0.5) with respect to a control group of 88 randomly selected patients treated with CsA in the same period.

Five patients presented with AR before the drug combination treatment. The general incidence of AR was 34% with the CsA–PNS treatment protocol and 16% with the CsA–ALG–PNS treatment protocol. Biopsy-proven chronic rejection occurred in 16 patients and recurrent or transplant glomerulopathies in another five. *In this study we consider the remaining* **23 patients,** in whom the results of renal biopsy examination were compatible with CsA nephrotoxicity. In all of them we reduced the CsA dose and started AZA (1.01 mg/kg per day), 10.2 ± 16 months after RT.

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**Table 1.** CsA blood levels[a] before and after CsA–AZA combination treatment

| | Blood level (ng/ml ± SD) | *P* value |
|---|---|---|
| Before AZA association | 396 ± 169 | |
| After 6 months | 187 ± 67 | 0.0001 |
| After 12 months | 187 ± 75 | 0.0001 |
| After 24 months | 212 ± 76 | 0.001 |
| After 36 months | 140 ± 48 | 0.0005 |

[a] polyclonal RIA, $n$ = 300–800 ng/ml

**Table 2.** CsA dose before and after CsA–AZA combination treatment

| | CsA dose (mg/kg per day ± SD) | *P* value |
|---|---|---|
| Before AZA association | 5.1 ± 1.5 | |
| After 6 months | 2.7 ± 0.9 | 0.001 |
| After 12 months | 2.9 ± 1.2 | 0.0005 |
| After 24 months | 2.5 ± 1.03 | 0.0005 |
| After 36 months | 2.7 ± 1.05 | 0.001 |

**Table 3.** Plasma creatinine (μmol/l) before and after CsA–AZA combination treatment

| | Plasma creatinine (μmol/l ± SD) | *P* value |
|---|---|---|
| Before AZA association | 468 ± 228 | |
| After 6 months | 289 ± 184 | 0.012 |
| After 12 months | 236 ± 297 | 0.001 |
| After 24 months | 211 ± 67 | 0.0001 |
| After 36 months | 231 ± 81 | 0.008 |

CsA blood levels before, and at 6, 12, 24 and 36 months after, the combination treatment are shown in Table 1. CsA doses and plasma creatinine are shown in Tables 2 and 3. AR episodes after combination treatment were seen in two patients, one of whom lost the graft. No opportunistic viral, bacterial or other infections were observed in these patients. The number of urinary infection episodes decreased after the combination treatment (before 1.8 ± 1.43, after 1 ± 1.3).

In three patients we stopped AZA due to leucopenia, thrombopenia and a facial epithelioma 6 to 24 months after the combination treatment. Another two patients abandoned AZA treatment. After a 3-year follow-up, two out of the 24 patients (8.3%) had lost their graft due to AR and non-compliance. Five out of the 12 patients with a follow-up period of more than 4 years lost the graft due to chronic rejection ($n$ = 4) and transplant glomerulopathy ($n$ = 1). The remaining 17 patients have functioning grafts 40 ± 10 months after RT with a mean plasma creatinine of 231 ± 81 μmol/l after 34 ± 13 months of combination treatment.

## Discussion

The problem of CsA nephrotoxicity has been under discussion for many years. It is not clear whether conversion from CsA to AZA due to poor renal function improves renal allograft outcome [4]. Routine conversion is not always advisable due to the high risk of rejection and loss of graft function.

In order to avoid CsA nephrotoxicity some authors [6, 7, 9] have reported introducing varions induction treatments, such as triple therapy including CsA, AZA and PNS. In our experience the CsA–AZA–PNS combination has given good results, minimizing CsA nephrotoxicity and preserving long-term renal function. On the other hand infections or neoplasms have been suggested as very frequent complications associated with triple immunosuppression. In our patients urinary infections decreased after combination treatment, and other opportunistic infections were not present. Only one patient suffered a facial epithelioma, with a successful outcome after skin surgery and AZA withdrawal.

In conclusion we think that the CsA–AZA–PNS association is a simple alternative that, applied in an individualized and selective fashion, can reduce CsA nephrotoxicity, allowing an improvement in graft function, without increasing the risk of rejection or opportunistic infections.

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