Cyclosporin A Used Alone or in Combination with Low-dose Steroids in Cadaveric Renal Transplantation

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Summary. The actual survival rate of 25 primary cadaveric kidney grafts in recipients treated initially with cyclosporin A (CyA) alone was 84%. The survival rate in 37 patients under conventional immunosuppression was 76%. The mean number of dialyses required in the first 4 weeks after transplantation was 1.2 per patient in both groups. At 15–28 months posttransplant, mean serum creatinine levels have remained stable at 175 µmol/l in the CyA group.

The mean daily dose of steroids (including methylprednisolone i.v.) in the first two months was 2.07 mg/kg/d in patients under conventional immunosuppression and 0.76 mg/kg/d in the patients receiving CyA (p < 0.001).

The combination of CyA with low-dose steroids enabled the dose of CyA to be rapidly tapered off in once-weekly steps. CyA levels were monitored by determination of whole blood trough concentrations (target level: 300–800 ng/ml). At 60 days posttransplant the average dose of CyA was 6.0 ± 0.5 mg/kg/d compared with an average daily dose of 11.4 ± 0.9 as recommended for CyA alone in the protocol for the European multicentre study. This more rapid reduction in the CyA dose reduced nephrotoxicity (serum creatinine levels 174 ± 14 as compared with 289 ± 31 µmol/l) (p < 0.05) and almost halved the number of methylprednisolone pulses given up to the end of the second month.

We conclude from these results (1) that previously the dosage of CyA administered at this centre was probably too high, and (2) early adjustment of dose levels on the basis of blood concentrations and with low-dose prednisone cover appears to be safe and effective, but requires further verification.

Key words: Cyclosporin A – Steroid – Cadaveric renal transplantation – Nephrotoxicity

Introduction
It is no longer necessary to maintain all cadaveric kidney transplant recipients permanently on steroids. After the discovery of cyclosporin A (CyA), a polypeptide of fungal origin, by Borel et al. [1], Calne et al. were the first to achieve sustained functioning of primary cadaveric kidney transplants in recipients treated with CyA alone, without prednisone cover [2]. The superiority of this treatment regimen over conventional immunosuppression with azathioprine and prednisone has been confirmed in an European [3] and in an Australian study [18]. However, some authors combine CyA with low-dose prednisone, a regimen adapted in a Canadian multicentre trial ([4, 5, 11, 19, 20] and others).

In this paper we report our own experience with CyA alone and CyA in combination with prednisone and compare the results so obtained with those achieved previously by conventional immunosuppression.

Patients and Methods
In a series of 72 cadaveric kidney transplant recipients, three different immunosuppressive treatment protocols were compared: 1. conventional immunosuppression (n = 37 patients), 2. initial treatment with CyA alone (n = 25 patients) and 3. a combination of low-dose CyA and low-dose prednisone (n = 10 patients). All patients had received 5 or more blood transfusions before kidney transplantation. Moreover, 500 mg methylprednisolone was administered i.v. intraoperatively in every case.

The first two treatment groups comprised all 62 patients who had received primary cadaveric kidney transplants between...
1.1.1980 and 30.3.1982 at the Cantonal Hospital, Basle. No patients were excluded. The results in these two groups were analysed on April 1, 1983 by which date at least one year had elapsed since transplantation. It was therefore possible to calculate the actual one year survival.

The third group comprised all ten consecutive cadaveric kidney transplant recipients (9 primary transplants and 1 second transplant) between 1.1.1983 and 30.4.1983. The results for this group were analysed on 1.7.1983, i.e. at least 2 months after transplantation.

**Conventional immunosuppression** (conv. IS) consisted of azathioprine 1–3 mg/kg/day and prednisone starting at a dose of 100 mg/day then tapering off to a maintenance dose of 10–15 mg/day within 6–8 weeks. For the treatment of rejection methylprednisolone was administered i.v. at a dose of 0.5 g in 3 pulses or alternatively the oral dose of prednisone was increased to 300 mg and then tapered off again to the original dosage within 2–3 weeks. To calculate the mean cumulative steroid dose, the amounts of prednisone given orally and methylprednisolone given i.v. during the first 2 months were added and then expressed as a daily mean (mg/kg/day). For comparing the number of methylprednisolone pulses in the three groups, one course of high-dose oral prednisone (used as an alternative to i.v. methylprednisolone only in the conv. IS group), was taken to be therapeutically equivalent to 3 doses of 0.5 g methylprednisolone.

**Initial treatment with CyA alone** was carried out until 31.12.1981 i.e. in 16 patients, according to the protocol for the European multicentre study. On the first two days (first dose 6 h posttransplant) a dose of 17 mg/kg/day CyA was administered i.m. This dose was then given orally as two divided doses in the morning and evening. After 14 days the dosage was reduced to 15 mg/kg/day and then reduced by further 2 mg/kg every month to a maintenance dose of 6–8 mg/kg/day after about 5–6 months. In individual patients the dosage was gradually adjusted until trough serum levels were within the desired range of 100–400 ng/ml. In the period from 1.1.1982 to 30.3.1982, when a further 9 patients were assigned to this group, the sole deviation from this regimen was that a loading dose of CyA (3.4 mg/kg) was given by intravenous infusion over 4 h, followed by a daily i.v. dose of 10 mg/kg on the first 2 days. Subsequently, treatment was continued with oral daily doses of 15 mg/kg/day which were then tapered off as recommended in the protocol for the European multicentre study. Rejection episodes diagnosed clinically or confirmed by biopsy, were treated with 0.5 g methylprednisolone i.v., usually for three consecutive days, in some cases followed by 3 further injections given every other day.

The third group (CyA + Pred.) recruited from 1.1.1983 no longer received the loading dose of CyA, but were given daily doses of 5 mg/kg CyA i.v. on the first 2–3 days, starting 4–12 h before transplantation. CyA was then given orally at a dosage of 15 mg/kg/day, but this dosage was maintained for only 7 days and then reduced by 2–4 mg/kg weekly until a trough serum level of 50–150 ng/ml or a trough whole blood level of 300–800 ng/ml was attained. On this regimen the CyA dosage was reduced to less than 5 mg/kg/day by as early as 30 days in some patients. In addition, on the first two days all the patients received 40 mg methylprednisolone daily by the intravenous route followed by 0.5 mg/kg/day prednisone orally, the actual dose being rounded down to the nearest 5 mg. Every 14 days the dose of prednisone was reduced by 5 mg down to a daily dosage of 15 mg and then by a further 2.5 mg every 14 days. The stepwise reduction in the dosage was temporarily halted if serum creatinine levels exceeded 200 μmol/l. The aim of the tapering procedure was to discontinue prednisone after 5–6 months in primary cadaveric kidney graft recipients or to lower the dose to 0.1 mg/kg/day (rounded up to the nearest 2.5 mg) in recipients of second cadaveric transplants. If rejection was suspected, 0.5 g methylprednisolone was administered i.v. on three consecutive days, as in the CyA alone group, without changing the oral medication.

From 1.12. till 31.12.1981 26 patients were randomly allocated to the first two treatment regimen provided their urinary output attained a mean value of 50 ml/h in the first 6 h. Patients with primary oliguria and patients positive for hepatitis B received only conventional immunosuppressive treatment. From 1.1.1982 all patients received CyA, regardless of their initial urinary output or the results of serological tests for hepatitis. Episodes of impaired renal function of unknown origin or resistant to treatment were investigated by percutaneous renal biopsy. Some patients were biopsied up to 5 times. The methodology and the results of these histological investigations are described in detail elsewhere [16].

CyA in serum or whole blood was determined using the Sandoz RIA kit. The blood samples were always taken in the morning before the morning dose, i.e. about 12 h after the last dose taken the previous evening. Beginning in 1983, CyA has been assayed in heparinized haemolysed whole blood instead of serum. This method of assay avoids the problem of temperature-dependent changes in CyA distribution between the serum and the red blood cells [6]. The main source of error in the RIA technique is that some metabolites which have accumulated in the blood are determined along with the parent compound. This may be avoided by using HPLC. However, RIA procedure is quite adequate for clinical purposes. Replicate RIA analysis of control samples containing 250 and 1,000 ng/ml CyA resulted in between-assay coefficients of variation of 9.1 and 10.8% for serum (n = 8) and 7.8, and 10.3% for whole blood (n = 34). The ratio between whole blood and plasma levels (separated at 20°C) was 5.1 ± 1.9 (SD) (n = 72).

The unpaired Student’s t-test was used for the statistical analysis. The mean values are given together with the standard error.

**Results**

The characteristics of the three groups of patients are summarized in Table 1. The groups were fairly homogeneous for sex ratio, mean age, HLA matching and the disease which led to the renal damage. Poor matching at the HLA-A/B/DR loci up to level 1 and Fig. 2), provided that the T cell cross match was negative.

The mortality in the 12 months after transplantation was 3% (i.e. one patient out of 37) in the conv. IS group and 4% in the CyA alone group (i.e. 1 patient out of 25). All patients in the CyA + Pred. group are still alive.

The patient in the conv. IS group who died was a 57 years old woman who succumbed to a myocardial infarction 3 months after transplantation. The patient in the CyA alone group who died was a 27 year old woman with very severe disabling lupus erythematosus. She was on 10 mg/kg CyA daily when her trough serum level reached 2,910 ng/ml and was given 7 methylprednisolone.