COMPARISON OF THREE IMMUNOSUPPRESSIVE REGIMENS IN KIDNEY TRANSPLANTATION: A SINGLE-CENTRE RANDOMISED STUDY

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Summary

Three immunosuppressive regimens have been compared: conventional treatment including anti-thymocyte globulin (ATG) (32 patients) with cyclosporine (Cys) alone (21 patients), sequential combination of ATG with Cys (35 patients). Actuarial graft survivals were: ATG 73 per cent, Cys alone 88 per cent at nine months and ATG/Cys 92 per cent at one to two years. Transplant function was significantly worse with Cys as initial treatment compared with that in controls, while it was similar with ATG/Cys. The Cys dose used was low and no severe infection nor immunoglobulin abnormalities were noticed. Corticosteroids were withdrawn with both Cys protocols, except for rejection treatment.

Introduction

Cyclosporine (Cys) has dramatically improved graft survival rates in kidney transplantation [1,2]. However, in most of the trials, the control treatment was prednisone-azathioprine combination and when Cys was compared with anti-thymocyte globulin (ATG) as reported by Najarian [3] and others [4], the results were found to be similar. In addition, Cys nephrotoxicity appeared to be a major complication, leading to significantly worse renal function in patients treated by Cys than in controls [1,2,4]. In the following single-centre randomised study, three immunosuppressive regimens were compared: Cys as the initial treatment for transplantation, conventional therapy, including ATG, the sequential combination of ATG and late low dose Cys monotherapy, the aims being to retain the benefits of ATG in the early weeks, decrease the incidence of Cys nephrotoxicity and to reduce corticosteroid dose.

Patients and methods

A total of 92 kidney recipients were included in the study. Initial randomisation took place on the day of transplantation and patients received (1) either standard treatment: ATG (for 3 weeks, and then for treating rejection), prednisone
(1mg/kg/day), azathioprine (2–3mg/kg/day), or (2) Cys (15mg/kg/day) with prednisone (1mg/kg/day): Cys group II. After a second randomisation, during the third month, the former either stayed under standard treatment: STD group, or were converted to low dose Cys monotherapy (6mg/kg/day): Cys group I. Cys therapy was adjusted according to Cys through blood concentrations. Rejection was treated with either ATG if patients received standard treatment, pulse steroids if they were under Cys. The STD group consisted of 32 first transplants, Cys group II of 20 first and one second, Cys group I of 32 first and three second grafts. The three groups were similar in their pre-transplant characteristics. Follow-up was seven (3 to 10) months in Cys group II, and 14 (4 to 24) for the other two groups.

Results

Only one patient died during the common step to groups STD and Cys I. The actuarial graft survival (Figure 1) was 95 per cent at three months in the three groups; 88 per cent in Cys group II, 84 per cent in STD group, and 95 per cent in Cys group I at nine months; 73 per cent in STD group and 92 per cent in Cys group I at one to two years (p<0.5).

![Diagram showing actuarial graft survival](image)

**Figure 1. Actuarial graft survival**
Cys group II

Cys therapy did not prevent rejection and 57 per cent of these patients exhibited at least one rejection episode compared with 59 per cent in the STD group, within the first three months. Renal function was significantly worse than with standard therapy (Table I). Although Cys dose was quickly tapered from 15 to 10±3mg/kg/day at one month, 7.5±3mg/kg/day at three months and 6±2mg/kg/day at six months, Cys nephrotoxicity occurred in 66 per cent of these patients, as either a dose-related serum creatinine increase, or a long-lasting nephropathy (Cys II: 16±14 days vs STD and Cys I: 6±5 days, p<0.001). Conversions to STD treatment were performed in six patients (28%), including two cases of uncontrollable rejection and three of severe Cys nephrotoxicity. Steroid therapy could be stopped in 38 per cent of the 21 patients.

| TABLE I. Serum creatinine (μmol – X ± SD) in groups STD, Cys I, Cys II |
|-----------------------------|------------|----------|----------|------------|
| Months after grafting       | 3          | 6        | 12       | 18         |
| STD group                   | 120±64     | 154±145  | 138±67   | 133±50     |
| Cys group I                 | 113±45*    | 140±57   | 150±47   | 123±9      |
| Cys group II                | 210±100    | 166±63   |           |            |
| Cys II vs STD               | p<0.001    | p<0.001  |           |            |
| Cys I vs STD                | NS         | NS       | NS       | NS         |

* Pre-Cys values

Cys group I

Rejection episodes were as frequent as in the STD group after the second randomisation (39% vs 42%), but they appeared milder in terms of complete reversibility and recurrence; Cys I: 70 per cent and 21 per cent, STD: 16 per cent and 50 per cent respectively. Transplant function (Table I) was normal at the time of Cys introduction and remained similar to controls throughout the survey. Cys dose (mg/kg/day) was remarkably stable, from a starting dose of 6 to 5±1.5 at one and two years. Acute nephrotoxicity was found in 28 per cent of patients but chronic nephrotoxicity occurred in only half of them. Conversions to conventional treatment were few (5%). Steroid therapy was definitively stopped in 48 per cent of Cys group I patients; with restriction of steroids to rejection treatment, the others received significantly lower amounts (3370±1840mg) than in the STD group (6240±2520mg) for the following nine months (p<0.001).

In both Cys groups frequency and severity of infection were similar to the STD group.

Discussion

Our study compares three immunosuppressive regimens: conventional combined with ATG and two strategies of Cys administration. The association of ATG and
Cys (Cys group I) gave better actuarial graft survival than standard treatment with ATG (STD group) and even than Cys given as initial treatment (Cys group II). This was probably more related to the mildness of rejection episodes than their decrease of frequency. In addition, transplant function was normal at the time of Cys introduction; Cys doses used were low and few patients developed Cys nephrotoxicity. Consequently long-term serum creatinine were found to be similar to controls. In contrast, as reported in other trials in kidney transplantation [1,2,4], where Cys is given on the day of grafting, renal function was significantly lower in Cys group II.

To date in our study, although two powerful immunosuppressants are administered, their association, because sequential, has proved to be safe with regard to infection and immunoglobulin abnormalities [5].

Conclusions

Although a longer and larger survey is needed to evaluate Cys administration as the initial treatment, we favour the sequential association of ATG and Cys, which gave the best graft survival (92% at 1–2 years, including retransplantation), long-term good transplant function, and allowed reduction in steroid therapy, while avoiding, so far, severe infections or oncogenic complications.

References


Open Discussion

BONOMINI (Chairman) We must be clear on what exactly you mean by nephrotoxicity? You mentioned only the increasing serum creatinine or other clinical, biochemical or morphological signs.

HOURMANT We consider chronic nephrotoxicity as an increasing serum creatinine with histological changes.

BONOMINI In that case all patients on cyclosporine have nephrotoxicity because in all cases serum creatinine increases.

HOURMANT No, only 10 of our patients on cyclosporine had acute nephrotoxicity.

BONOMINI I would like to open the discussion on this point, because we must be clear about the toxicity of cyclosporine in terms of haemodynamic changes, glomerular tubular imbalance, vascular changes, interstitial changes and urinary

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changes. If we measure the toxicity of cyclosporine only by measuring the serum creatinine I would say that in my experience all cases are toxic.

WAUTERS (Lausanne) Just a short comment on the relationship between cyclosporine dose and nephrotoxicity. In our group we try to achieve a blood, not serum, value below 400ng/ml. In 20 patients our long-term mean serum creatinine was 135µmol/L which was comparable to our conventional therapy group.

BRYNGER (Chairman) I found it quite surprising that you had such a high incidence of rejection after three months.

HOURMANT Before three months.

BRYNGER In the cyclosporine literature and from my experience rejection after three months is very uncommon. You have quite a substantial number. Did you diagnose them by biopsy?

HOURMANT Yes, most of the time.