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D. Kahn
J. F. Botha
M. D. Pascoe
A. R. Pontin
J. Halkett
V. Tandon

Withdrawal of cyclosporine in renal transplant recipients with acute tubular necrosis improves renal function

D. Kahn · J. F. Botha · M. D. Pascoe · A. R. Pontin · J. Halkett · V. Tandon
Department of Surgery, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa

D. Kahn (✉)
Organ Transplant Unit, Department of Surgery, UCT Medical School, Observatory 7925, Cape Town, South Africa
Fax: + 27-21-4486461
e-mail: kannemey@uctgsh1.uct.ac.za

Abstract In this study, patients with acute tubular necrosis (ATN) after renal transplantation were prospectively randomized to either conventional immunosuppression or withdrawal of cyclosporine and replacement with anti-thymocyte globulin (ATG). The patients treated with cyclosporine withdrawal and ATG had a significantly shorter duration of ATN (8.9 ± 1.5 vs 10.8 ± 1.4 days; $P < 0.05$) and better renal function (mean serum creatinine on day 5 postoperatively: 740 ± 49 vs 918 ± 73 μmol/l; $P < 0.05$). The incidence of acute rejection was lower in the patients with cyclosporine withdrawal and ATG. In conclusion, cyclosporine is toxic to the renal allograft with ATN, and withdrawal of cyclosporine shortens the duration of ATN and improves renal function.

Key words Acute tubular necrosis · Cyclosporine withdrawal · Anti-thymocyte globulin

Introduction

The impact of cyclosporine on improving graft survival has been extensively documented. Unfortunately one of the major limiting factors in using cyclosporine is its nephrotoxicity. It is for this latter reason that sequential immunosuppression, whereby cyclosporine is withheld until the onset of renal allograft function, was introduced [1, 2]. During this period, patients are treated with either a polyclonal or a monoclonal anti-T cell antibody. Sequential immunosuppression is expensive and exposes many patients with immediate graft function unnecessarily to the risks of overimmunosuppression. Ideally, one would like to include cyclosporine in the immunosuppression regimen for patients with immediate graft function and withhold cyclosporine from the patients with acute tubular necrosis (ATN). Thus, in the present study, patients with ATN after renal transplantation were prospectively randomized to either continuing cyclosporine or withdrawal of cyclosporine and replacement with anti-thymocyte globulin (ATG).

Patients and methods

All patients undergoing renal transplantation at Groote Schuur Hospital in Cape Town between March 1995 and March 1998 were evaluated. All patients with ATN after renal transplantation were prospectively randomized to either conventional immunosuppression (group 1) or cyclosporine withdrawal and replacement with ATG (group 2). ATN was defined as the need for dialysis during the 1st week after the renal transplant.

All patients received standardized perioperative management. Conventional surgical techniques were used for the procurement of the donor organs and the subsequent implantation into the recipients. The induction immunosuppression, which was commenced intraoperatively, consisted of cyclosporine 5 mg/kg as an intravenous infusion over 24 h, methylprednisolone 500 mg IVI and azathioprine 100 mg IVI. Oral immunosuppression was commenced on the 1st postoperative day and included cyclosporine 10 mg/kg per day in two divided doses, azathioprine 100 mg/day and prednisone 30 mg/day. The dose of cyclosporine was adjusted to maintain cyclosporine levels between 150 and 300 ng/ml.

As soon as the diagnosis of ATN was made, the patients were randomized to either continuing with the conventional immunosuppression, as above, or the cyclosporine was withdrawn and the patients were treated with ATG. The patients received ATG 1.5 mg/kg per day and the dose was adjusted according to the absolute lymphocyte count (target level < 200 cells/ml). The ATG was discontinued and cyclosporine recommenced on the 7th postoper-

ative day or sooner if the renal function recovered before day 7. The patients were maintained on conventional immunosuppression thereafter.

Acute rejection episodes were diagnosed clinically and occasionally confirmed histologically. Acute rejection episodes were treated with intravenous bolus doses of methylprednisolone 500 mg/day for 4 days. There were no episodes of steroid-resistant rejection.

Results

During the study period, 35 patients with ATN after renal transplantation were prospectively randomized to either conventional immunosuppression ($n = 18$) or cyclosporine withdrawal and ATG ($n = 17$). The two groups of patients were comparable with regard to age (36.1 ± 2.7 vs 42.8 ± 1.7 years), gender (male: female 11:7 vs 9:8), retransplantation (10 vs 4), mode of dialysis (HD:PD 17:1 vs 13:4). The mean cold ischaemic time (CIT) was significantly shorter in the patients treated with conventional immunosuppression (17.8 ± 1.2 h) compared to the patients treated with cyclosporine withdrawal and ATG (22.6 ± 1.0 h; $P < 0.05$). Two patients who were randomized to the cyclosporine withdrawal and ATG group and one patient in the conventional immunosuppression group were excluded from the subsequent analysis because of non-function of the renal allograft. These three patients remained on dialysis.

The duration of ATN was significantly shorter in the patients treated with cyclosporine withdrawal and ATG (8.9 ± 1.5 days) compared to the patients treated with conventional immunosuppression (10.8 ± 1.4 days; $P < 0.05$). The mean serum creatinine in the patients treated with cyclosporine withdrawal and ATG (740 ± 49 μmol/l) was significantly lower than in the patients treated with conventional immunosuppression (918 ± 73 μmol/l) on the 5th postoperative day ($P < 0.05$). The patients in the cyclosporine withdrawal and ATG group had better renal function despite having a longer CIT. The incidence of acute rejection in the cyclosporine withdrawal and ATG group (40%) was significantly lower than in the patients treated with conventional immunosuppression (70%; $P < 0.05$). In this study, all the acute rejection episodes responded to the course of steroids.

Discussion

Nephrotoxicity is a well-known side effect of cyclosporine. Sequential immunosuppression whereby cyclosporine is withheld from the immunosuppression regimen until the onset of renal function of the renal allograft was introduced because of the nephrotoxic nature of cyclosporine and to reduce the incidence of ATN [1, 2]. In sequential immunosuppression, the cyclosporine is replaced with a monoclonal or a polyclonal anti-T cell antibody. However, the use of anti-T cell antibodies in all patients following renal transplantation is expensive. Furthermore, several patients with immediate graft function will be unnecessarily exposed to the risks of over-immunosuppression. In the above study, only patients with ATN after renal transplantation were prospectively randomized to either continuing with cyclosporine or having cyclosporine replaced with ATG.

In the present study, the patients in whom cyclosporine was withdrawn and replaced with ATG, had a shorter duration of ATN (8.9 vs 10.8 days). The patients also had better renal function in the immediate postoperative period. This finding has greater significance because of the longer CIT in the patients treated with cyclosporine withdrawal and ATG. The patients treated with ATG also had a lower incidence of acute rejection in the immediate postoperative period. Thus, the withdrawal of cyclosporine and replacement with ATG resulted in an improvement in renal function in the patients with ATN after renal transplantation.

This specific nephrotoxic effect of cyclosporine in renal allografts with ATN has not been documented previously. Withdrawal of cyclosporine in these patients resulted in improved renal function. The addition of the ATG in the patients with ATN has the advantage of decreasing the incidence of acute rejection which is helpful because of the difficulty in making the diagnosis of rejection in patients with no renal allograft function. Thus, the withdrawal of cyclosporine and replacement with ATG in renal transplant recipients with ATN decreases the duration of ATN and improves renal function. This policy is less expensive and does not expose patients with immediate graft function to the risks of overimmunosuppression.

References

1. Frey DJ, Matas AJ, Gillingham KJ, et al (1992) Sequential therapy – a prospective randomized trial of MALG versus OKT3 for prophylactic immunosuppression in cadaver renal allograft recipients. Transplantation 54: 50–56

2. Bock HA, Gallati H, Zurcher RM, et al (1995) A randomized prospective trial of prophylactic immunosuppression with ATG-Fresenius versus OKT3 after renal transplantation. Transplantation 59: 830–840