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Single-bolus high-dose ATG for prophylaxis of rejection in renal transplantation – a prospective, randomized study

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Abstract Currently, most centers use antithymocyte globulin (ATG) for induction or treatment of acute rejection. In the literature, postponement of introduction of cyclosporine or delay in acute rejection following ATG induction are well documented [1–4]. In contrast, data are very scant on the reduction of incidence of rejection or improvement of graft survival following ATG prophylaxis [5, 6]. The objective of this study was to compare the efficacy and safety of ATG high-dose single-bolus therapy with that of a standard cyclosporine-based protocol in prophylaxis of acute rejection in renal transplantation in an adult population. Rabbit ATG (Fresenius, Oberursel) was administered intraoperatively (before revascularization) to 19 renal transplant recipients as a single intravenous injection in a dose of 9 mg/kg body weight (high dose, single bolus). Treatment results were compared with those of a control group comprising 19 recipients receiving the same cyclosporin-Neoral-based protocol as the study group. In all patients concomitant medication consisted of steroids and azathioprine. The incidence of acute rejection in the high-dose ATG bolus group was 26%, compared with 58% in controls ($P < 0.05$). In the ATG treated group no grafts were lost to acute rejection in both high- and low-risk recipients, versus compared with a loss of 37% of rejecting grafts in controls. Though the observed difference in 1-year graft survival between study and control groups (84.2% vs 73.6%) did not reach statistical significance, the same trend was also observed in patients ($n = 9$ and $n = 12$ respectively) who, at he time of this report, had completed a 2nd post-transplantation year. The bolus and control groups had a similar incidence of complications and comparable renal function. We conclude that a single-bolus high-ATG protocol is efficient and safe in prophylaxis of renal allograft rejection.

Key words ATG · Immunosuppression · Rejection prophylaxis · Renal transplantation

Introduction

Currently, most centers use ATG for induction or treatment of acute rejection. In the literature, the postponement of introduction of cyclosporine or delay in acute rejection following ATG induction are well documented [1–4]. In contrast, data are very scant on the reduction of incidence of rejection or improvement of graft survival following ATG prophylaxis [5, 6]. The objective of this study was to compare the efficacy and safety of ATG high-dose single-bolus therapy with a standard cyclosporine-based protocol in prophylaxis of acute rejection in renal transplantation in an adult population.

Materials and methods

A total of 38 renal transplant recipients (28 low-risk; 10 high-risk: PRA > 50%, and/or retransplant) were prospectively randomized into a study (ATG bolus) and a control group, each comprising 14 low-risk and 5 high-risk patients. The ATG bolus group received intraoperatively 500 mg methylprednisolone followed by infusion of 9 mg/kg/bw ATG-Fresenius diluted in 500 ml saline, which was completed before revascularization. The controls received intraoperatively 500 mg methylprednisolone alone. In both groups identical cyclosporine, azathioprine and prednisone immunosuppressive protocol was commenced immediately after the operation. Rejection was diagnosed by elevation of serum creatinine and/or biopsy and evaluated in accordance with Banff criteria. Antirejection treatment consisted of three pulses of 500 mg methylprednisolone followed when required by a 7-day course of OKT3 given at a 5-mg/day dose. The clinical characteristics and the differences in treatment outcome were compared using the two-tailed unpaired *t*-test of the Fisher exact test. A P value < 0.05 was considered significant in all tests.

Results

The study and control groups were highly comparable with regard to distribution of sex, age, retransplantation, PRA and HLA match. In the 1st post-transplant year, rejection occurred in 5 out of 19 patients (26%) on ATG, compared with 11 out of 19 patients (58%) in the control group ($P = 0.05$). In the 2nd year, all rejections were reversed and no grafts were lost to rejection in the ATG group. In contrast, in the control group the reversal rate was 63%, with one of the rejecting grafts (37%) being lost to chronic rejection ($P = 0.1$). No significant difference between patients in the ATG and the control group was found in incidence of complications or adverse effects (delayed function: 7 vs 6 pts, viral infection: 4 vs 2 pts, urinary tract infection: 15 vs 12 pts, infection: 11 vs 8 pts, leukopenia: 4 vs 3 pts, cardiac death: 1 vs 1 pt; P = ns) or serum creatinine levels (2.2 + 1.7 mg/dl vs 2.3 + 1.9 mg/dl). The 1- and 2-year patient survival rates in the two groups were identical at 94.8%, while graft survival was 84.2% in the ATG group and 73.6% in controls in the 1st year and 84.2% and 69.5% in the respective groups in the 2nd year (P = ns).

Discussion

The objective of this study was to compare the efficacy and safety of ATG high-dose single-bolus therapy with a standard cyclosporine-based protocol in prophylaxis of acute rejection in renal transplantation in an adult population. The primary endpoints were incidence of acute rejection and complications. The secondary endpoints were patient and graft survival, reversal of rejection and renal function. In this series, compared with a standard cyclosporine-based protocol, ATG-F bolus therapy was found to be efficient in reduction of incidence of acute rejection in both high- and low-risk recipients. ATG single-bolus treatment was safe, as shown by a similar incidence of complications and comparable renal function in the two groups. The ATG group also showed a tendency for better long-term graft survival, which may become more significant after further follow-up.

We conclude that this study may suggest a renewal of interest in polyclonal antibody therapy in organ transplantation, this time for prophylaxis of rejection as a part of new strategies to achieve long-term graft acceptance.

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