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Steroid-resistant rejection in kidney-transplanted patients: is ATG treatment for three or ten days preferable?

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Abstract We carried out a randomized prospective trial to compare a 3-day with a 10-day course of antithymocyte globulin (ATG)- (Fresenius) for treatment of steroid-resistant rejection after renal transplantation. The aim was to study whether a short 3-day course was as safe and effective as the longer 10-day treatment. Thirty patients over a 3-year period were included. Patients that did not respond to treatment after 3 days received additional ATG from day 5 to day 10. The graft survival and the proportion of rejections reversed with the treatment were compared. Fifty percent responded promptly in the 3-day group and a further 29 % after additional treatment. In the 10-day group, 62 % reponded to the treatment. There was no significant difference between the groups. We, therefore, suggest that the standard antirejection treatment with ATG could be shortened without an increased risk of graft failure.

Key words ATG · Steroid-resistant rejection · Kidney transplantation

Introduction

Antithymocyte globulin (ATG) has been used in clinical practice for more than 20 years as a potent drug for prophylaxis against allograft rejection as well as in the treatment of steroid-resistant rejection [1–5]. The recommended duration of the treatment usually varies between 7 and 14 days. The standard antirejection treatment with steroids after transplantation usually includes 3 or 4 days with methylprednisolone bolus injections. An extended time of ATG treatment is expensive, possibly harmful [4], and might not be necessary. The present study aimed to investigate whether a 3-day ATG course was sufficient as treatment for steroid-resistant allograft rejection in kidney-transplanted recipients, or if a standard 10-day course was required.

Materials and methods

Study design

The study was designed as a randomized, prospective, open study. Patients were not stratified according to immunological risk factors. All patients with steroid-resistant rejection and a clinical decision to commence ATG treatment were included.

Patients and immunosuppressive therapy

For 3 years, 30 patients undergoing kidney transplantation were studied. All recipients received standard triple-drug treatment with prednisolone, azathioprine, and cyclosporine. Prednisolone was started on the day of surgery at a dose of 100 mg, followed by a reducing dose over 2 weeks down to 20 mg. Azathioprine was given preoperatively (2 mg/kg per day) and then adjusted according to daily levels of white blood cells. Oral cyclosporine (8 mg/kg per day) was started as soon as the kidney began to function, usually the day after transplantation. The cyclosporine dose was adjusted to levels of cyclosporine in whole blood (monoclonal RIA assays) corresponding to 150–200 ng/ml).

Table 1 Demographic data and graft survival (*M/F* male/female, *LD* live donor, *ReTx* retransplantation, *PRA* + panel-reacting antibodies in pretransplant sera, *PrDia* pretransplant dialysis, *Rev* number of patients with reversed rejection (A vs B n.s.)

Group	Number	Mean age (95 % confidence)	M/F	LD	ReTx	PRA+	PrDia	Rev
A	14	34.5 ± 4.6	9/5	7	2	6	10	11
B	13	43.1 ± 8.0	9/4	3	0	5	12	8

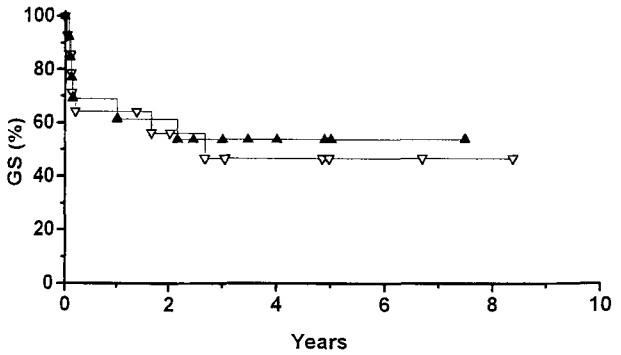

Fig. 1 Actuarial graft survival in patients treated with 3 or 10 days of antithymocyte globulin (ATG) for steroid-resistant rejection (—▽— ATG 3 days, —▲— ATG 10 days)

Diagnosis and treatment of rejection

Rejection was diagnosed clinically and verified with a core needle biopsy. All patients with allograft rejection received standard antirejection treatment consisting of a bolus dose of methylprednisolone i.v. for 4 consecutive days (500 + 250 + 250 + 250 mg). Recipients not responding with improved kidney function on the fifth day of the steroid treatment were defined as having a steroid-resistant rejection.

Randomization and treatment protocol

After a steroid-resistant rejection had been defined and the decision taken to commence ATG therapy, patients were randomized to either a 3-day (group A) or a 10-day (group B) ATG (Fresenius AG) course. ATG was given i.v. at a dose rate corresponding to 3 mg/kg body weight daily. Patients in the 3-day treatment group were evaluated on day 4. If the creatinine had leveled off or decreased, no further ATG was given. If on the other hand the creatinine level continued to rise on the fourth day, ATG was continued from day 5 to day 10. All recipients were evaluated after 10 days to establish whether the treatment had been effective in reversing the rejection episode. The number of grafts rejected after 3 months were registered and the graft survival was calculated.

Statistical analysis

Categorical data were analyzed using Fisher's exact test for two-by-two tables. The Kaplan-Meir method with the Cox-Mantel log-rank test was used to calculate graft actuarial survival rates.

Results

All patients that completed at least 3 days of ATG therapy were eligible for analysis. One patient in group A lost his graft on day 2 after starting ATG and was, therefore, excluded. One patient in group B was excluded due to early graft failure (day 2) during the ATG therapy and another patient in the same group received only one dose of ATG due to severe thrombocytopenia and was, therefore, excluded as well. Demographic data and graft survival of the remaining 27 patients eligible for analysis are presented in Table 1. Seven patients in group A (50 %) responded primarily to the 3-day course and an additional 4 responded after prolonged therapy, resulting in 11/14 patients (79 %) in total, responding in group A. In group B, 8 patients (62 %) responded to treatment. There was no statistically significant difference between the two groups with respect to the ability to reverse allograft rejection. The actuarial graft survival of groups A and B were compared. No statistically significant difference could be seen. The follow-up was 5–8 years.

Discussion

Since the first clinical application of antilymphocyte globulin in 1967 by Starzl, many investigators have confirmed the powerful effect of this and other antithymocyte drugs in suppressing T-cell activation as well as their ability to prevent and reverse allograft rejection [1–5]. It is also known that, although a high dose of ATG is effective in preventing or reversing allograft rejection, it is at the cost of many undesirable side effects such as a high incidence of viral and bacterial infections [4]. One way to reduce the total immunosuppressive load on the patient is to reduce the ATG dose after T-cell monitoring using flow cytometry, as shown by Abouna and co-workers [4]. A reduction both in treatment costs and number of infections was seen with a lower ATG dose [5]. Another way to reduce the amount of ATG given would be to shorten the length of the treatment period.

In the present study we have demonstrated that both short- and long-term results measured as rejected grafts at 3 months and actuarial graft survivals were similar, irrespective of the length of treatment. Although not all

of the patients receiving an initial 3-day ATG course reversed, it was possible and safe to commence ATG treatment again on day 5. No graft was lost due to too short a treatment period with ATG. We, therefore, suggest that the standard antirejection treatment with ATG could be short. A prolonged course could be initiated in cases not responding promptly.

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