ACUTE REJECTION AND STEROID DOSAGE IN RENAL TRANSPLANTATION

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SYNOPSIS

Thirty-eight renal allograft recipients from living related donors were studied. The relationships between acute rejection and steroid therapy, azathioprine dosage and HLA matching were analysed.

There were no significant differences in the cumulative steroid doses at the time of rejection; rates of reduction of steroid dosage and the azathioprine dosage between the patients who had acute rejection and those who did not. Donor recipient compatibility on the HLA - A and B loci did not affect the incidence of acute rejections.

INTRODUCTION

Rejection in renal transplant patients remain the most important factor in determining graft survival. Immunosuppression to control or prevent rejection of the renal allograft has led to significant morbidity in allograft recipients. Large doses of corticosteroids have been given to patients in the early post transplant periods, when the need for immunosuppression is felt to be the greatest. The challenge remains to find the minimum steroid dose necessary to prevent rejection episodes so as to reduce the steroid associated morbidity.

In this retrospective study, 38 patients who had received allografts from living related donors were reviewed. The purpose of this study was to investigate the relationship, if any, between the pattern and incidence of acute rejection episodes and (a) steroid therapy (b) histocompatibility matching of the HLA-A and HLA-B antigens (c) the dose of azathioprine at the time of first acute rejection. The immunosuppressive regime in brief consisted of azathioprine (mean dose 1.5 mgm/kgm B.W.) and prednisolone (100 mgm/day initially gradually reducing to 10 to 15 mgm/day at 6 months post graft).

PATIENTS AND METHODS

Thirty-eight patients (22 males, 16 females) who had received allografts from living related donors were reviewed. The mean age was 29 years ± 7 years (± SD). The mean follow up period from August 1977 to February 1981 was 18 ± 12 months (± SD) with a range of 1 - 42 months. All the patients had at least one haplotype matching for the HLA-A and HLA-B loci. All had functioning grafts at the time of this review.

The occurrence of the first acute rejection episode and the total number of acute rejection episodes were studied. An acute rejection episode was defined as a rise in the serum creatinine of 0.3 mgm/dl or more with or without other clinical signs such as graft swelling and tenderness, a rise in the blood pressure and fever; occurring in the first 6 months after the transplant.

To study the relationship between the occurrence of the first acute rejection episode and steroid therapy, 10 patients who had acute rejection episodes were matched with 10 other patients who had no rejection episodes as the remaining patients could not be matched. Matching was done with respect to age, sex and the degree of haplotype matching for the HLA-A and B loci. The cumulative steroid dose up to the time of the first rejection episode was calculated and compared. The rates of reduction of steroid dosage (mgm/prednisolone/day) in both groups were also analysed.

RESULTS

15/38 patients (39%) had 19 episodes of acute rejection. The mean time of onset of the first acute rejection episode (15) was 46 ± 48 days (± SD) after the transplant and that of the second rejection episodes (4) was 113 ± 63 days (± SD).

Twenty-six patients had donor-recipient compatibility for only one haplotype and the other 12 were identical for two haplotypes. There was no significant difference in the number of rejection episodes between the two groups (14/26 vs 5/12; $x^2 = 0.63$, $p<0.2$). (Table 1).

We could not demonstrate any significant difference in the cumulative steroid doses at 6 months when we compared patients who had acute rejection episodes (rejectors, 15/38 patients) and those who did not (non-rejectors, 23/38 patients) ($t = 0.22$, $p<0.5$).

In the 10 pairs of matched patients (acute rejectors vs non rejectors) there was no significant difference in the cumulative steroid dosages up to the time of the first acute rejection. The mean steroid dose was 2362.6 ± 1444.8 mgm (± SD) for the rejectors and 2180.5 ± 1184.1 mgm (± SD) for non rejectors ($t = 0.097$, $p<0.95$) (Table 2).

Comparison of the rate of reduction of prednisolone dosage also showed no significant difference between the two groups. The mean steroid dose reduction per day was 12.5 ± 15.3 mgm/day in the rejectors and 9.3 ± 7.9 mgm/day in the non rejectors ($t = 0.66$, $p<0.5$).

No significant difference was also found between the mean daily dosage of azathioprine at the time of first rejection in these two matched groups of patients. The mean daily dose of azathioprine in the rejectors was 71.3 ± 27.6 mgm and that for the non rejectors was 73.8 ± 20.8 mgm ($t = 0.25$, $p<0.8$).

TABLE 1 : HLA MATCHING AND REJECTION EPISODES

HLA - Matching on A, B loci	No. of Patients	No. of Rejection Episodes	Statistical Significance
One haplotype match	26	14	$x^2 = 0.63$
Two haplotype match	12	5	$p<0.2$ (N.S.)

DISCUSSION

Acute rejection poses a major problem in the management of post renal transplant patients. Despite immunosuppression, acute rejection still occurs in many patients. It has been observed that high dose steroids could reverse acute rejection episodes and based on this steroids have almost been universally and routinely used in the immunosuppressive regimes for patients receiving renal transplants. Other agents included are azathioprine and less frequently cyclophosphamide, anti-lymphocyte globulin and cyclosporin. The high-dose maneuverability of steroids and the greater need of immunosuppression in the early post transplant period almost inevitably translates into high doses of steroids being used in the first week after the transplant.

The high morbidity associated with steroid treat-

TABLE 2 : STEROID THERAPY IN 10 PAIRS OF MATCHED PATIENTS

Steroid therapy in 10 matched pairs of patients	Patients with acute rejection	Patients with no acute rejection	Statistical Significance
1. Cumulative steroid dose till time of first rejection (Mean ± S.D.)	2362.6 ± 1444.8 mg	2180.5 ± 1184.1 mg	$t = 0.097$ $p < 0.95$ (N.S.)
2. Rate of reduction of steroid dose till time of first acute rejection (Mean ± S.D.)	12.5 ± 15.3 mg/day	9.3 ± 7.9 mg/day	$t = 0.66$ $p < 0.5$ (N.S.)
3. Mean (± SD) daily dose of azathioprine at time of first rejection	71.3 ± 27.6 mg	73.8 ± 20.8 mg	$t = 0.25$ $p < 0.8$ (N.S.)

ment however, requires a constant re-examination and revaluation of its place in any post transplant immunosuppressive regime.

In this context, two points have to be considered. First, although it is possible to treat acute rejection episodes with high pulse doses steroids, it is almost impossible to predict the patients who are going to develop acute rejection.

The second factor that needs to be considered is the minimum dose of steroids required to prevent rejection of the graft. Large doses of steroids have traditionally been used (1) but recently in a study of 151 renal transplants, McGeown et al (1980) showed that 20 mg of prednisolone a day starting from the day of transplant was as effective as higher doses in maintaining graft survival (2). Kreis et al (1978) also showed no significant difference in the number of renal failure episodes (RFE) between patients who were routinely treated with prednisolone before the first episode of RFE and those who were not (3).

Our data, although in a relatively small group of patients showed no significant differences in the 6 month cumulative steroid dose between rejectors and non rejectors. The cumulative steroid dose till the first rejection episode and the rate of reduction of the steroids given were also not significantly different in matched pairs of rejectors and non-rejectors.

One reason for these findings may be, as suggested by Kreis et al (1978), that there are RFE which are not prevented or reversed by steroids (steroid independent) (3).

Histocompatibility matching in the HLA-A and B loci also had no effect on the number of acute rejection episode. Most series report a better graft survival in transplants from living related HLA identical donor-recipient combinations when compared to those with semi-identical or non identical combinations (4, 5, 6). Graft survival however does not necessarily mean the absence of acute rejection episodes. Also Duquesuoy et al (1980) showed that matching for the MB system appears to be more important than matching for the HLA-A, B or DR loci and that no correlation could be demonstrated between transplant survival and donor-recipient compatibility for antigens of the HLA-A, B or DR loci (7).

The need for steroids in the immunosuppression of renal transplant recipients is generally accepted by most workers although some dispute this (3). Others advocate a lower dose to minimize morbidity (2). Our study shows that despite very similar immunosuppressive regimes, acute rejection still occurs in some patients irrespective of steroid or azathioprine dosage. Matching for the HLA-A and HLA-B loci also does not affect the incidence of acute rejection. A greater understanding of transplant antigen systems and matching together with a clearer definition of the acute rejection process may result in a smaller dose of steroids being used for a shorter period of time. Until then the acute rejection episode remains a common occurrence for the transplant recipient and a continuing problem for the transplant physician.

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