Transplant Int (1992) 5 [Suppl 1]: S54–S57

TRANSPLANT
International

Value of panel reactive antibodies (PRA) as a guide to the treatment of hyperimmunized patients in renal transplantation

A. Buscaroli, A. Nanni Costa, S. Iannelli, G. Cianciolo, L. De Santis, G. La Manna, S. Stefoni, A. Vangelista, and V. Bonomini

Institute of Nephrology, St. Orsola University Hospital, Bologna, Italy

Abstract. Patient presensitization represents a considerable problem in candidacy for renal transplantation. While it is well known that hyperimmunized patients – panel reactive antibody (PRA) higher than 60% – create difficulties in donor matching and have a worse outcome than non-hyperimmunized patients, less information is available on patients with an intermediate degree of sensitization (30–60%). In order to evaluate how graft outcome relates to such degrees of sensitization, 241 consecutive transplanted patients were divided into two groups on the basis of their previous year's PRA peak: group A, PRA 0–29%; group B, PRA 30–60%. Group A showed a significantly better survival both in the first year (90% vs 79%, $P < 0.05$) and in the third year (82% vs 64%, $P < 0.01$). However, detailed analysis of group B demonstrated that some parameters may significantly influence graft outcome: (1) better compatibility on locus DR; (2) a primary kidney transplant; (3) a dialysis duration of less than 6 months; and (4) the prophylactic use of anti-lymphocyte globulin (ALG).

Key words: Panel reactive antibodies – Locus DR – Dialytic age – Primary kidney transplant – Anti-lymphocyte globulin

The presence of the hyperimmunized patient is a growing problem for kidney transplantation centres where the number of donors is always on the decline while the list of uraemic patients waiting for a graft dramatically increases. Hyperimmunized patients represent a considerable percentage of the waiting list (20–40%) and create a real dilemma in decision making. While it is well known that more than 60% of panel reactive antibodies (PRA) create difficulties both in donor matching and in graft outcome, less information is available on patients with an intermediate degree of sensitization [2, 6, 7]. The aim of this study was to analyse the influence of an intermediate degree of sensitization (30–60%) on graft outcome and to assess the best therapeutic strategy for such patients.

Offprint requests to: Dr. Andrea Buscaroli, Institute of Nephrology, St. Orsola University Hospital, Bologna, Via Massarenti 9, 40138, Bologna, Italy

Materials and methods

The present study draws on data from 241 kidney transplant patients transplanted in the Nephrology Department of the St. Orsola University Hospital of Bologna from 1985 to 1990 from cadaver donors.

In all patients an accurate pre-transplant study was carried out determining the percentage of antibodies in the serum against a panel of frozen lymphocytes from normal subjects (PRA). The technique used to detect cytotoxicity was complement-dependent NIH standard. Fresh sera were collected from waiting-list patients every 2 months and tested. For this study evaluation was made only on the basis of the PRA peak value in the previons 12 months. Patients were divided into two groups: group A (174 patients, 72%), PRA 0–29%; group B (63 patients, 26%), PRA 30–60%. Over 60% of our case material was confined to isolated episodes (4/241, 1.6%). The distribution of PRA in the patients studied is shown in Fig. 1.

Patients with less than 1 year of follow-up and those with graft failure caused by a primary surgical problem or an accident were excluded from the study. In all cases, steroids plus cyclosporine was the standard initial immunosuppressive therapy. Transplantation in all patients was performed only after a negative donor–recipient cross-match.

The study was developed in two steps. The first step consisted of comparing groups A and B and determining if there were any dif-

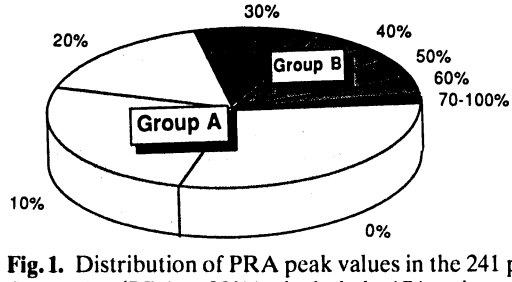

Fig. 1. Distribution of PRA peak values in the 241 patients studied. Group A (PRA < 30%) included 174 patients and group B (PRA 30–60%) 63 patients. Four patients with PRA > 60% were excluded from the study as being non-evaluable

ferences between the two groups, apart from the PRA peak value, potentially influencing the graft outcome. The second step, and main aim of the study, was to analyse group B alone, in an attempt to define what pre- and post-transplant factors influence graft outcome.

The choice of parameters to be examined for graft outcome related to the following 27 items: (1) *individual characteristics:* sex, age, primary renal disease, blood group, duration of dialysis treatment (months), previous pregnancy, polytransfused or not; (2) *donor characteristics:* provenance of donor (local, shipped), multiorgan graft or not, age difference between donor and recipient; (3) *transplant characteristics:* HLA mismatches on locus A, locus B and locus DR, first or second graft, PRA (latest and highest serum level), cold ischaemia time (h); (4) *clinical characteristics:* time for renal functional recovery after transplantation (days), patient current status (graft functioning, graft failure, death), date of graft failure or death, cause of graft failure or death, survival of graft if failed (months), survival of graft if functioning (months), renal function after 1 year (serum creatinine mg/dl), number of rejection episodes in the first year, number of steroid pulses in the first year, enhancing immunosuppressive therapy (ATG/ALG, OKT3, etc.) in the first 6 weeks, any prophylactic use of antilymphocyte globulin (ALG) in the first weeks [3, 9, 11].

Two kinds of tests were used to evaluate patient outcome after the transplantation: actuarial survival rates using error standard and Z tests to compare two or more groups, and the relative risk (of graft failure in the first year) evaluated for a single field by the odds-ratio test [1].

Results

Comparison of the two groups showed a significantly better survival in group A: 90.4% vs 79.3% in the first year ($P < 0.05$); 87.8% vs 71.1% in the second year ($P < 0.01$); 82.5% vs 64.1% in the third year ($P < 0.01$) (Fig. 2). The relative risk of graft failure in the first year (odds ratio) was also significantly different between groups A and B (0.4 vs 2.3, $P < 0.05$).

Individual, donor, transplant and clinical characteristics did not differ significantly between the two groups (Table 1). Serum creatinine after 1 year was

Table 1. Detailed results of the most significant parameters considered

	Group A – PRA < 30% ($n = 174$)		Group B – PRA 30–60% ($n = 63$)		1-year survival (%) (group B)
	No.	%	No.	%	
Sex					
Male	140	80.6	47	74.6	79.5
Female	34	19.4	16	25.4	78.6
Previous pregnancy	4	11.7	3	18.6	–
Age					
0–14 years	2	0.9	0	0.0	–
15–35 years	40	23.1	18	28.6	76.5
35–56 years	116	66.7	39	61.9	80.6
> 55 years	16	9.3	6	9.5	81.8
Dialysis duration					
0–6 months	19	11.0	9	14.3	88.2
7–24 months	64	36.8	25	39.7	78.3
> 24 months	91	52.2	29	46.0	77.4
Polytransfused					
> 5 transfusion	67	38.5	22	34.9	76.2
< 5 transfusion	107	61.5	41	65.1	81.3
HLA-A mismatches					
0	11	6.5	4	6.3	71.4
1	70	40.2	24	38.1	76.7
2	93	53.3	35	55.5	78.1
HLA-B mismatches					
0	2	1.1	0	0.0	–
1	41	23.6	20	31.7	83.3
2	131	75.3	43	68.3	77.5
HLA-DR mismatches					
0	14	8.1	6	9.5	100
1	86	49.4	32	50.8	83.1
2	74	42.5	25	39.7	68.9
Transplant number					
1st graft	168	96.3	55	87.5	82.2
2nd graft	6	3.7	8	12.5	60.0
First 6 weeks enhancement immunosuppression					
Antilymphocyte globulin	75	43.1	32	50.8	[a]
Plasma exchange	21	12.1	8	12.7	[a]
OKT3	5	2.9	3	4.8	[a]
Not treated	83	47.7	35	55.6	72.3

[a] 20 patients were submitted to more than one treatment

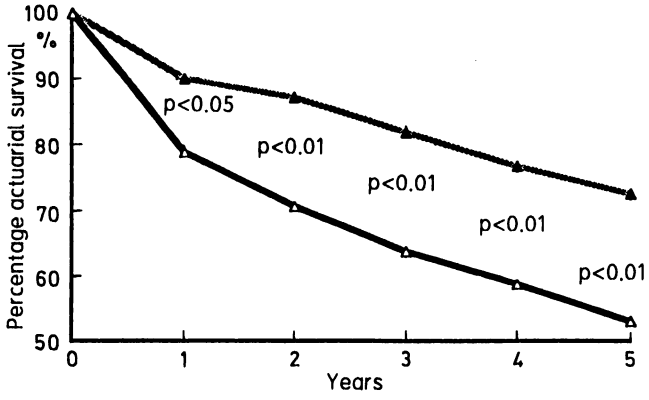

Fig. 2. Actuarial graft survival of group A (PRA < 30%, 174 patients) and group B (PRA 30–60%, 63 patients). ▲, PRA < 30%; △, PRA 30–60%

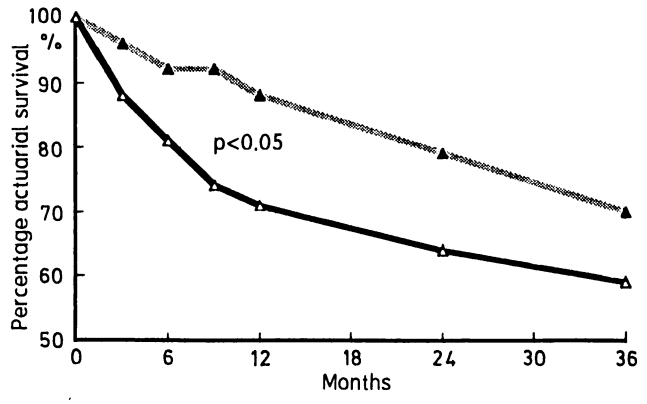

Fig. 3. Effect of the prophylactic use of antilymphocyte globulin (ALG, 28 patients) (not treated, 35 patients) on graft outcome in hyperimmunized patients (PRA 30–60%). ▲, ALG; △, not treated

1.44 ± 0.38 mg/dl in group A and 1.53 ± 0.32 mg/dl in group B, the number of rejection episodes in the first year was 0.70 ± 0.85 vs 1.17 ± 0.94 ($P < 0.001$), respectively, and the number of steroid pulses in the first year 1.27 ± 1.89 vs 2.63 ± 2.98 ($P < 0.001$).

Detailed analysis of group B suggested that some parameters may influence graft outcome:

1. *Compatibility on locus DR:* With no mismatches ($n = 6$) the actuarial survival after 3 years was still 100%; with one mismatch ($n = 32$) it was 83.1% in the first year ($P < 0.01$), 74.9% in the second year ($P < 0.001$) and 65.6% in the third year ($P < 0.001$); and with two mismatches ($n = 25$) it was 68.9%, 57.4% and 50.7% respectively (all $P < 0.001$).
2. *Primary transplant vs retransplant:* Survival for first graft ($n = 55$) was 82.2% in the first year, and 75.1% in the second year while for regrafted patients ($n = 8$) it was 60.0% and 42.9%, respectively. Relative risk for first transplant was 0.3 vs 2.9.
3. *Dialysis time:* Patients who were transplanted without dialysis or with a dialysis duration < 6 months ($n = 9$) showed a better survival (88.2% in the first year) than those with a dialysis duration of 6–24 months (78.3%) ($n = 25$) and those with a dialysis duration > 24 months (77.4%) ($n = 29$), while the difference became less significant at 3 years (74.7%, 61.9% and 62.4%, respectively). The relative risk of the group with a short dialysis duration was 0.5 vs 1.9 in the two latter groups.

Details of the most important items considered are summarized in Table 1.

The prophylactic use of immunosuppressive enhancement therapy – in this case antilymphocyte globulin (ALG) employed in the first weeks from surgery, and usually at the beginning of the second week, before the onset of a rejection crisis – improved graft outcome: 1 year survival was 84.6% in patients treated with prophylactic ALG ($n = 28$), but only 75.0% in untreated patients ($n = 35$). At 3 years, survival still differed but was less significant: 70.0% vs 59.5% in untreated patients (Fig. 3). Serum creatinine after 1 year was 1.51 ± 0.41 mg/dl in the group treated with prophylactic ALG and 1.55 ± 0.15 mg/dl in those not treated. The number of rejection episodes in the first year was 1.01 ± 0.67 for the ALG group vs 1.35 ± 1.15, respectively. Finally the number of steroid pulses in the first year was 1.40 ± 1.34 in the ALG treated patients vs 3.68 ± 3.62 ($P < 0.01$). The relative risk was 0.3 vs 2.9.

Conclusions

This study confirmed that presensitization represents a considerable problem in candidacy for renal transplantation. Based on restricted yet homogeneous case material, the data reported highlight the importance of transplanting as soon as possible. This is, perhaps, the easiest factor on which to work: prolonging dialysis time tends to make the patient more immunologically reactive owing both to repeated contact with artificial material [10] and to the likely clinical need for more transfusions – though our data do not show any significant differences in survival for polytransfused patients, in agreement with previous reports [5]. In this connection the use of erythropoietin is to be welcomed [4]. However, hyperimmunization may also be seen as evidence of a different, more pronounced, immunological reactivity towards the graft. It may thus be helpful to indicate how to manage such patients.

Our data suggest that it is with these patients that greater accuracy in the search for optimum compatibility on the DR locus seems useful, and this can only come about through coordination of transplant centres in organ or recipient exchange. In addition, this study indicates that, once the previous suggestions have been followed, another card can be played to improve the hyperimmunized patient's destiny. By using treatment such as a cycle of ALG to boost immunosuppression in the first weeks after surgery, one both improves late graft outcome and decreases the number of rejection episodes (and consequently the amount of steroids), thus achieving two goals: first, bringing the survival probability of hyperimmunized patients as close as possible to that of non-immunized patients, and second, probably avoiding more infection and steroid-induced complications.

Acknowledgements. This study was supported in part by the Dott. Carlo Fornasini Foundation, Bologna.

References

1. Appleton DR (1988) Analysis of data in nephrology I. Choosing the correct statistical test: dichotomous variables. Nephrol Dial Transplant 3: 91–94
2. Claas FHJ, de Waal LP, Beelen J, Reekers P, Berg-Loonen PVD, de Gast E, D'Amaro J, Persijn GG, Zantvoort F, van Rood JJ (1990) Transplantation of highly sensitized patients on the basis of acceptable HLA-A and B mismatches. In: Terasaki P (ed) Clinical transplant 1989. UCLA Tissue Typing Laboratory, Los Angeles, pp 185–190
3. Gore SM (1983) Graft survival after renal transplantation: agenda for analysis. Kidney Int 24: 516–525
4. Grimm PC, Sinai Trieman L, Sekiya NM (1990) Effect of recombinant human erythropoietin on HLA sensitization and cell mediated immunity. Kidney Int 38: 12–15
5. Iwachi Y, Cecka JM, Terasaki PI (1989) The transfusion effect. In: Terasaki P (ed) Clinical Transplant 1988. UCLA Tissue Typing Laboratory, Los Angeles, pp 283–292
6. Lundgren G, Groth CG, Albrechtsen D (1986) HLA-matching and pretransplant blood transfusion in cadaveric renal transplantation – a changing picture with cyclosporine. Lancet II: 66–69
7. Opelz G (1987) Improved kidney graft survival in non-transfused recipients. Transplant Proc 19: 149–152
8. Rankin GW, Wang X, Terasaki P (1991) Sensitization to kidney transplant. In: Terasaki P (ed), Clinical Transplant 1990. UCLA Tissue Typing Laboratory, Los Angeles, pp 417–424
9. Sanfilippo F, Vaughn WK, LeFor WM, Spees EK (1986) Multivariate analysis of risk factors in cadaver donor kidney transplantation. Transplantation 42: 28–34
10. Stefoni S, Nanni Costa A, Buscaroli A, Colì L, Feliciangeli G, Mosconi G, Scolari MP, Iannelli S, Borgnino LC, Bonomini V (1991) Cellular immunology in regular dialysis: a biological model for biocompatibility evaluation. Nephrol Dial Transplant 6 [Suppl 2]: 4–9
11. Tufveson G, Geerlings W, Brunner FP, Brynger H, Dykes SR, Ehrich JHH, Fassbinder W, Rizzoni G, Selwood NH, Wing AJ (1990) Combined report on regular dialysis and transplantation in Europe, XIX, 1988. Nephrol Dial Transplant 4 [Suppl 2]: 5–32