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Superiority of B locus matching over other HLA matching in renal graft survival

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Abstract

Graft survival after 348 consecutive first cadaver-donor renal transplants was significantly improved by HLA matching when recipients who had received pretransplant blood transfusions were matched with their kidney donor for two HLA-B locus antigens. No other type of HLA matching significantly improved graft survival in transfused recipients nor did any type of HLA matching in non-transfused recipients. Matching for one HLA-DR antigen had no benefit in transfused recipients. Only two patients received kidneys matched for both DR antigens and only two of those in whom DR matching had been performed had not been transfused.

These results indicate that pretransplant blood transfusion and selection of graft recipients predominantly on the basis of HLA-B matching has significantly reduced the renal graft rejection rate in Newcastle upon Tyne over two years. Thus, HLA-B antigen matching should be adopted as the main criterion for kidney sharing between transplant centres.

Introduction

The beneficial effect of pretransplant blood transfusion^{1 2} on first transplants of cadaver-donor kidneys is now widely accepted, but the value of matching for HLA antigens is less clear.

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Cadaver-donor kidneys are, however, shared and transported between transplant centres mainly on the basis of the number of HLA antigens in common between donor and recipient. It is important to assess whether this is the best and most efficient basis of kidney sharing.

We have, therefore, analysed the kidney transplant results in Newcastle upon Tyne, where clinical care, serological testing, and accuracy of transfusion records have been uniform, to determine the value of HLA matching in cadaver-donor transplantation and to compare these results with those of live-related donor kidney grafts.

Material and methods

Three hundred and forty-eight first cadaver-donor transplants were performed from 30 October 1969 to 10 May 1980 and 81 first live-related donor transplants from 30 January 1967 to 26 February 1980. All cases were assessed for graft survival in July 1980.

Tissue typing and crossmatching—Tissue typing for HLA-A and HLA-B antigens was carried out as described.² HLA-DR antigens (DR1-DRw8) were determined prospectively on donor-recipient pairs from May 1978. The antisera used for DR typing were assessed against cells typed for HLA-DR antigens by Seventh and Eighth Histocompatibility Workshop antisera. Pretransplant lymphocytotoxic cross-matching was performed as described³ using both fresh recipient serum and all previous samples stored frozen at -20°C . The first 232 cross-matches were performed using whole lymphocyte suspensions prepared from peripheral blood, lymph node, or spleen. In the subsequent 116 cases separated T and B lymphocytes from the cadaver material were used, and only lymphocytotoxic antibody in the recipient's serum reactive against the T lymphocytes was regarded as a contraindication to transplantation. Cross-match tests were performed at 37°C for the first 102 cases but at both 20°C and 37°C for all subsequent cases.

Pretransplant transfusion history—Transfusion histories were compiled as described.⁴

Clinical management and immunosuppression

Our methods of clinical care have been described^{2 4} but have been modified slightly. Because of the availability of serial technetium-99m DTPA gamma-camera scans we could sometimes avoid transplant biopsy at day 18 in patients with oliguria, as the pattern shown was of tubular necrosis rather than rejection. In February 1978 we adopted

the policy of giving soluble methylprednisolone 1.0 g intravenously at the time of the vascular anastomosis and again 24 hours after transplantation. At the same time we increased the preoperative dose of intravenous azathioprine to 300 mg. The initial daily dose of prednisone had been reduced from 100 mg to 40 mg in October 1972 and was reduced further to 30 mg daily in September 1979. This regimen was continued for two months and then the dose gradually reduced to 10 mg daily at the end of the first year. In May 1980 we substituted prednisolone for prednisone because of its more consistent bio-availability.

For the first six months after transplantation prednisolone was taken in divided doses in the morning and evening and thereafter in a single morning dose. This policy has not been changed during the study, apart from a period in 1978 and 1979 when daily and alternate day prednisone treatment was compared in some patients who had been transplanted for one year.

In November 1978 we introduced single-dose prophylactic treatment with antibiotics at the time of transplant and at any subsequent operation. Ampicillin 2 g, flucloxacillin 2 g, and gentamicin 120 mg were given intravenously just before surgery. Anticoagulants were no longer given for severe rejection or for the treatment of renal artery stenosis.

Early in 1978 we adopted a policy of giving blood transfusions to all patients before transplantation. Three units of packed cells were given to each patient who had not previously been transfused at intervals of one week or more. At the same time we attached greater importance to HLA-B locus matching in cadaver transplants; only recipients with uncommon B locus antigens were offered kidneys with incompatibilities at this locus.

ANALYSIS OF GRAFT SURVIVAL

Actuarial graft survival was calculated according to the method of Barnes.⁵ The analysis was carried out both including and excluding non-immunological failures. The advantages of both approaches have been debated many times.^{6,7} If non-immunological failures are included the benefits of tissue typing may be obscured by the inclusion of failures which are unrelated to immunosuppression. If they are omitted the results may be distorted by excluding patients whose death was hastened by immunosuppressive regimens adjusted to rejection. The causes of non-immunological failure in our series (tables I and II) indicated that the defects of the first of the two approaches were more serious, so the results in our figures and tables exclude non-immunological failures. Nevertheless, the effect on each analysis of including all failures had been indicated in the text. (Figures analysed by the second approach are available on request with reprints.)

Results and comment

Live-related donor transplants—Among 81 first live-related transplants there were 32 total rejections and nine non-immunological failures. Sufficient information was obtained from 67 donor-recipient pairs and their families to give a clear indication of the HLA haplotype matches. While the survival in group with two matched HLA haplotypes (A) was very good that in the groups with only one matched haplotype (B and C) fell to 60% at three years whether or not the donor was a parent or a sibling (fig 1). As only four recipients had not been transfused, the effect of transfusion in the live-related transplant group could not be assessed.

Cadaver-donor transplants—Among the 348 first cadaver-donor kidney transplants, there were 113 total rejections, 72 non-immunological failures (table I), and 17 deaths, which occurred from 18 months after transplantation (table II). As these 17 patients had a functioning graft at the time of death they have been regarded as "lost to follow-up" in the analysis. Each of the nine non-immunological failures listed in table I as "other causes" was due to one of the following: cerebral haemorrhage, acute pancreatitis, heart failure, serum hepatitis, chest infection, status epilepticus with cerebral anoxia, acute gastric dilatation, superior mesenteric arterial embolus, and renal trauma caused by biopsy.

Pretransplant blood transfusion—The beneficial effect of pre-transplant blood transfusion is shown in fig 2. The one-year graft survival in 188 transfused patients was 79% compared with 47% in 88 non-transfused patients ($p=0.0005$). The effect of transfusion remained statistically significant up to six years after transplantation ($p=0.025$) even when the non-immunological failures were included in the analysis ($p=0.05$). Ninety-five of the 188 transfused patients

TABLE I—Non-immunological causes of failure in first renal cadaver-donor grafts

Causes of failure	No of cases
Urinary extravasation	11
Haemorrhage from renal artery or vein	11
Thrombosis of renal artery or vein	11
Septicaemia	7
Cortical necrosis or dead kidney (prolonged warm ischaemia)	5
Myocardial infarction	5
Renal artery stenosis	3
Dialysis dementia	3
Pulmonary embolus	3
Gastrointestinal haemorrhage	2
Cytomegalovirus infection	2
Other causes	9
Total	72

TABLE II—Causes of death and duration of renal graft function in 17 patients considered lost to follow-up

Cause of death	No of patients	Mean age (years)*	Graft function (months)†
Myocardial infarction	10	51	45
Congestive heart failure	2	49	71
Pontine haemorrhage	1	39	24
Subarachnoid haemorrhage	1	49	21
Azathioprine-induced liver disease	1	30	104
Chronic aggressive hepatitis	1	59	21
Carcinoma of rectum	1	54	64

*Range: myocardial infarction, 40–62 years; congestive heart failure, 45–53 years.

†Range: myocardial infarction, 19–70 months; congestive heart failure, 69–73 months.

FIG 1—Graft survival in first live-related donor transplants matched for two and one HLA haplotypes (sibling to sibling) and one HLA haplotype (parent to child). (Non-immunological failures excluded.)

had received between 2 and 5 units of blood, seven had received 1 unit, and 28 more than 20 units. Nevertheless, neither the number of units of blood transfused nor the timing of transfusion before transplantation appeared to influence the effect of transfusion. The transfused and non-transfused groups did not differ significantly from each other in age, sex distribution, the degree of tissue matching, or duration of dialysis before transplantation.

HLA MATCHING

Because of the significant immunological benefit of pretransplant blood transfusion the effect of HLA matching was analysed within the separate groups of transfused and non-transfused graft recipients.

The only type of HLA matching which significantly improved graft survival was that of matching donor and recipient for two HLA-B locus antigens. This improvement occurred only in the transfused group of recipients (fig 3, group A); these 73 patients had a three-year graft survival of 83% compared with 65% in 115 transfused patients who were not matched for HLA-B antigens (group B)

FIG 2—Effect of pretransplant blood transfusion on graft survival in first cadaver-donor kidney transplants. (Non-immunological failures excluded.)

FIG 3—Separate effects of transfusion and matching of two HLA-B locus antigens on survival of first cadaver-donor kidney grafts. (Non-immunological failures excluded.)

TABLE III—Graft survival at 24 months after transplantation

HLA antigens in common	Transfused cases		Non-transfused cases	
	No	%	No	%
B locus identity				
4	11	90	10	40
3	53	82	25	56
2	9	76	3	33
Non-B locus identity				
3	32	70	15	47
2	53	70	27	44
1	21	67	5	40
0	9	67	3	33

($p=0.01$). The difference remained significant up to seven years after transplantation ($p=0.025$), and up to six years after transplantation when the non-immunological failures were included in the analysis ($p=0.025$).

The transfused patients with two HLA-B antigen matches did not differ from those unmatched for HLA-B antigens in the number of units of blood transfused, age or sex distribution, or the duration of dialysis before transplantation.

Within the transfused group seven patients received two HLA-B locus antigen matches combined with two HLA-A antigen compatibilities; only one of the seven grafts was rejected. HLA matching in the non-transfused graft recipients produced no significant benefit.

Number of HLA antigens in common—The 24-month actuarial graft survival according to transfusion status and number of HLA antigens

in common between donor and recipients is shown in table III. Apart from the cases in the transfused group matched for HLA-B antigen there was no benefit in simply matching for a greater number of common HLA antigens.

HLA-DR matching—Sixty-four consecutive first cadaver-donor transplants were typed for HLA-DR antigens. Two cases were excluded because no HLA-DR typing results could be obtained for the donor owing to the poor condition of the cadaver material. Eleven transplants failed for reasons unconnected with rejection. Of the 51 recipients available for analysis, 49 had been transfused. Two recipients matched their donors for two DR antigens and in both cases the grafts were surviving at the time of assessment. Nevertheless, both patients were transfused recipients and matched for HLA-B antigens, who in our study represented a privileged group. Twenty-two recipients were matched for one DR antigen and their 12-month graft survival was 79%, while 25 recipients had no measurable DR antigens in common and had a graft survival of 80%. Thus, in this group of transfused graft recipients matching for one DR antigen appeared to offer no advantage.

HLA-B and DR matching—In this series of 62 HLA-DR typed transplants the number of cases matched for two, one, and no DR antigens within the group matched for HLA-B antigens were 2, 19, and 18 respectively and in the non-HLA-B matched group, 0, 11, and 12 respectively. The advantages of HLA-B antigen matching were not, therefore, due to matching for DR by linkage disequilibrium.

CHANGE OF POLICY IN NEWCASTLE

Early in 1978 we decided to perform transplants only on patients who had been transfused and to attempt to increase the proportion of HLA-B antigen matches. In addition, the other minor changes in initial immunosuppressive and antibiotic treatment were introduced. Sixty-four first transplants have been performed under this policy. The proportion of transfused recipients rose from 63% to 95% and of HLA-B antigen matches from 34% to 62%.

Since the implementation of these changes the actuarial graft survival at 24 months has improved significantly from 63% to 78% ($p=0.025$); furthermore, the graft survival was 82% in 32 HLA-B matched cases compared with 74% in 19 unmatched recipients ($p>0.1$). The HLA-B matched and unmatched patients did not differ in transfusion history, age or sex distribution, or duration of dialysis before transplantation.

Discussion

The results of first cadaver-donor transplants in Newcastle upon Tyne show that matching for two HLA-B locus antigens continues to give significantly improved graft survival in previously transfused recipients. Indeed, the graft survival in this group of recipients is better than that achieved in the one haplotype matches from either parent or sibling live-donor transplants.

The beneficial effect of matching for two HLA-B locus antigens was first reported by Oliver *et al*⁸ and supported by earlier reports from the Newcastle centre.^{2,4} Brynner and Gelin⁹ have recently reported graft loss to be significantly associated with HLA-B antigen incompatibility.

When we began DR typing it had been reported that DR matching for one or two antigens gave a graded benefit.¹⁰⁻¹² A more recent study, however, shows that DR matching confers benefit only if there are no mismatches.¹³ Only two of our donor-recipient pairs were matched for two DR antigens; our analysis consisted of comparing 22 patients matched for one DR antigen with 25 who had no measurable DR antigens in common. Furthermore, although Ting and Morris¹³ found benefit from DR matching in transfused patients, this was small. Most of our patients in whom DR typing was performed had been transfused (49 out of 51 recipients analysed). We have no data on the effect of DR matching in non-transfused recipients. Until further evidence on the value of DR matching becomes available we intend to continue with our present policy of pretransplant transfusion and of matching for HLA-B locus antigens.

We have been encouraged that both pretransplant blood transfusion and HLA-B antigen matching have, over two years,

been accompanied by a significantly reduced rate of total rejection in our patients. We cannot, of course, be certain that the introduction of the initial higher dose of azathioprine and of the two early boluses of methylprednisolone did not also contribute to the improved results. Nevertheless, the improvement was in keeping with our previous finding of benefit from transfusion and HLA-B matching.

The object of a kidney-sharing scheme must be to ensure that the recipients of the organs receive the maximum benefit and that rejection rates are kept as low as possible by suitable tissue matching. Furthermore, the shortage of donor organs and the cost of matching, sharing, and transporting kidneys demands that the best use should be made of available resources.

In our patients matching for B locus antigens was more important than that for A locus antigens and (in a small sample) one DR locus antigen. The accuracy and completeness of the data are likely to be greater in a single-centre analysis than in multicentre national or international studies. We invite other centres to examine their data to see if they agree or disagree with this conclusion. If there are no conflicting results we urge the UK Transplant Service to change over to B locus matching as its main criterion for distributing kidneys pending further information on the value of full DR matching.

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Trimethoprim resistance in hospitals

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Abstract

During November 1980 to April 1981, 1561 urinary tract pathogens were collected from Turku City Hospital, Turku University Central Hospital, and Kuopio University Central Hospital. Resistance of the strains was tested by agar-plate dilution against trimethoprim, sulphamethoxazole-trimethoprim, sulphamethoxazole, ampicillin, and nitrofurantoin. Resistance to trimethoprim (≥ 8 mg/l) occurred in 8.6-12.2% of strains from the university hospitals (*Pseudomonas* excluded) and 38.3% of strains from Turku City Hospital. Resistance of *Escherichia coli* occurred in 4.1-6.2% of strains from the university hospitals and 21% of strains from Turku City Hospital. *Proteus mirabilis* was the most resistant of the clinically important bacterial species with resistance to trimethoprim in 29-78%.

Attention is called for in defining the type of hospital used for a particular study: bacterial resistance in different hospitals cannot be compared direct and one hospital is not necessarily representative for a whole country. After seven years' use of plain trimethoprim the prevalence of resistance in the two university hospitals

in Finland was similar to that in a London hospital just before plain trimethoprim was registered for use in Britain.

Introduction

Trimethoprim is now registered in several countries for prophylaxis and treatment of urinary tract infections: in Finland this happened as early as 1973.¹ In 1980 we found that 31.6% of bacterial strains isolated from hospital patients (*Pseudomonas* excluded) were resistant to trimethoprim.² The specimens were received from Turku City Hospital and the health centre wards in Turku. We have now compared the prevalence of resistance in Turku City Hospital with that in two university hospitals. We also studied bacterial resistance to sulphamethoxazole-trimethoprim, sulphamethoxazole, ampicillin, and nitrofurantoin.

Materials and methods

Consecutive urinary samples were collected during November 1980 to April 1981, from Turku City Hospital for six months and from Turku University Central Hospital and Kuopio University Central Hospital for two months in the beginning of the period. Only one specimen from each patient was accepted.

Strains were isolated by the dipslide technique (Uricult; CLED and MacConkey agars) and bacterial isolates identified by routine methods including the API 20E procedure.^{3,4} Resistance of all bacteria to five antimicrobial drugs was tested by agar-plate dilution using PDM-ASM agar (Ab Biodisk, Solna, Sweden).⁵ *Escherichia coli* K 12 and *Staphylococcus aureus* K 209 were inoculated as control strains on each plate. Minimum inhibitory concentrations (MIC) generally used in Scandinavia to determine the resistance breakpoints were applied (trimethoprim ≥ 8 mg/l; sulphamethoxazole-trimethoprim (20:1)

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