TRANSPARENT SURVIVAL AND CLINICAL COURSE
AFTER PRETRANSPLANT HLA-A AND B MATCHED
BLOOD TRANSFUSIONS: A SINGLE CENTRE STUDY

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Summary

The effects of HLA-A and B matched pretransplant blood transfusions on the
outcome of primary cadaveric kidney transplantation were studied prospectively
in a group of 15 patients who had never received a transplant and had never been
pregnant.

From our study, prolongation of graft survival could be demonstrated for
patients receiving pretransplant HLA-A and B matched blood transfusions.

The clinical course was comparable to that found in a group of patients who
received random pretransplant blood transfusions, although there were consider-
ably more patients in this latter group hospitalised for a very long period, a fact
which could be attributed mainly to viral infections.

Introduction

There is a little doubt about the favourable influence of pretransplant blood
transfusions on cadaveric kidney graft survival [1]. However, the administration
of blood transfusions carries the risk of the formation of lymphocytotoxic anti-
bodies, which have been correlated with an unfavourable graft survival [2] and
prolonged dialysis times [3].

In an attempt to reduce the risk of sensitisation leucocyte-free [4] and frozen
[5, 6] blood transfusions have been administered to prospective recipients. As
none of these approaches appeared to be as effective as the administration of
whole blood or packed cell suspensions [6], this might indicate that leucocytes
are indispensable for inducing the ‘transfusion effect’.

Another approach which avoids lymphocytotoxic antibody formation, but
maintains the presence of leucocytes, is the administration of blood transfusions
matched for the HLA-A and B locus antigens: this was the subject of our study.
By avoiding the formation of lymphocytotoxic antibodies insofar as possible, it
was expected that the clinical course would be somewhat better than that
observed after random pretransplant blood transfusions.
On the basis of this expectation an evaluation was carried out with regard to graft and patient survival, the number of rejection treatments, the amounts of corticosteroids administered, the function of the transplant measured by creatinine clearance, the incidence of viral infections and the period of hospitalisation.

Materials and methods

To investigate the problem of sensitisation a prospective trial was started in 1977. Non-transfused dialysis patients received a limited number of leucocyte-poor, HLA-A and B matched, identical or compatible, blood transfusions at three-week intervals (PG = protocol group).

Due to the fact that non-transfused patients were no longer considered for transplantation after 1977, most dialysis centres gave their patients random transfusions. Therefore, it was impossible to obtain a control group which would receive prospectively the same number of random blood transfusions as the protocol group and administered in the same way. Therefore we decided to consider patients who underwent transplantation just before and after each protocol patient as controls (RTCG = random transfused control group).

All patients from the RTCG underwent transplantation in the same centre and in the same period, followed the same immunosuppressive regimen and were treated by the same medical staff as patients from the PG. Both groups consisted of patients who had never been pregnant and received a primary cadaveric graft.

As the details of this study were extensively described before [7], only the most relevant information about both groups will be given below.

Control groups

a) Protocol group (PG) In 1977/78 20 non-transfused haemodialysis patients received a limited number (1–3) of HLA-A and B matched blood transfusions. Fifteen patients (up to December 1981) have received a primary cadaveric kidney graft. Their age varied from 19 to 52 years, with a median of 32 years. Haemodialysis had lasted from 7 to 59 months, with a median of 31 months. Male-to-female ratio was 14:1. The interval between the last transfusion and the date of transplantation varied from 2 to 30 months, with a median of five months. The mean number of HLA-A and B mismatches between kidney donor and recipient was 1.4; the mean number of HLA-DR mismatches was 1.0. For the 13 patients with a successfully transplanted graft, follow-up time after transplantation has been more than one year (20 to 49 months) (Table 1).

b) Random transfused control group (RTCG) All patients had received pre-transplant blood transfusions from random blood bank donors, varying in quantity from one to 21 units with a median of two units. Their ages ranged between 17 and 53 years, with a median of 31 years. They had been on haemodialysis from four to 52 months, with a median of 23 months. Mean HLA-A and B mismatch between kidney donor and recipient was 1.2, mean HLA-DR mismatch was 0.7. Male-to-female ratio was 19:7 (Table 1).
<table>
<thead>
<tr>
<th>TABLE I. Patient data</th>
<th>Protocol group (n = 15)</th>
<th>Random transfused control group (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>32 (19–52)</td>
<td>31 (17–53)</td>
</tr>
<tr>
<td>Median dialysis time (months)</td>
<td>31 (7–59)</td>
<td>23 (4–52)</td>
</tr>
<tr>
<td>Mean HLA-A/B MM*</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean HLA-DR MM*</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Median number of pretransplant blood transfusions</td>
<td>2 (1–3)</td>
<td>2 (1–21)</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>14:1</td>
<td>19:7</td>
</tr>
</tbody>
</table>

* mismatch between kidney donor and recipient

Rejection episodes

Rejection episodes were diagnosed on clinical grounds. In a number of cases angiographic studies of the transplant and renal scintigraphy were performed. In many instances a renal biopsy was taken. Acute rejection episodes were treated according to a standard regimen of prednisone 2.5mg/kg body weight/day for the first five days, gradually tapering off in 14 days to 0.5mg/kg body weight/day or three intravenous doses of methylprednisolone 15mg/kg body weight on three alternate days.

Viral infections

Routinely post-transplant serum samples were taken from the patients for viral antibody determinations. Onset of viral infections was defined as a four-fold or greater increase in antibody titres in paired serum samples. Both a standard complement fixation and an immune adherence haemagglutination test [8] were used. Where indicated, viruses were isolated from blood, urine and saliva as described elsewhere [9].

Results

Transplant and patient survival

Figure 1 shows actuarial kidney graft survival for both groups. The difference is not significant (log rank test p = 0.14). Transplant survival at one and two years was 87 per cent for the PG and 76 per cent and 50 per cent, respectively, for the RTCG.

There were no deaths in the PG whereas four patients out of the RTCG died within the first two years after transplantation. The difference is not significant.
Figure 1. Actuarial kidney graft survival after HLA-A and B matched pretransplant blood transfusions. The difference between the PG and the RTCG was not significant (log rank test $p = 0.14$). The figures indicate the numbers of patients at risk.

Clinical course

Two patients from the PG underwent transplantation elsewhere due to unforeseen circumstances. The remaining 13 received a transplant in the same centre as the RTCG and are therefore eligible for this part of the study.

Table II lists the mean of the total number of rejection treatments, successful and unsuccessful, for both groups: PG ($n=13$) 2.5, RTCG ($n=26$) 1.6 ($p=0.08$).
TABLE II. Post-transplantation data

<table>
<thead>
<tr>
<th></th>
<th>Protocol group</th>
<th>Random transfused control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 13)</td>
<td>(n = 26)</td>
</tr>
<tr>
<td>Mean number of rejection* treatments (first year)</td>
<td>2.5</td>
<td>1.6 (p = 0.08)</td>
</tr>
<tr>
<td>Median amount of corticosteroids in mg (first half year)</td>
<td>8894 (2225–13359)</td>
<td>5800 (p = 0.03) (1747–12522)</td>
</tr>
<tr>
<td>Median creatinine clearance in ml/min (at one year)</td>
<td>59 (40–109)</td>
<td>52.5 (7–107)</td>
</tr>
<tr>
<td>Cumulative transplant survival (at one year)</td>
<td>87%</td>
<td>74%</td>
</tr>
<tr>
<td>Cumulative patient survival (at one year)</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>Incidence of viral infections‡ (first year)</td>
<td>8/12 (66%)</td>
<td>14/23 (60%)</td>
</tr>
<tr>
<td>Median hospitalisation in days (first year)</td>
<td>53 (23–72)</td>
<td>60 (28–280)</td>
</tr>
</tbody>
</table>

* for functioning grafts only; PG 2.4; RTCG 1.4 (p = 0.048)
‡ viral infections could only be evaluated in 12 PG and 23 RTCG patients

The same tendency, but even more pronounced, is seen when only functioning grafts are considered: PG (n = 11) mean 2.4, RTCG (n = 17) mean 1.4 (p = 0.048).

Similarly the total amount of corticosteroids administered is listed in Table II for both groups, including patients with graft failures. Median values: PG 8894, RTCG 5800 (p = 0.03).

Median graft function for transplant functioning at one year, given as the creatinine clearance expressed in ml/min, was 59ml for the PG and 52.5ml for the RTCG. The difference is not significant (Table II).

The incidence of viral, mainly cytomegalovirus, infections during the first year after transplantation could be evaluated in 12 PG and 23 RTCG patients. No marked differences were observed: PG 8/12 (66%), RTCG 14/23 (60%) (Table II).

The median hospitalisation period during the first year after transplantation for all patients, was 53 days for PG patients and 60 days for RTCG patients, which is statistically not different (Table II). Ten patients from the RTCG were hospitalised for more than 70 days, in contrast to only one from the PG (p = 0.09). The median hospitalisation period for 14 RTCG patients with viral infections was 92.5 days. A significant difference could be demonstrated with nine RTCG patients (median 44; p < 0.01) and eight PG patients (median 54.5; p = 0.01) without viral infections.
Discussion

Our study clearly shows that a high transplant and patient survival can be obtained after a limited number of pretransplant HLA-A and B matched blood transfusions. However, in contrast to our initial expectations, more rejection treatments and significantly larger amounts of corticosteroids administered were observed in the PG than in the RTCG. Despite these observations the outcome of transplantation was not worse for PG patients. On the contrary, most clinical parameters appeared to be slightly better for the PG, although statistical significance could not be reached (Figure 1 and Table II). Moreover, 10 patients from the RTCG were hospitalised for more than 70 days in contrast to only one from the PG (p = 0.09). A positive correlation between prolonged hospitalisation and post-transplant viral infections could be demonstrated (p = 0.005). This observation was illustrated by the fact that the median hospitalisation period for patients from the RTCG with viral infections was 92.5 days and for patients without 44 days (p = 0.01). Such differences were not found in the PG (54.5 and 46.5 days, respectively).

Thus, whereas the incidence in viral infections was not different between the two groups, the morbidity differed markedly. Viral infections in the RTCG were significantly correlated with a long hospitalisation period, which was almost twice that noted for PG patients.

Our study seems to give rise to a paradox. Despite more rejection treatments and significantly larger amounts of corticosteroids, graft survival and morbidity were not worse in the PG. On the contrary, we had the impression that the clinical course was somewhat better for PG patients. A possible explanation for these apparently contradictory and unexpected findings has been given elsewhere [10].

On the basis of our findings we suggest that the administration of HLA-A and B matched pretransplant blood transfusions is an almost ideal method for inducing a favourable outcome of renal transplantation without the concomitant risk of the formation of lymphocytotoxic antibodies.

Acknowledgments

The authors are much indebted to Mrs L H Nubé-Wiemer and Miss C Rijvordt for typing the manuscript.

References

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2. d'Apice AJF, Tait BD et al. Transplantation 1982; 33.2: 191
5. Fuller TC, Delmonico FL, Rubin NT et al. Transplant Proc 1982; 14.2: 293
Open Discussion

BRYNGER (Gothenburg) One thing that worries me about this material is the large difference in the steroids used in these two groups which might indicate that you are dealing with very fit patients. Were the transfusions random so that the doctors did not know into which category these two patient groups fell, because I think the difference was quite substantial and it worries me a little.

NUBÉ The groups were not randomised because at the time the study was initiated there were so few patients without prior transfusions. We had to do it in this way and only regard the patients as control if they were transfused, which was the case from 1978 onwards. We have tried to compare similar groups by taking them only if they were transfused just before and after, without prior pregnancies and without prior grafts. In this way we tried to get about equal groups, but you could see there were somewhat more DR mis-matches between kidney donor and recipient in our control group.

BRYNGER I accept that and I realise the problems very well. I still think that what you showed is that you will have a reduced number of sensitisations. The survival may be better because you are giving more immunosuppression to this group.

BROYER (Paris) It has been shown that the results of transplantation in patients having cytotoxic antibodies is strongly influenced by HLA compatibility matching and I wonder what was the grade of matching in your patients having lymphocytotoxic antibodies and rejection.

NUBÉ There was no difference in the matching of the group who developed lymphocytotoxicity.

PAPADIMITRIOU (Thessalonika) I wondered what you are going to do with patients who do not need blood transfusions such as those with a PCV of over 35 per cent due to polycystic disease. I saw a letter from your unit indicating that you are giving platelet transfusions experimentally. Do you use this clinically?

NUBÉ No, not yet. As far as I know the only study with platelets was in a monkey model and not in humans. Actually the monkey study was not from our group.
BARNES (Birmingham) Did you use one donor for each recipient of blood or were you using several different HLA identical blood donors?

NUBÉ Several different donors, and first we started with three transfusions and only four patients received three transfusions from different donors and then we went back to two transfusions for logistical reasons.

BARNES So you were giving a wide variety of non HLA factors?

NUBÉ Yes, correct.

BARNES Nobody therefore had more than one transfusion from one donor as in donor specific transfusion or living related kidney transplant patients?

NUBÉ No, nobody.