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HOW CAN HLA MATCHING IMPROVE KIDNEY GRAFT SURVIVAL?

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Introduction

The question formulated in the title is really incomplete. To it should be added: ‘in unrelated donor-recipient pairs’. because evidence that HLA matching can improve kidney graft survival between siblings was presented more than ten years ago and is unanimously accepted [1, 2]. In contrast it is only in the last few years that consensus has been reached that HLA—A and —B matching can also improve kidney allograft survival if donor and recipient are unrelated [3]. Although significant, improvement is not impressive: ± 15% at five years post-transplantation. It is furthermore striking that in almost all series one-third of the transplants fail within the first three to six months after transplantation. If we want to improve overall kidney graft survival it is imperative that we find means by which this early graft loss can be prevented. In this publication we will discuss three possible avenues to attain this goal: HLA—DR matching, blood transfusion and the prevention of non-HLA incompatibility.

HLA—DR Matching

Almost from the beginning of clinical kidney allografting evidence has been accumulating which indicates that a low or negative MLC test is indicative of a good transplant prognosis. This was in itself an important impetus to develop methods of typing for the HLA—D determinants which are the strongest stimuli in the MLC test [4]. The methods all used the MLC test or variants of it. However, because the MLC test is so time consuming it is only suitable for the selection of living related donors.

Thus a method was developed which would allow rapid identification of HLA—D identical donor-recipient pairs, and which could be applied in the cadaveric donor situation. A systematic search for antibodies which could recognise the HLA—D determinants was begun. This effort was successful and antibodies were identified which allowed the recognition of HLA—D antigens or determinants closely linked to them, called HLA—DR [5, 6].
To assess the importance of HLA–DR matching in kidney transplantation, DR typing was performed on peripheral blood cells of the recipient and frozen spleen cells from the corresponding kidney donor [7]. Figure 1 shows the influence of DR matching on kidney graft survival [8]. The data strongly suggest that: (a) matching for both DR antigens appears to result in excellent graft survival; and (b) even matching for one HLA–DR determinant can significantly reduce early graft loss.

![Graph showing graft survival over time](image)

Figure 1. HLA–DR matching in Eurotransplant (N = 237)

Other groups have done similar studies [9–15] and came to similar conclusions. The available data show that matching for two HLA–DR antigens improves graft survival significantly. Whether this is also the case for grafts matched for one HLA–DR antigen only is still controversial.

**The Relation Between A, B and DR Matching**

To evaluate the relative importance of HLA–A and –B matching versus HLA–DR matching results of A and B matching at six months were compared with HLA–DR matching in a group of patients typed for all three loci (Table I). It is quite clear that at six months DR matching is already far more effective than A and B.
TABLE I. Comparison of HLA−A and −B Versus HLA−DR Mismatches

<table>
<thead>
<tr>
<th>Number of Mismatches</th>
<th>% kidney graft survival at six months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HLA−A + −B</td>
</tr>
<tr>
<td>0</td>
<td>81 (36)</td>
</tr>
<tr>
<td>1</td>
<td>76 (63)</td>
</tr>
<tr>
<td>2</td>
<td>70 (34)</td>
</tr>
<tr>
<td>Difference between 0−2 mismatches</td>
<td>11%</td>
</tr>
</tbody>
</table>

Numbers between parentheses indicate number of patients [8]

matching. The data suggest that if one matches for one DR antigen, kidney graft prognosis is as good as when one matches for four A−B antigens.

It is clear that only for a minority of the patients will it be possible to find an A, B and DR identical graft and that it will not even always be possible to find a graft which is at least matched for two DR antigens. To develop a guideline how to proceed in such a situation we calculated graft prognosis taking the sum of the A, B and DR matches as a dividing point. Table II shows that if there are zero incompatibilities for A, B and DR, graft survival at six months is 100%. However, these data have to be regarded as provisional (N = 5). If there is one incompatibility, either at the HLA−A, −B or at the −DR locus then graft survival is 94% (N = 21). If there are two incompatibilities graft survival is 74% and it drops with increasing numbers of incompatibilities. The data strongly suggest that two DR antigen mismatched grafts do less well than one DR antigen mismatched grafts in these groups (64% and 67% respectively).

TABLE II. Combined Effect of HLA−A, −B and −DR matching [8]

<table>
<thead>
<tr>
<th>Incompatibilities for HLA−A + −B</th>
<th>Incompatibilities for HLA−DR</th>
<th>Total of incompatibilities</th>
<th>% graft survival at six months Per category</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100 (5)</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>1</td>
<td>100</td>
<td>91 (21)</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>2</td>
<td>64</td>
<td>74 (48)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>2</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>3</td>
<td>80</td>
<td>69 (42)</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td></td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Etc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Both HLA—A—B matching and HLA—DR matching are thus able to improve graft survival. If an A—B—DR identical graft cannot be found, one should try to find one which is identical at the HLA—DR locus and which has only one mismatch for the HLA—A or —B loci or vice versa. In that case good graft survival might also be expected. If such a match cannot be realised either, one should strive to keep the number of HLA—DR mismatches at one, and select a recipient with a minimal number of HLA—A and/or —B mismatches.

**Blood Transfusion**

Opelz and Terasaki were the first to present significant evidence that blood transfusion not only causes immunisation which endangers graft survival, but also prolongs graft survival [16, 17]. Van Es and Balner produced experimental evidence for this in the Rhesus monkey [18]. We want to stress in this connection two points of importance from our own work. The first is that we have confirmed in a prospective study our previous finding that a single transfusion improves graft survival.

![Graph](image)

Figure 2. Graft survival in relation to a single blood transfusion. Only leucocyte-poor blood transfusions had a graft protecting effect [22, by kind permission of the publishers]
survival [19, 20]. 19 non-transfused patients received a single washed i.e. buffy-coat-poor blood transfusion before transplantation and of these only three transplants failed, for non-immunological reasons (one with coronary occlusion and two with viral pneumonia). The second, and this was a new finding, was that six of the eight patients who received blood made completely free from buffy-coat cells by passage through a cotton wool filter [21], rejected their kidney. These results were as poor as when no transfusions were given (Figure 2) [19, 22]. Thus for graft protection one needed the equivalent of about 50ml of allogeneic ACD blood. Although not randomised, this was a prospective study. The mechanism by which a graft protecting effect is obtained by a single blood transfusion is unclear.

**Non-HLA Incompatibility**

Very little attention has so far been paid to the influence of cell or tissue line specific systems other than the HLA antigens on graft survival, although such influences have been documented for sex and the Lewis, Rhesus and ABO system. Only the latter is taken into account in clinical organ transplantation (for review see 22). However, Moraes and Stastny [23] have identified a multi-allelic system which occurs on both endothelial cells and monocytes. Paul et al [24] and Claas et al [25] have independently identified antibodies against similar antigens and have shown that in all probability these play an important role in rejection of kidneys (Table III) and bone marrow grafts. Little is known of the precise con-

<table>
<thead>
<tr>
<th>Clinical results</th>
<th>CEAb present</th>
<th>CEAb absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irreversible vascular rejection &lt; 50 days</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Graft survival &gt; 50 days</td>
<td>2†</td>
<td>74</td>
</tr>
<tr>
<td>Non-immunological failure</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>88</td>
</tr>
</tbody>
</table>

* Two patients are excluded, one because of ABO-incompatibility and another because donor kidney tissue was not available

† CEAb present during rejection episodes

ditions under which these antibodies can be formed, but they can arise after pregnancy, repeated transfusions and/or kidney graft rejection. It is also uncertain whether the locus or loci coding for the determinants recognised by them lies in, near or outside the HLA complex but Thompson et al [26] have identified a polymorphic locus not linked to HLA coding for determinants on monocytes, endothelial cells and neutrophils. Now that the technical difficulties originally met in the recognition of the monocyte antigens have been solved and their clinical rel-
Evidence has been established, it will not take long before a more complete description of the system will be possible.

**Summary**

Matching both for HLA–A and –B and HLA–DR can improve kidney graft survival but DR matching is far more effective than HLA–A and –B matching. Because DR matching results in excellent graft survival and because of the apparent restricted polymorphism of the DR locus, recipient pools of a few hundred persons might be sufficient to find adequately matched recipients for the majority of the donor kidneys. This contrasts favourably with the pools of thousands of recipients now in use which enable one to realise only 10–20% HLA–A and –B identical matches. This might be true not only for renal but also for other tissue transplants, including hearts. If no HLA–DR full house match can be found one should try to find a donor who is only mismatched for one HLA–A, –B or –DR antigen. Blood transfusions improve graft survival and reinforce the effect of DR matching [27]. One blood transfusion appears to be sufficient for this graft protecting effect. The mechanism by which graft facilitation is obtained is unclear.

It is surprising that no studies have been done on the importance of HLA matching for patient survival. Recently we have been able to link up the computer file of Eurotransplant with that of the EDTA. The combined EDTA and Eurotransplant data show that patient survival is strongly influenced by HLA–A and –B matching, all other variables apparently being equal. If there are no mismatches (N = 150) patient survival after five years is well over 85%. In contrast if there are three to four mismatches only 57% of the patients survive after five years (Figure 3). We think this is a finding no physician involved in kidney transplantation can ignore.

![Graph showing patient survival and HLA–A and –B matching in Eurotransplant (N = 1885, unrelated first transplants)](image)

Figure 3. Patient survival and HLA–A and –B matching in Eurotransplant (N = 1885, unrelated first transplants)
Acknowledgments

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