Significant Factors Influencing Kidney Graft Survival

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MANY factors influence the outcome of a graft. This explains in part why it took so long to come to some degree of agreement on which factors determine graft survival and their relative importance. As far as the HLA-A and B antigens are concerned, there is now more or less a general agreement that they are of importance, although there is still disagreement on the question how much difference HLA-A and B matching can make for graft survival. Some groups claim that they can find a 40% difference between unrelated HLA-A and B identical and HLA mismatched grafts, while others find only a difference of 10% or 15%.[1,2]

The influence of HLA matching not on graft but on patient survival and the relation between the match and immunosuppression is still under study. In a collaborative analysis between Eurotransplant and the European Dialysis and Transplantation Association, a clear-cut and quite significant influence of HLA-A and B matching on patient survival was found.[3] It is logical to assume that this is due to the large amount of immunosuppression that must be given if the donor and recipient are severely mismatched for the HLA-A and B antigens. That this might indeed be true was shown by the clear-cut correlation found between the number of HLA-A and B mismatches and the number of rejection crisis treatments given.[1]

As far as pretransplant blood transfusion is concerned, there is general agreement that blood transfusions should be given, but more study is needed to determine whether the transfusion should be given pre- or pertransplantation and the optimal number of transfusions needed.[4] As far as HLA-DR is concerned, the only real agreement is that more data are needed. The majority of the published studies show a clear-cut effect of HLA-DR matching, but the data collected during the Eighth Histocompatibility Workshop were not convincing.[5] Our data still indicate a significant influence of DR matching: the DR-identical grafts are doing much better than those that are mismatched for 1 or 2 DR antigens.[6]

Next of course comes the question, whether if one matches for HLA-DR one can "forget" about HLA-A and B matching. Our graft survival data indicate that the effect of HLA-DR matching is potentiated by HLA-A and B matching. In the HLA-DR-identical group, graft survival is near 90% 1 year posttransplant if donor and recipient are also HLA-A and B matched or mismatched for only 1 antigen. On the other hand, HLA-DR matching and blood transfusions do not potentiate each other, or to a far lesser extent. In other words, one can give either pretransplant blood transfusions or one can select an HLA-DR-identical donor to obtain almost optimal results. Findings in the rhesus monkey model are in agreement with the human data.[7] However, some of the kidney grafts that were HLA-A and B matched and/or HLA-DR matched were rejected in the

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first 2 months after transplantation. This might indicate that factors outside HLA influence graft survival as well. This problem was systematically studied by Paul et al.[8] The protocol they used is extremely simple. Before transplantation, a biopsy of the donor kidney is taken, snap frozen, and at different intervals after transplantation, and of course if graft rejection occurs, sections of this biopsy are incubated with the serum of the patient, washed, and then stained with FITC-labeled antiimmunoglobulin. In this way antibodies could be demonstrated in the serum of about half of the patients who had rejected their kidney allograft within 2 months after transplantation. These antibodies only bind to the endothelium of the peritubular capillaries. It is tempting to speculate that the occurrence of such antibodies could for instance lead to platelet aggregation, and this to an irreversible vascular rejection. It could also be proven that the same antigen that is present on the endothelium is also present on monocytes. In other words, the endothelium and the monocytes share alloantigens that can be recognized on the endothelium by immunofluorescence and on the monocytes by complement-dependent cytotoxicity.[9] These endothelium-monocyte (EM) antibodies are formed especially in kidney graft recipients that are HLA-DRw6 positive. Although the data are significant, they should be interpreted with caution because the number of observations is still quite small, and secondly because the recognition of HLA-DRw6 is still quite difficult. If the correlation with HLA-DRw6 is correct, this could indicate that the formation of these EM antibodies is under Ir gene control (manuscript in preparation).

Also, the distribution of the EM and other alloantigens in kidney tissue was investigated. Alloimmune and both polymorphic and monomorphic monoclonal antibodies were used. To our great surprise, we could not demonstrate the HLA-A and B or the HLA-Bw4 or Bw6 or the HLA-DR antigens in a reproducible fashion in renal tissue. The HLA-B7 antigen is perhaps an exception. At least some of the anti-B7 sera reacted with vascular endothelium. Moreover monoclonal polymorphic anti-HLA-A2 and anti-HLA-B7 antibodies were negative. In contrast, the monomorphic monoclonal antibody against the HLA-A, B, C molecules and against HLA-DR molecules was strongly positive. The HLA-LB antisera, which recognize long or supertypic antigens on B cells (possibly identical or very similar to the MBl, 2, and 3 antigens described by Duquesnoy et al.),[10] gave positive staining reactions in the kidney. A monoclonal anti-MBl antibody, however, was only doubtfully positive.

The ABO antigens are present on the endothelium of arteries, arterioles, and peritubular capillaries.[11] These findings raise more questions than they answer. In the first place, how can we find a correlation between matching for HLA-A and B and HLA-DR if these antigens are not present in kidney tissue? Of course one can argue that the test was not sensitive enough for the detection of these antigens. The fact that more potent monoclonal monomorphic antibodies were positive could be in agreement with such an assumption.

The finding that the LB or MB antigens could be easily demonstrated on kidney tissue seems to lend support to the findings of Duquesnoy et al. that matching for these antigens improves graft survival.[12] We have so far not been able to substantiate their data, but further studies in this direction are certainly warranted. All this emphasizes the important role EM antigens might have as targets in graft rejection.

Finally, we want to discuss the evidence for a role of host factors in graft survival. Wilson and Kirkpatrick studied a group of patients with skin tests for microbial antigens and could show that those patients who had positive skin tests had first rejection crises which were on the average, on day 4, and thus a lot earlier than those who had negative skin tests (first rejection on day 14).[13] A few years later, Ceppellini studied the difference in graft survival if one donor gives a skin graft to two

recipients with the difference in graft survival if two donors give a skin graft to one recipient. It turns out that in the first case, the difference in graft survival is significantly greater. All these grafts were obtained from unrelated donors and were HLA-mismatched. This can be interpreted as an argument for the existance of host factors and their relevance for graft survival.[14] More recently, Diamondopoulos et al. performed skin tests with DNCB in a quantitative manner. Seventy percent of grafts with a DNCB score of less than 3 were still functioning after 6 months, while those that had a DNCB score of greater than 3 had a graft survival of 11% only.[15]

Our group and others[16–18] have approached the problem by using the cell-mediated lympholysis (CML) test. We consider the CML test as the best in vitro equivalent of the homograft reaction. Lymphocytes from the spleen of the kidney donor were frozen in liquid nitrogen. This was also done with lymphocytes from the kidney recipient at several intervals before blood transfusion, after blood transfusion, and before transplantation and after transplantation. The samples of one patient were tested all on the same day against the splenocytes of his specific kidney donor.

Goulmy studied 55 patients and found that about two-thirds of them became CML-nonresponsive to the specific kidney donor. This CML nonreactivity is donor-specific because the lymphocytes of the recipient, when tested against the lymphocytes of an unrelated donor in the CML test, gave a positive reaction. It turned out that CML nonreactivity coincides in a significant manner with good renal function. What we are studying is thus also clinically relevant. Recipients of male to male grafts and those that were HLA-B compatible had the best chance to become CML nonreactive against their donor. It was further of interest that recipients who were DR4-positive appear to be especially prone to develop CML nonreactivity. This might be an indication that the occurrence of CML nonreactivity is also under Ir gene control. It is clear that these data must be considered as preliminary and further studies are needed.[20]

In summary, we think that the most important factor in the determination of graft survival might be the responsiveness of the graft recipient (Table 1). If the recipient is a low responder, neither matching for DR, blood transfusion, or matching for the HLA-A or B or EM antigens is necessary. However, if the recipient is a responder, these factors become important. If a blood transfusion is given, the recognition phase initiated through differences for the HLA-DR antigens between donor and recipient can be blocked. Matching for HLA-DR is then not of such great importance and matching for the HLA-A and B and EM antigens is not necessary either. If no blood transfusion is given, or the blood transfusions were ineffective, then matching for DR can still block the recognition phase and matching for HLA-A and B is not (or less) necessary. If no blood transfusion is given and the kidney is DR mismatched, matching for the HLA-A and B antigens and possibly the EM antigens could still predispose for good kidney graft survival. However, if no blood transfusions are given or

Table 1. Factors Determining the Outcome of the Homograft Reaction in Clinical Renal Transplantation

Responder Status	Low Responder			High Responder	
HLA-DR (recognition)	Irrelevant	Identical	Mismatched	Mismatched	Mismatched
Blood transfusions (blocking of recognitions)	Irrelevant	Irrelevant	Blocking	No blocking	No blocking
HLA-A, B or EM? (effector)	Irrelevant	Irrelevant?	Irrelevant	Matched	Mismatched
Outcome	Functioning	Functioning	Functioning	Functioning	Rejection

the blood transfusion has not been effective in blocking the effect of an HLA-DR mismatch and donor and recipient are mismatched for the HLA-A and B and EM antigens as well, graft failure will ensue in most instances. Of course this is only a schematic summary of what we have discussed and must be regarded as a working hypothesis. However, it is certain that many factors influence graft survival and that there are many different levels that determine whether the graft will be successful or will be rejected.

REFERENCES

1 van Hooff JP, van Es A, Persijn GG, et al Proc EDTA 16 359, 1979

2 Persijn GG, Cohen B, van Rood JJ Dial Transplant 8 493, 1979

3 van Rood JJ, Persijn GG, Lansbergen Q, et al Proc EDTA 16 297, 1979

4 Persijn GG, Cohen B, Lansbergen Q, et al Transplantation 28 396, 1979

5 Opelz G, Terasaki P XIIth International Course on Transplantation and Clinical Immunology 1980 (in press)

6 Persijn GG, Cohen B, Lansbergen Q Dial Transplant 9 176, 1980

7 van Es AA, Balner H Transplantation 28 2, 1979

8 Paul I C, van Es LA, van Rood JJ, et al Transplantation 27 175, 1979

9 Claas FHJ, Paul LC, van Es LA, et al Tissue Antigens 5 19, 1980

10 Duquesnoy RJ, Marrari M, Annen K Transplant Proc 11 1757, 1979

11 Paul LC, van Es LA, Brutel de la Rivière G, et al Transplantation 26 268, 1978

12 Duquesnoy R, Annen KB, Marrari MM, et al N Engl J Med 302 821, 1980

13 Wilson WEC, Kirkpatrick CH In Starzl TE (ed) Experience in Renal Transplantation Philadelphia, Saunders, 1964, p 239

14 Ceppellini R, Curtoni ES, Mattiuz PI, et al Ann NY Acad Sci 129 421, 1966

15 Diamandopoulos AA, Hamilton DNH, Briggs JD Proc EDTA 15 283, 1978

16 van Rood JJ, Persijn GG, Goulmy E, et al Transplant Proc 11 36, 1979

17 Thomas J, Thomas F, Lee HM Transplant Proc 9 85, 1977

18 Wonigeit K, Pichlmayr R Dial Transplant 6 58, 1977

19 Dossetor JB, Liburd EM, Kovithavongs T, et al Transplant Proc 11 1260, 1979

20 Goulmy E, Persijn GG, Blokland E, et al Transplantation (in press)