

IMPROVED KIDNEY GRAFT SURVIVAL THROUGH HLA-DR-MT MATCHING

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Summary

The influence of prospective HLA-DR matching on cadaver kidney graft survival rate was investigated in 85 transplants performed during 1979 and 1980 within the South German Cooperative Study Group for Kidney Transplantation. Prospective HLA-DR matching showed a clear influence on graft outcome as all HLA-DR identical grafts were still functioning after a period of one year and reached a two year graft survival rate of 82 per cent compared to 60/43 per cent of the groups mismatched for one/two HLA-DR antigens. Seventy-four donors and recipients were simultaneously typed for their MT-specificities. In a retrospective analysis seventeen grafts matched for two MT-specificities had a two year graft survival rate of 94 per cent which was significantly better than that of grafts mismatched for one (53%) or both (17%) MT-specificities. According to these results MT matching of donors and recipients seems to have a superior influence on kidney graft outcome than donor-recipient selection due to HLA-DR identity.

Introduction

Antigens encoded by the MHC (Major Histocompatibility Complex) play a major role in cadaver kidney transplantation. Matching of donor and recipient for HLA-A and B antigens was shown to improve graft survival rates significantly [1,2]. Retrospective studies demonstrated that HLA-DR identity of graft and recipient is of more importance in transplant prognosis than HLA-A and B matching [3,4]. Therefore during the 8th International Histocompatibility Workshop an international transplant analysis was performed to investigate the influence of HLA-DR matching on kidney graft outcome in a prospective study. In this multicentre study no significant influence of HLA-DR matching on kidney graft survival was observed [5]. As single centre analysis continued to report superior graft prognosis for HLA-DR matched kidneys [6,7], other variables

like standardisation of pretreatment and HLA-DR typing, pretransplant blood transfusions or matching for second locus antigens of the HLA-D/DR region had to be considered to explain this discrepancy. Recently identity in MB-antigens, which represent another B-cell alloantigen system in high genetic linkage to the HLA-DR locus, has been reported to have a significant effect on kidney graft survival in related donor-recipient combinations [8]. In this study the beneficial effect of prospective HLA-DR matching and the importance of matching for further B-cell alloantigen systems, like HLA-MT, on graft outcome is demonstrated in a multicentre analysis.

Materials and methods

Patients

Eighty-five waiting list patients of the South German Cooperative Study Group for Kidney Transplantation (Centres: Tübingen, Frankfurt, Freiburg, Heidelberg, Kaiserslautern, Mannheim, Ulm) who received a cadaver kidney during 1979 and 1980 were analysed. Eighty patients were grafted for the first time and five patients received a second allograft. Thirty-three patients had received four or more blood transfusions and 47 recipients one to three blood transfusions prior to transplantation. One patient did not receive any blood and in four patients no precise transfusion history was available.

HLA-typing

HLA-typing of all recipients was performed on peripheral blood lymphocytes. Typing of donors was carried out on isolated lymphocytes of lymph nodes or from spleen. HLA-ABC typing was done according to the standard NIH technique [9]. HLA-DR as well as MT antigens were determined on isolated B-lymphocytes, enriched by nylon-wool filtration [10]. Locally well characterised HLA-DR antisera and the 'disease set' of the 8th International Histocompatibility Workshop were used to define the specificities HLA-DR 1-9 and HLA-MT 1-3 in a modified microcytotoxicity assay with prolonged incubation times for the antibody and complement phase [10]. Recipients were selected by EURO-TRANSPLANT for the best HLA-DR match as first priority. Sixty recipients and their respective organ donors were retyped in the Immunology Laboratory, Department of Medicine II, University of Tübingen to guarantee standardisation of HLA-typing.

Analysis of results

Actuarial graft survival rates were generated [11] and statistically evaluated by the 'log rank' test [12]. Graft failure was diagnosed at transplant removal, at the patient's death or if the patient had to return to chronic haemodialysis.

Results

Eleven patients received a HLA-DR identical graft, 60 patients shared at least

NUMBER OF IDENTITIES:

- A = 2 MT
- B = 2 DR
- C = 1 DR
- D = 1 MT
- E = 0 DR
- F = 0 MT

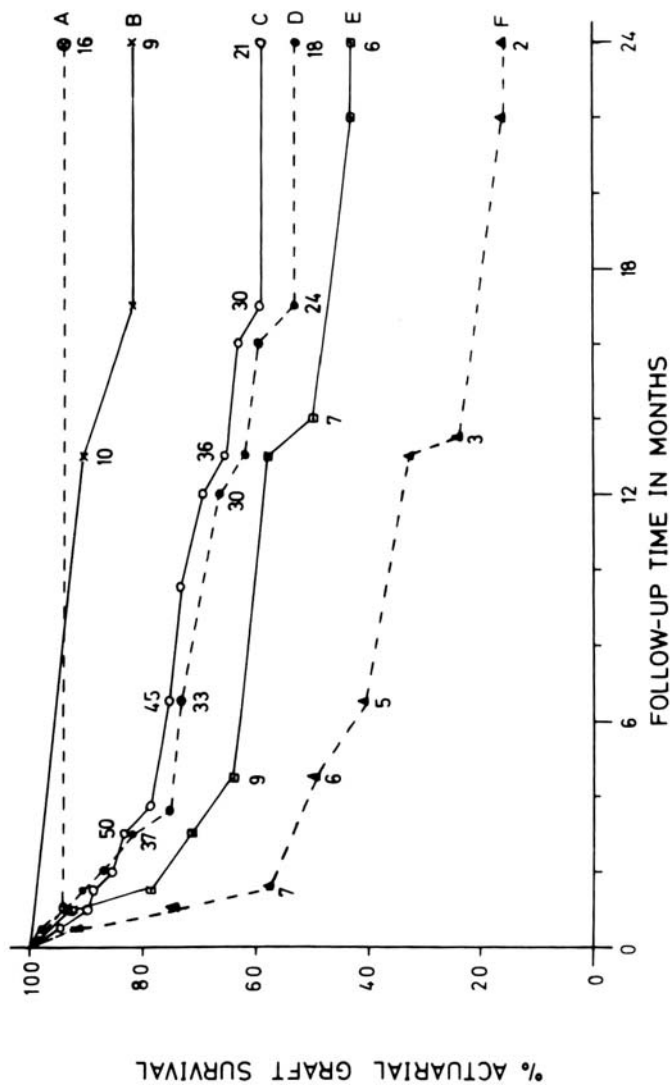


Figure 1. Influence of HLA-DR-MT matching in cadaver kidney transplantation

one HLA-DR antigen with their donor, but 14 grafts were completely HLA-DR mismatched. All HLA-DR identical grafts were still functioning one year after transplantation. In donor-recipient combinations with two mismatched HLA-DR antigens only 64 per cent of recipients had a functioning graft after one year. This difference in graft outcome was statistically significant ($p < 0.05$). After a two year follow-up only two HLA-DR identical grafts were lost, whereas grafts mismatched for one HLA-DR antigen reached a two year graft survival rate of only 60 per cent. A graft survival of 43 per cent was observed in the group mismatched for both HLA-DR antigens (Figure 1).

According to the retrospective analysis 17 patients shared two MT-specificities with their organ donors. In this group only one graft failed during an observation time of two years. This excellent graft prognosis of 94 per cent was in contrast to the graft outcome in 12 patients mismatched for two MT-specificities (17%). Seven cadaver kidney transplants of the latter group failed within the first year after grafting and three further organs were lost in the following 12 months, thus the two year graft survival rate in this particular patient group was only 17 per cent. This difference between graft prognosis of well (two MT antigens identical) and poorly (two MT antigens mismatched) HLA-MT matched transplants was statistically significant at two years ($p < 0.001$). To investigate the value of pretransplant blood transfusions two groups of patients were analysed. Patients with four and more blood transfusions (group A) had a one year graft prognosis of 84 per cent compared to 60 per cent in group B with three or less blood transfusions. Graft prognosis after one year of group B, however, was up 72 per cent in HLA-DR compatible or identical recipients.

Discussion

The results of this prospective multicentre study demonstrate the importance of HLA-DR matching in cadaver kidney transplantation. These data are in accordance with the results of single centre analysis [6,7] which reported improved graft survival rate in HLA-DR matched grafts. In our study graft prognosis was significantly improved in the two versus zero HLA-DR matched transplant group. Matching for only one HLA-DR antigen did not seem to have a superior effect on graft outcome than completely HLA-DR mismatched grafts (Figure 1). The discrepancy with the transplant study of the 8th International Histocompatibility Workshop could be explained by several factors such as the heterogeneity of the investigated patients in the international pool as well as by difficulties in HLA-DR typing. Mistakes in HLA-DR typing in our study were minimised by the retyping of donors and recipients in our laboratory.

In the retrospective analysis of 74 cadaver kidney transplantations 17 recipients were also shown to share two MT-specificities with their kidney donors. The two year graft survival rate of 94 per cent in this group was superior to the outcome of HLA-DR identical transplants. The improvement of graft prognosis for MT identical grafts was also highly significant statistically compared to the

disappointing results in grafts completely mismatched for the MT-specificities. The slightly better graft survival rate of grafts compatible for one HLA-DR antigen compared to those mismatched for one MT-specificity (Figure 1) could be explained by the fact that 11 grafts identical for one HLA-DR antigen were also identical for two MT-specificities. These results indicate that matching for HLA-MT might be of more importance for clinical graft prognosis than matching for HLA-DR. In related donor transplantation compatibility at another B-cell alloantigen system (MB) also has been reported [8] to improve graft survival rate. These alloantigens, MB as well as MT, are thought to be gene products of further loci of the HLA-D region [13].

In addition, the previously reported beneficial influence of pretransplant blood transfusions [5] on graft outcome has been confirmed in this study. Blood transfusions particularly seem to have an additive effect on graft prognosis in poorly HLA-DR-MT matched grafts.

Further studies will be necessary to evaluate the relative importance of matching for different gene products of the Ia region and of other factors like blood transfusions and clinical treatment influencing transplant outcome.

Acknowledgments

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