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Success rate and impact of HLA matching on kidney graft survival in highly immunized recipients

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Abstract. From 1985 to 1990, 225 highly immunized recipients were transplanted based on a program of serum exchange and priority allocation of kidneys to crossmatch negative recipients. The 1-year graft survival rate in first transplant recipients was 73% and in second transplant recipients, 71%. Recipients of third or fourth transplants had a 25% lower success rate. HLA matching exerted a significant influence on graft outcome. Twenty-five first or second grafts with zero mismatches for HLA-B,-DR had a 91% 1-year survival rate, in contrast to a 58% survival rate of 38 grafts with of three or four HLA-B,-DR mismatches (log rank $P < 0.001$).

Key words: Highly immunized recipients – HLA matching

The transplantation of highly immunized recipients continues to be a problem. Because the serum of these patients contains lymphocytotoxic antibodies that react against most potential donors, it is difficult to identify donors against whom the crossmatch test is negative. In 1985 we initiated a project aimed at identifying suitable donors for this special risk category of recipients. The current report is an extension of our previous publication in which we reported on the first 100 transplants. Since 1988, the number of patients who received transplants as a result of this project has more than doubled.

Patients and methods

A detailed description of the project's technical nature is provided in a previous publication [1]. Briefly, sera of highly immunized recipients (> 80% lymphocytotoxic panel reactivity in at least two consecutive recent screening) were collected every 2–3 months, added to tissue typing trays, and the trays were distributed to the participating transplant centers. Lymphocytes of potential kidney donors were added to the trays to identify patients with a negative crossmatch. A second crossmatch was performed in the laboratory of the recipient center. Whereas the HLA match was disregarded during the initial 3 years, a recommendation was made in 1988 to transplant kidneys only if dondor and recipient shared at least one HLA antigen on each HLA locus (HLA-A,-B,-DR). The mean number of patients enrolled for each serum exchange "cycle" was 151 and the mean number of transplants performed during each cycle was eight.

The following centers participated in this project:
Aachen, Barcelona, Basel, Bern, Berlin-Friedrichshain, Brussels, Cologne, Düsseldorf, Essen, Frankfurt, Freiburg, Geneva, Gent, Gothenburg, Hannover, Heidelberg, Helsinki, Innsbruck, Kaiserslautern, Lausanne, Leuven, Lübeck, Lund-Malmö, Madrid, Marburg, Milan, Munich, Münster, Paris, Prague, Tübingen, Vienna, Warsaw, Zürich.

Graft survival rates were computed by actuarial methods. One transplant was excluded from the analysis because the repeat crossmatch in the recipient center was positive but the transplant operation had been completed without awaiting the crossmatch results. No other exclusions were made.

Results

Figure 1 demonstrates the overall graft survival rates for first, second, third, and fourth cadaver transplants. First and second grafts had a nearly identical success rate of approximately 70% at 1 year. This result was identical with the one reported 3 years ago for the first 100 patients [1]. The survival of a fifth transplant which is still functioning is not shown in Fig. 1.

The effect on graft survival of matching for HLA-A,-B antigens is shown in Fig. 2. Although a trend towards improved survival with better matching was noticeable, this was not statistically significant. Figure 3 shows the effect of matching for HLA-DR antigens. Whereas there was no difference in outcome between grafts with zero or one mismatch, grafts with two mismatches did significantly worse. The impact of matching for the combination of HLA-B and HLA-DR antigens is illustrated in Fig. 4. Graft outcome worsened as the number of mismatches increased.

We felt it was of interest, primarily because the "acceptable mismatch" program of Claas and van Rood is

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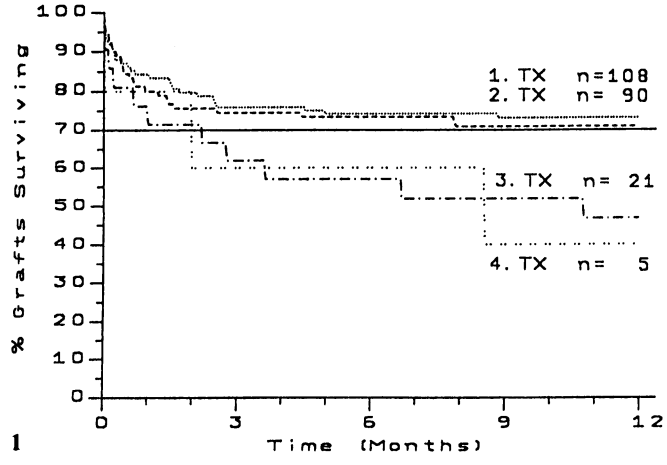

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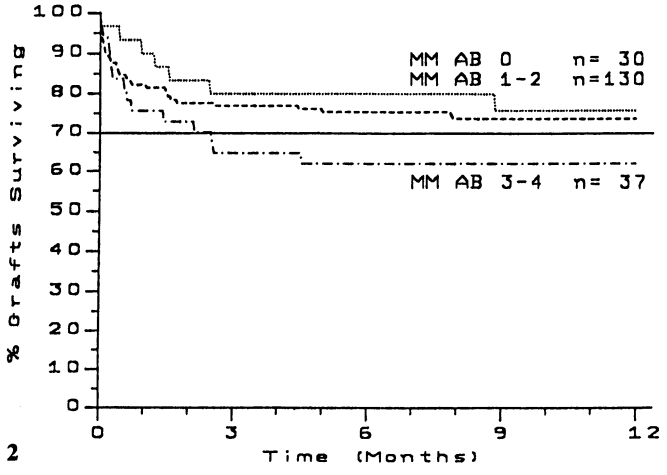

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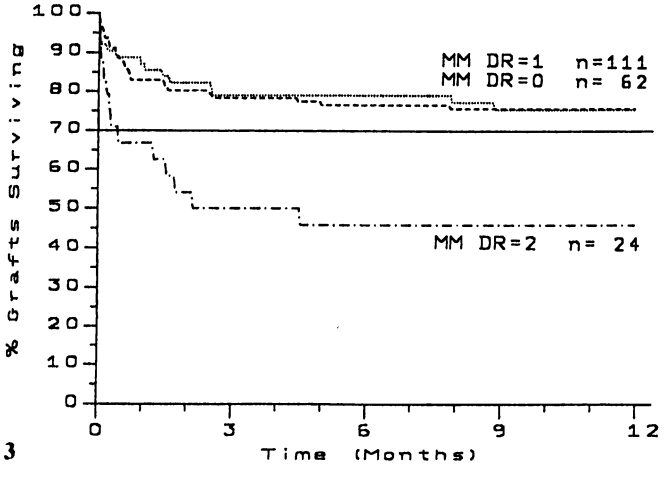

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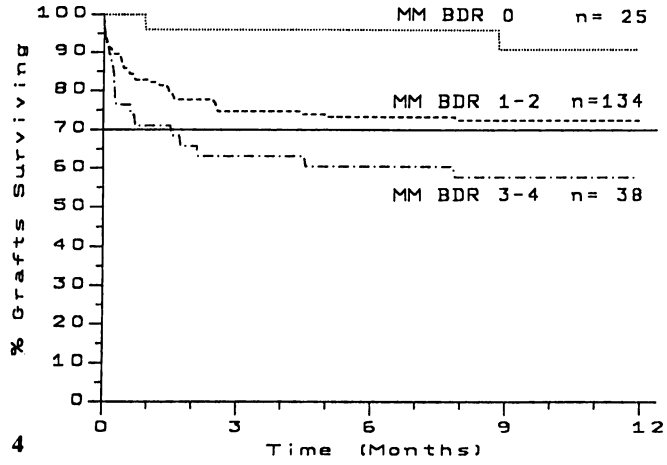
Fig. 1. Graft survival rates in highly immunized cadaver kidney recipients. First, second, third, and fourth transplants are plotted separately. The numbers of patients are indicated for each curve

Fig. 2. Influence of mismatches for HLA-A,-B antigens on graft survival (first and second grafts) in highly immunized recipients. The trend towards impaired survival with an increase in the number of mismatches is not statistically significant

Fig. 3. Impact of matching for HLA-DR antigens on graft survival (first and second grafts) in highly immunized recipients. Transplants with two HLA-DR mismatches had a 30% lower survival rate on



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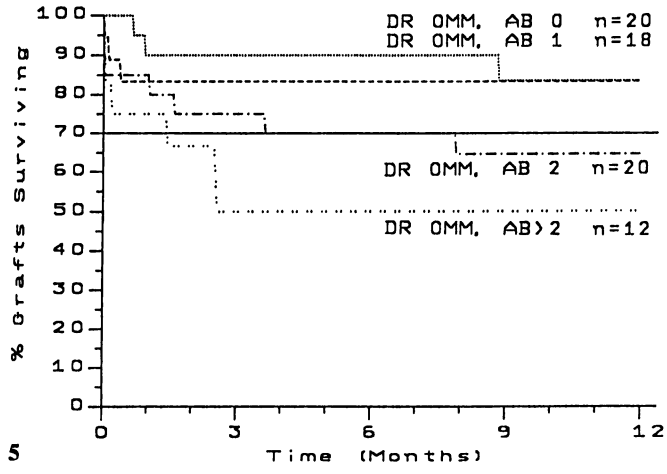

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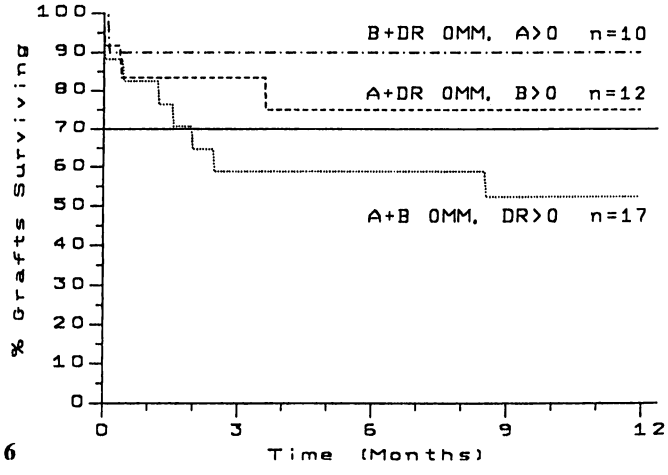

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1 year than transplants with zero or one mismatches (log rank $P < 0.001$)

Fig. 4. Analysis of HLA-B and HLA-DR mismatches on graft survival (first and second grafts) in highly immunized recipients. The influence of matching was statistically significant (P regression < 0.01)

Fig. 5. Influence of mismatches for HLA-A and HLA-B antigens in HLA-DR matched transplants. Mismatches for HLA-A,-B appear to have a deleterious influence

Fig. 6. Attempt at comparing the strength of indivdiual HLA loci. When the two complementary loci were matched, HLA-DR antigens had the strongest influence on graft outcome

based on grafts with zero HLA-DR mismatches [2], to analyze the impact of HLA-A,-B mismatching in HLA-DR compatible transplants. As shown in Fig. 5, even though all transplants were done after two negative crossmatches, there was a deleterious influence of mismatching for HLA-A and -B antigens. Fig. 6 shows an attempt to compare the strength of mismatches at the HLA-A, HLA-B, or HLA-DR locus in situations where the other two loci were compatible. Although the numbers of patients studied were small, it appeared that mismatches for HLA-DR had the greatest impact followed by HLA-B, whereas HLA-A mismatches were not deleterious in the absence of HLA-B,-DR mismatches.

Discussion

It is impressive that the current results for first and second grafts were identical to those published for half the number of patients 3 years ago [1]. It appears that a stable 70% 1-year success rate in highly immunized patients can be expected from this program. The success rate of third and fourth grafts was approximately 25% lower.

The analysis of HLA matching clearly demonstrated that, in spite of the absence of crossmatch reactivity, matching did have an important influence in this patient population. The rationale that HLA-A,-B mismatches should not be deleterious if a highly sensitized recipient does not react against the mismatched antigens on donor cells in the crossmatch test apparently is flawed. It is important to note that even in the HLA-DR zero-mismatch group, HLA-A,-B mismatches increased the risk of failure.

It is important to point out that grafts with one HLA-DR mismatch had a success rate indistinguishable from that with a zero HLA-DR mismatch (Fig. 3). We do not feel that transplantation of highly sensitized patients should be limited to the zero HLA-DR mismatch group. Rather, we believe that our policy of avoiding two-antigen mismatches on each of the three loci is sensible, and that beyond that, the best possible match grade should be aimed for. There is a suggestion in our data that two mismatches for HLA-A can be accepted in the absence of HLA-B,-DR mismatches. However, because the number of transplants studied in this respect is very small, we must await further evidence before reaching a conclusion.

The results shown here for transplantation in highly sensitized recipients are gratifying. These patients have long been considered high risks and they experience prolonged waiting times. With good HLA matching, success rates indistinguishable from those in nonsensitized recipients can be obtained. We believe that the results shown here provide ample justification for the continuation of priority kidney allocation based on our serum exchange program.

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