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Strength of HLA-A, HLA-B, and HLA-DR mismatches in relation to short- and long-term kidney graft survival

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Abstract. The separate influence of HLA-A, HLA-B, and HLA-DR mismatches on short- and long-term kidney graft survival was analyzed in a series of over 40,000 recipients of first cadaver kidney transplants. As expected, during the early posttransplant period, HLA-DR mismatches had a stronger influence on graft survival than HLA-B mismatches, and HLA-A mismatches had a very small influence. Surprisingly, during the period from 6 months to 5 years post transplantation, all three HLA loci had approximately the same influence. When the graft survival computation was started at 100% at 6 months, the difference between grafts with zero or two mismatches at the end of 5 years was 6%, regardless of whether HLA-A, HLA-B, or HLA-DR antigens were analyzed. The influence of the three loci was additive so that the survival rate difference between transplants with zero or six mismatches for HLA-A, -B, -DR was 17% at 5 years. We concluded that, although the HLA-A locus exerts only a weak influence during the early posttransplant course, its influence on long-term survival is comparable to that of HLA-B and HLA-DR. In order to obtain optimal long-term survival, all three loci must be considered in the donor-recipient matching procedure.

Key words: Strength of HLA mismatches – Long-term graft survival.

It has been recognized for many years that HLA-DR mismatches have a stronger influence on graft survival than HLA-B mismatches, and that HLA-A mismatches have the smallest impact. Understandably, kidney sharing organizations have adopted policies whereby compatibility for HLA-DR was given greater weight than that for HLA-B, and HLA-A was considered even less important. Recently, Thorogood et al. have shown that, whereas this hierarchy was applicable to the first 5 months post transplantation, only the HLA-B locus had a significant impact on graft survival during the period from 5 months to 3 years [1]. The HLA-A locus appeared to have no significant influence on either short-term or long-term survival, suggesting that HLA-A could be ignored in the matching procedure. We report here on an analysis of over 40,000 primary transplants in cyclosporine-treated recipients. The results lead us to argue that HLA-A mismatches should not be ignored.

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Methods

The transplants were reported to the Collaborative Transplant Study by 297 transplant centers in 41 countries. HLA typings were performed at the individual centers' tissue typing laboratories and reported to the study center for analysis. The distinction of HLA antigen "splits" and "broad antigens" has been published previously [2]. Graft survival rates were computed by the Kaplan-Meier method. Statistical significance was estimated by weighted regression analysis [3]. Only first transplants were analyzed and the immunosuppressive protocol of all patients included cyclosporine. The transplants were performed from 1982 to 1990. No exclusions of any types of failures were made.

Results

Figure 1 demonstrates the importance of separating transplants which were typed for HLA-A,-B antigen "splits" from those that were typed merely for the "broad" antigen specificities. "Splits" are the best defined specificities. Among transplants typed for "broad" specificities, a correlation of antigen matching with graft outcome was not apparent. Therefore, we restricted all subsequent analysis steps to transplants in which both the recipient and donor were typed for antigen "splits".

The well known hierarchy of importance with respect to their influence on early graft survival is illustrated for the HLA-A, HLA-B, and HLA-DR loci in Figs. 2–4. Dur-

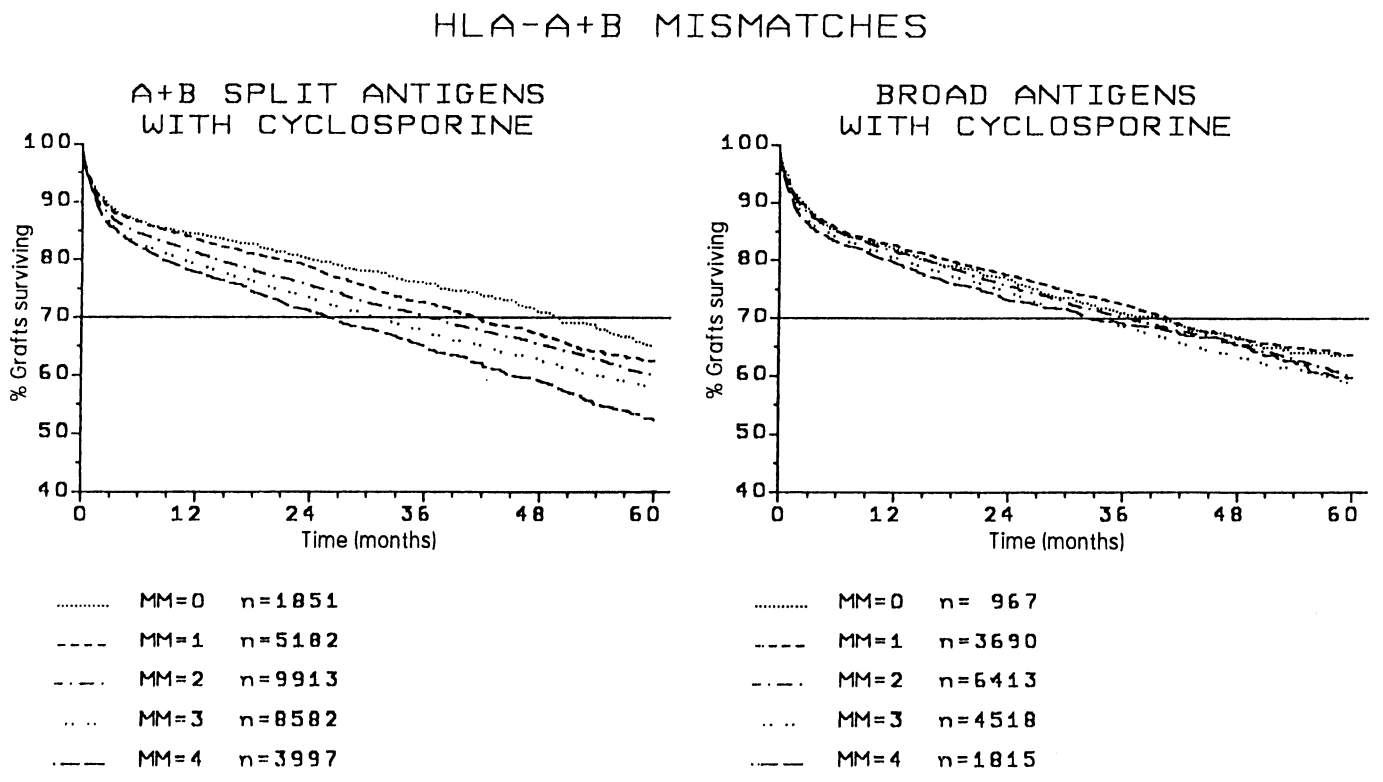

Fig. 1. Influence of HLA-A and HLA-B antigen mismatches on the survival rate of first cadaver kidney transplants. All patients were immunosuppressed with cyclosporine. A strong influence of matching for HLA-A,-B is apparent only when recipients and donors were typed for "split antigens" (*left* half of figure) and not when typing was performed for "broad" antigens (*right* half of figure)

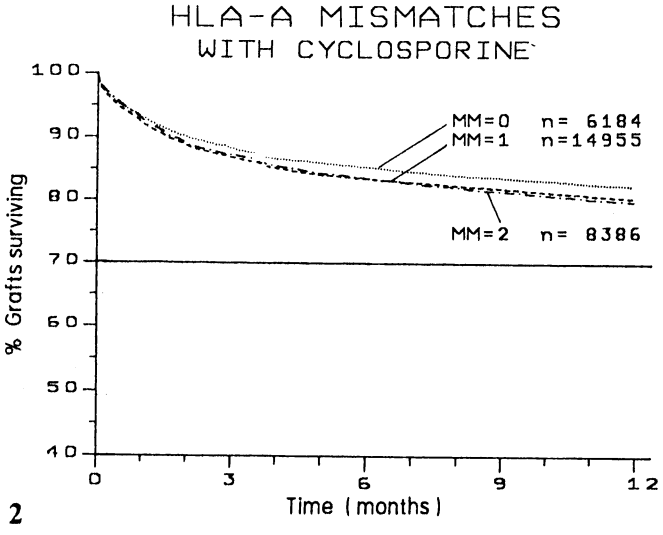

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Fig. 2. Effect of HLA-A mismatches on first cadaver transplant survival. During the 1st year, the effet of the HLA-A locus was small, although statistically significant (P regression = 0.001). Numbers of mismatched antigens and numbers of patients studied are indicated at ends of curves

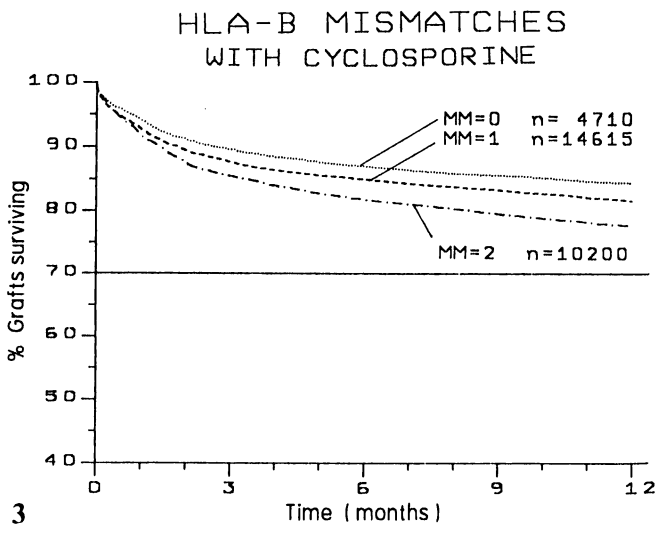

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Fig. 3. Influence of HLA-B mismatches on first cadaver transplant survival. HLA-B mismatches had a stronger influence than mismatches for HLA-A (compare Fig. 2). Statistical significance: P regression < 0.0001

ing the 1st post-transplant year, the influence of the HLA-A locus was barely noticeable. HLA-DR had the strongest impact.

Quite different was our assessment for the period following the first 6 months after transplantation. At the end of 5 years, each of the three loci contributed approximately 6 percentage points to the graft survival rate (Figs. 5–7). We thus did not confirm the report by Thorogood that it is only the HLA-B locus that influences long-term graft outcome. In our experience, all three loci were of approximately equal influence. Moreover, the individual influences were apparently additive as shown in Fig. 8. Starting from a 100% rate at 6 months, all three loci together contributed to a 17% difference in graft survival at 5 years between transplants with zero or six mismatches.

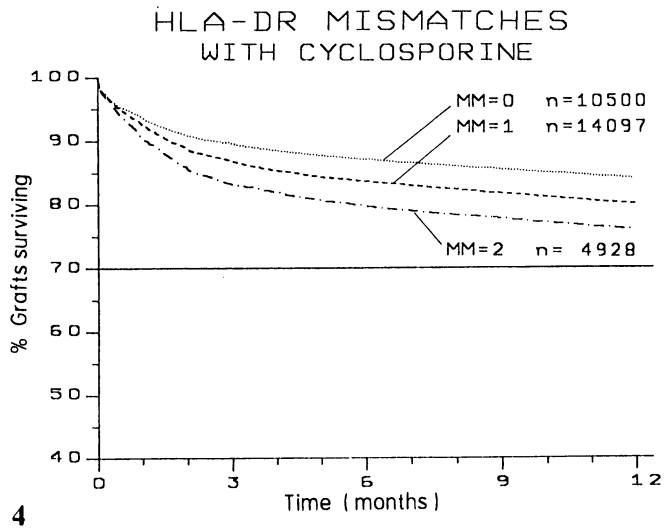

Fig. 4. Influence of HLA-DR antigens on graft survival. DR locus mismatches had a slightly stronger influence during the 1st year than HLA-B mismatches (compare Fig. 3). Statistical significance: *P* regression < 0.0001

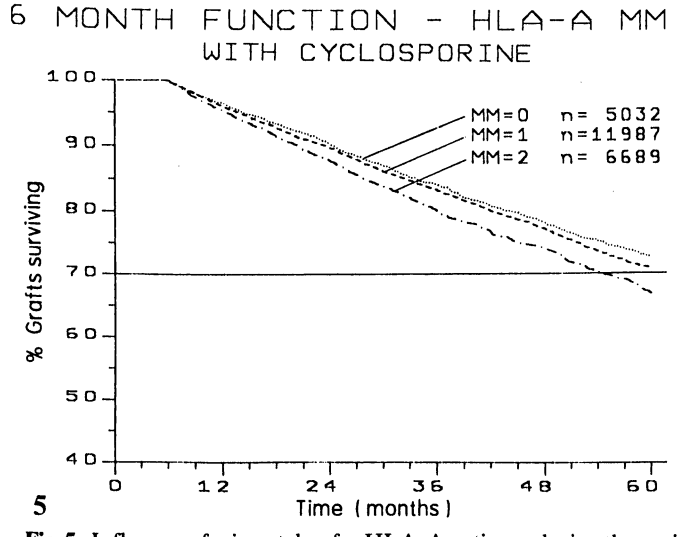

Fig. 5. Influence of mismatches for HLA-A antigens during the period from 6 months to 5 years post transplantation. All transplants analyzed had a functioning graft at 6 months. First cadaver transplants in patients on immunosuppression including cyclosporine were analyzed. At 5 years: *P* regression < 0.0001

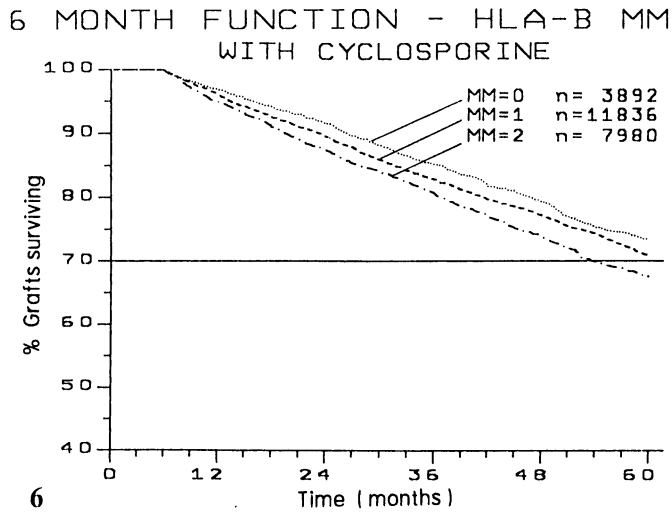

Fig. 6. Influence of HLA-B antigen mismatches during the period from 6 months to 5 years. The effect was comparable to that of HLA-A mismatches (see Fig. 5). At 5 years: *P* regression < 0.0001

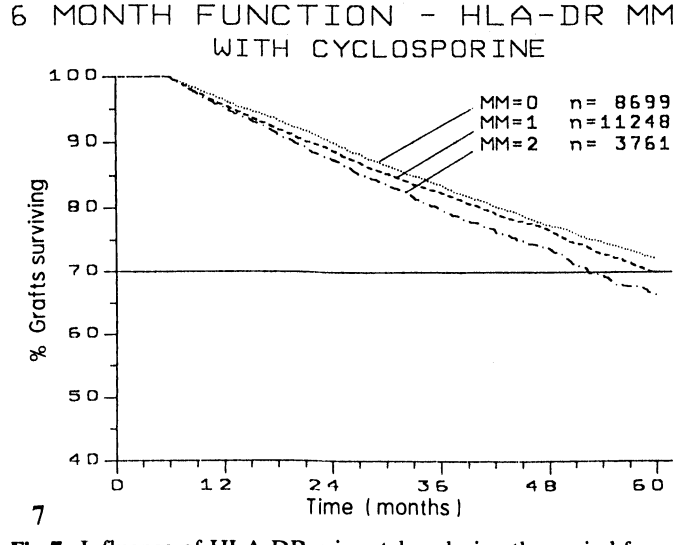

Fig. 7. Influence of HLA-DR mismatches during the period from 6 months to 5 years. The influence was equivalent to that shown for HLA-A and HLA-B in the two previous figures. At 5 years, *P* regression < 0.0001

We concluded that it would be a mistake to ignore the HLA-A locus in the matching procedure because of its long-term impact. For an optimal matching effect to be realized, all three loci must be considered. This was also demonstrated in the computation of long-term half-life risks for the period beyond 6 months. The combined impact of HLA-A,-B,-DR resulted in a difference from a half-life time of 11.8 years for zero-mismatch grafts to 6.6 years for six-mismatch transplants (Fig. 9). If the HLA-A locus was left out, the half-life time for HLA-B,-DR zero-mismatch transplants was 10.6 years and that for four-mismatch grafts was 7.1 years. Thus, including the HLA-A locus improved the power of resolution.

Discussion

Our results demonstrated that whereas there is a hierarchy of a decreasing influence during the early posttransplant period from HLA-DR to HLA-B to HLA-A, no such distinction could be made for the period from 6 months to 5 years. Our assessment did not agree with that by Thorogood et al., possibly because we restricted our analysis to transplants typed for HLA-A and HLA-B "split antigens" and due to the larger number of patients studied and the longer follow up.

In practical terms, for the purpose of organ allocation, this still means that greater weight should be attached to the HLA-DR and HLA-B loci than to HLA-A, simply be-

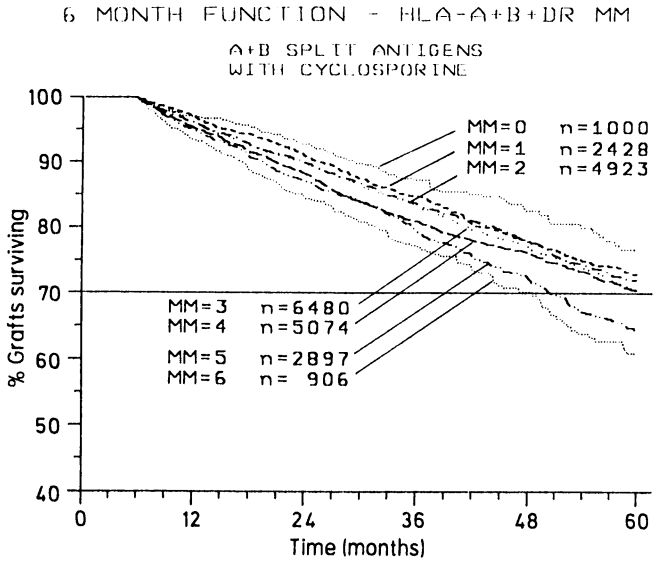

Fig. 8. Combined effect of HLA-A,-B,-DR mismatches on graft survival during the period from 6 months to 5 years. First cadaver transplant recipients on cyclosporine immunosuppression were analyzed. The individual effects of the three loci were additive. Whereas the difference between zero and two mismatches for each individual locus was 6% at 5 years, all three loci together resulted in a 17% difference at 5 years. *P* regression < 0.0001

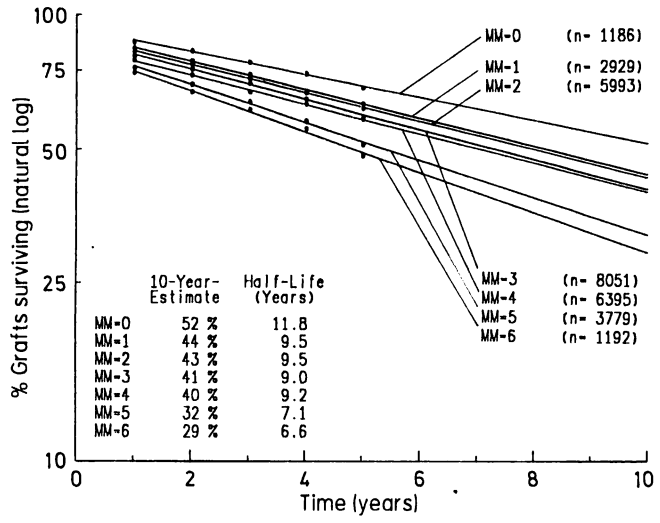

Fig. 9. Half-life computation for the period from 1 year to 5 years. First cadaver kidney transplants in cyclosporine-treated patients were analyzed. The combined impact of HLA-A,-B,-DR locus mismatches on the long-term attrition rate is shown. The individual influence of each of the three HLA loci was similar during this period

cause a greater early impact influences not only the early but also the late outcome. However, the results demonstrated that, when an optimal long-term graft outcome is aimed for, the HLA-A locus cannot be ignored.

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