HLA matching and cadaver kidney transplantation — status 1984

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SUMMARY

The effect of HLA matching on cadaver kidney graft survival was analysed in over 9000 transplants. Matching for HLA-A and -B accounted for an improvement of 8% in the one-year survival rate, matching for HLA-DR for 10%, and matching for HLA-B + DR for 19%. The matching effect of the HLA-B and HLA-DR loci was additive. Patients without pre-transplant transfusions had lower graft survival rates than transfused patients, even if their grafts were HLA matched. The highest success rate was obtained in transfused recipients who received HLA matched kidneys.

INTRODUCTION

The relevance of HLA matching, although unquestioned in the related donor situation where HLA identical siblings clearly represent an immunologically privileged category with superior graft outcome, has been difficult to establish in cadaver kidney transplantation. Conflicting reports have been published during the past 15 years with respect to matching for the HLA-A and -B antigens. The HLA-DR locus, which was introduced some five years ago, had a stronger effect according to early reports than HLA-A or -B; however, this was not substantiated in an international workshop study carried out in 1980. It was recognised at that time that the technical quality of HLA-DR typing was less than satisfactory because of early difficulties with the B cell isolation technique. The picture was complicated further by a shift in transfusion policies in the late seventies and early eighties. It had become firmly established that non-transfused recipients did less well than transfused ones, and as a result the fraction of patients who received transplants without transfusion pre-treatment decreased drastically. Concurrently, typing techniques for HLA-DR were standardised and refined. The need for a re-evaluation of HLA matching in cadaver kidney transplantation became evident. In 1982, an international collaborative project was initiated, with the primary purpose of establishing on a large multicentre basis whether HLA matching had a place in modern renal transplantation. This report is an account of the early results (up to one year) that were obtained in over 9000 patients transplanted during the last two years.

METHODS

The data on which this analysis was based were gathered as part of the Collaborative Transplant Study project. Two hundred and nine transplant centres in the following cities participated: Angers, Atlanta, Barcelona, Basel, Belfast,

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Berlin-East, Berlin-West, Bern, Birmingham (Alabama), Boston, Bristol, Brooklyn, Brussels, Budapest, Buenos Aires, Cambridge, Capetown, Cardiff, Chiba, Chicago, Cincinnati, Cleveland, Cologne, Dallas, Detroit, Dublin, Ehime, Erlangen, Essen, Frankfurt, Freiburg, Fukui, Fukuoka, Geneva, Glasgow, Gothenburg, Groningen, Halifax, Halle, Hamamatsu, Hamburg, Hannover, Hartford, Heidelberg, Helsinki, Hiroshima, Homburg, Hong Kong, Houston, Innsbruck, Iowa City, Ishikawa, Kaiserslautern, Kanagawa, Kansas City, Kashihara, Kiel, Kyoto, Lausanne, Leicester, Leningrad, Leuven, Lexington, Lisbon, London, Louisville, Luebeck, Lyon, Maastricht, Madrid, Lund-Malmo, Manchester, Marburg, Melbourne, Mexico City, Milan, Minneapolis, Montpellier, Montreal, Moscow, Munster, Munich, Muroran, Nagasaki, Nancy, Nantes, Nashville, New York, Newcastle, Nice, Nijmegen, Nishinomiya, Okayama, Omaha, Osaka, Ottawa, Oxford, Paris, Perth, Phoenix, Piraeus, Portland, Porto Alegre, Prague, Quebec, Rennes, Rio de Janeiro, Rochester (Minnesota), Rochester (New York), Rome, Rostock, Saitama, San Antonio, San Francisco, Santiago, Sapporo, Seattle, Shinagawa, St Etienne, St Louis, Sydney, Szeged, Takatsuki, Tel Aviv, Thessaloniki, Tokyo, Toledo (Ohio), Torino, Toronto, Toulouse, Tubingen, Ulm, Uppsala, Valencia, Vancouver, Villejuif, Vilnius, Warsaw, Winnipeg, Zagreb, Zurich. Participation in this study was entirely voluntary. The centres agreed to provide information on all consecutive transplants only. First cadaver transplants performed between January 1982 and July 1984 were analysed. All transplants had a minimum clinical follow-up of 3 months. No exclusions were made. Graft survival rates were computed by actuarial methods. Statistical significance was calculated by weighted regression.2

RESULTS

The effect on graft survival of matching for HLA-A and -B is shown in Fig 1. Although there is a stepwise decrease in success rates from 0 to 4 mismatches, the difference between the best and worst match grade is a disappointing 8% at one year. Separate analysis of the HLA-A and HLA-B loci shows that there is little difference in their individual weights (Fig 2).

Matching for HLA-DR can be seen to correlate with graft survival to about the same degree as HLA-A and -B combined (Fig 3). Although this degree of correlation is clinically useful, the discriminative power of HLA-DR alone is not as strong as one would ultimately wish to gain from tissue typing.

Both the 8th and 9th International Histocompatibility Workshop analyses showed an additive affect of HLA-B and HLA-DR on cadaver kidney transplant survival.1,3 The current analysis clearly supports this. A difference of 19% in the one-year survival rates was found between grafts with 0 or 4 HLA-B + DR mismatches, and

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1. TX, CADAVER, MISMATCHES A

1. TX, CADAVER, MISMATCHES B

Fig. 2. Separate analysis of influence on graft survival of the HLA-A or HLA-B loci. There was no clear difference in strength between the two loci.

1. TX, CADAVER, DR MISMATCHES

1. TX, CADAVER, B+DR MISMATCHES

Fig. 3. Effect of HLA-DR matching on cadaver kidney graft survival. The correlation was statistically highly significant (p < 0.0001).

Fig. 4. Combined effect of HLA-B + DR matching on cadaver kidney graft survival. The success rate declines stepwise from 0 to 4 mismatches. Statistical significance by weighted regression: p < 0.0001.

the graft survival rates declined stepwise from 0 to 4 mismatches (Fig 4). No significant further improvement was achieved by including HLA-A in the analysis. The combined consideration of the three loci HLA-A + B + DR resulted in a statistically highly significant correlation with graft survival; however, the correlation was similar to that obtained with HLA-B + DR (Fig 5). Because it is desirable for logistical reasons to limit the number of loci considered in the selection process to the minimum necessary, matching for HLA-B + DR has an obvious practical advantage over HLA-A + B + DR matching.

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Fig. 5. Combined analysis of HLA-A, HLA-B, and HLA-DR loci. Grafts with 0 mismatches had an approximately 20% higher survival rate than grafts with 5 mismatches. The correlation was not improved compared with the analysis of HLA-B + DR.

Fig. 6. Effect of pre-transplant transfusions on survival of cadaver kidney transplants. Patients without pre-transplant transfusions clearly have inferior graft outcome. 1 transfusion and > 20 transfusions result in intermediately good success rates. Possibly, additional risk factors play a role in patients who received multiple transfusions.

DISCUSSION
These preliminary results of the Collaborative Transplant Study show that HLA matching has a definite place in cadaver kidney transplantation. It remains to be seen whether the one-year results shown here will be valid also for the transplants’ long-term course. Based on previous work, one can assume that this will be so.1-6 Surely, if a method is known whereby the success rate can be improved by 20%, it must be utilised clinically.
The additive effect of the HLA-B and HLA-DR loci is confirmed in the current analysis. It appears that matching for HLA-DR alone is not sufficient for obtaining optimum results. HLA-A and B matching is also insufficient, a fact that has long been suspected. From a logistical standpoint, HLA-B + DR matching is not as convenient as matching for HLA-DR alone; it is, however, less cumbersome than HLA-A + B matching (at least for the time being, the polymorphism of HLA-A is greater than that of HLA-DR). Therefore, it should be possible to perform many HLA-B + DR matched transplants using established organ-sharing procedures. Our transfusion data indicate that the effect of matching can be enhanced by administering transfusions prior to transplantation. Transfused patients receiving HLA-DR matched grafts did exceedingly well, and we may anticipate that transfused HLA-B + DR matched patients will do even better.

Already, this type of analysis seems outdated in the face of cyclosporin, the new powerful immunosuppressant. First reports based on small series of patients suggest that cyclosporin may be able to overcome both the transfusion effect and the effect of HLA matching. Quite to the contrary, preliminary data (unpublished) of the Collaborative Transplant Study indicate that there is a strong transfusion as well as HLA matching effect even with the use of cyclosporin. With the rapidly increasing numbers of transplants that are becoming available for analysis (the Collaborative Transplant Study grows at a rate of approximately 800 additional transplants per month), this new controversy is certain to be resolved within a year or two. Our experience with partially additive effects of other factors would make it seem likely that the improved success rates attributed to cyclosporin might benefit even further from the addition of transfusions and HLA matching.
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