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A retrospective evaluation of HLA-A, B and -DRB1 matching in liver transplantation

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Abstract Studies on the influence of histocompatibility in liver transplantation have not produced clear-cut results. We retrospectively studied the influence of HLA-A, B and -DRB1 matching on the survival of 517 liver-transplanted patients using univariate analysis. The following parameters were also considered in relation to transplant outcome: donor and recipient age, original disease, transplant center, and pre-transplant blood transfusions. Twenty-four-month graft survival according to the number of HLA-A, B, DRB1 mismatches (MM) was 70.9% ($n = 28$) for zero to two MM, 76.6% ($n = 248$) for three to four MM, and 73.1% ($n = 241$) for five to six MM ($P = 0.7$). We obtained similar results when considering HLA-A, B MM alone. Survival rates according to HLA-DRB1 MM were 71.7% ($n = 36$) for zero MM, 73.7% ($n = 236$) for one MM, and 76.4% ($n = 245$) for two MM ($P = 0.6$). The same analyses, performed on cirrhotic patients alone, gave identical results. In conclusion, this study suggests, on a large series of patients, that HLA compatibility has no influence on liver transplant survival. On the contrary, an influence on transplant outcome was found for donor age, transplant center, and original disease.

Key words HLA matching · Liver transplantation

Introduction

In contrast to a clear demonstration for kidney transplantation, in liver transplantation HLA matching does not seem to exert a beneficial effect. Some studies [2, 3, 11] even report lower graft survival rates for better matched recipients. In order to explain these results, some authors have proposed a dual role for HLA in liver transplantation [2, 4]: on the one hand, HLA matching could reduce the incidence of acute rejection, on the other, it could diminish overall survival. At present, however, no clear-cut results [5, 6, 8, 9, 12] on the role of HLA matching in liver transplantation have been provided and transplant programs perform liver transplants regardless of HLA compatibility in donor and recipient pairs.

The aim of the present analysis was to investigate retrospectively the effect of HLA matching on liver outcome in 517 patients transplanted in the North Italy Transplant program (NITp) [10].

Materials and methods

Patients, organ allocation, immunosuppression

Since 1990 we have collected blood samples from donor/recipient pairs at transplantation in order to perform some retrospective immunological tests. Upon registering for the waiting list, all patients were informed that their blood samples would be used for histocompatibility testing. Out of 1116 patients transplanted from January 1990 to June 1997 in five of the nine liver transplant centers which take part in the NITp, 517 (46.3%) cases were eligible for this retrospective study on the basis of DNA availability. All 517

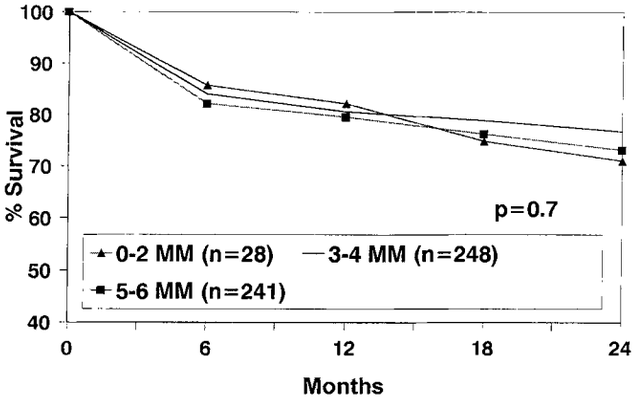

Fig. 1 Liver transplantation – 24-month graft survival according to the number of HLA-A, B, DRB1 mismatches *(MM)*

patients were first transplants and had a negative pretransplant cross-match. Except in the case of one patient, they were ABO compatible with their donor. Only four patients had panel-reactive antibodies (PRA) > 50%. Of the total, 342 patients were male (65.9%) and the mean age at transplantation was 42.5 years (5^{th} and 95^{th} percentiles were 5 and 60 years, respectively).

Post-hepatitis and alcoholic liver cirrhosis were the underlying diseases in 278 cases (54.7%). In our organization, allocation criteria include ABO compatibility and size matching but not HLA matching. The immunosuppressive treatment included cyclosporine, except for 25 patients who were treated with FK506 in association with other immunosuppressive drugs.

HLA-A, B and -DRB1 typing

HLA-A, B typing was performed using standard serology, whereas sequence-specific oligonucleotide (SSO) typing was carried out for HLA-DRB1 on polymerase chain reaction-amplified DNA. The SSO probes used allowed generic typing of HLA-DRB1 alleles (DRB1*01–14).

Graft function evaluation

The grading scheme adopted by the Collaborative Transplant Study (University of Heidelberg, Germany) was used to describe graft function at 3, 6, and 12 months following transplantation. Liver-transplanted patients were classified as having a good functioning graft or an impaired function (but no failure).

Statistical analysis

Graft survival rates according to HLA-A, B and -DRB1 mismatches (MM) were calculated by the actuarial method and the log-rank test. The effect of HLA matching was also investigated separately on patients for whom the underlying disease was post-hepatitis or alcoholic cirrhosis. Univariate analysis was also carried out taking into account other variables such as donor and recipient age (1–15 years, 16–30 years, 31–50 years, > 50 years), % PRA, pretransplant blood transfusions, original disease, and the transplant center.

Patient death or the need of a regraft were considered as failures.

Results

Overall graft survival was 74.5% (SE 1.9) at 2 years. Figure 1 summarizes 24-month graft survival rates according to the number of HLA-A, B, DRB1 MM. Grafts with zero to two MM ($n = 28$) had 70.9% (SE 8.7) survival, those with three to four MM ($n = 248$) and those with five to six MM ($n = 241$) had 76.6% (SE 2.3) and 73.1% (SE 3) survival, respectively ($P = 0.7$). Grafts with zero to one HLA-A, B MM ($n = 27$) had 61.7% (SE 9.3) survival, while those with two MM ($n = 133$) and with three to four MM ($n = 357$) had 80.2% (SE 3.4) and 73.7% (SE 2.4) survival, respectively ($P = 0.08$). Finally graft survival rates according to the number of HLA-DRB1 MM were as follows: 71.7% (SE 7.6) for zero MM ($n = 36$), 73.7% (SE 2.8) for one MM ($n = 236$), and 76.4% (SE 2.8) for two MM ($n = 245$) ($P = 0.6$). Similar results were obtained for patients with liver cirrhosis. At the third post-transplant month, 100% of patients with zero to two HLA-A, B, DRB1 MM had good graft function compared with 94.5% of patients with five to six MM (the difference was not statistically significant).

The other parameters tested in the univariate analysis, donor age, transplant center, and original disease, were highly significant. In fact, livers retrieved from donors from 1 to 15 years of age ($n = 67$) had 84.8% survival rate, those from 16 to 30 ($n = 227$), 80.3%, those ($n = 168$) from 31 to 50 years, 66.2%, and livers from donors above 50 years ($n = 54$), 64.5% ($P = 0.0001$). Among the five transplant centers considered in this study, there was a difference in liver survival ranging from 64.2% to 84.3% at 2 years following transplantation ($P = 0.04$). Finally, patients who underwent liver transplantation because of fulminant hepatitis or malignancy had 42% and 59% 24-month graft survival, respectively.

Discussion

Liver transplantation is at present a standard of care for end-stage organ failure. This is documented by the high survival rates achieved by most transplant centers. In our series, 24-month liver survival is 74.5%.

In liver transplantation, organ allocation relies mostly on ABO blood group, body weight, and clinical urgency; HLA matching is usually not taken into account and the literature is inconsistent on the role of this parameter [5, 6, 8, 11]. In our analysis we have evaluated the effect of HLA compatibility, employing molecular methods for DRB1 typing which proved to be more accurate than microcytotoxicity [7], on a large series of patients. However, due to the retrospective nature of our study, only a minority of donor–recipient pairs are HLA compatible.

Since, in this series, 278 (54.7 %) patients were affected by post-hepatitis and alcoholic liver cirrhosis, the analysis on HLA matching and liver outcome was carried out on this more homogeneous subset of patients for underlying disease. The results obtained in this subgroup did not show a different figure.

On the contrary, donor age was highly significant, suggesting that the use of livers from donors above 50 years of age implies additional risks and must be carefully monitored. The transplant center effect is still present in our setting. As expected, fulminant hepatitis and malignancies have an untoward effect on the outcome of liver transplantation.

In conclusion, even with the drawbacks of retrospective analyses, our study indicates that there is no evidence for the introduction of prospective HLA matching in this kind of transplant in our setting. In this respect, only international collaborative studies [1], enrolling a high number of patients, will allow the question on the role of histocompatibility, if any, in liver transplantation to be addressed.

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References

1. Dawson S 3rd, Imagawa DK, Cecka JM, Gjertson DW, Shackelton CM, Shaked A, Busuttil R (1994) UCLA liver transplantation: analysis of the first 1000 patients. In: Terasaki PI, Cecka JM (eds) Clinical transplants, vol 16. UCLA Tissue Typing Laboratory, Los Angeles, pp 189–195
2. Donaldson P, Underhill J, Doherty D, Hayllar K, Calne R, Tan KC, O'Grady J, Wight D, Portmann B, Williams R (1993) Influence of human leukocyte antigen matching on liver allograft survival and rejection: "the dualistic effect". Hepatology 17: 1008–1015
3. Gunson BK, Hathaway M, Buckels JAC, Mayer AD, Elias E, McMaster P, Neuberger JM (1992) HLA matching in liver transplantation: a retrospective analysis. Transplant Proc 24: 2434–2435
4. Markus BH, Duquesnoy RJ, Gordon RD, Fung JJ, Vanek M, Klintmalm G, Bryan C, Thiel D van, Starzl TE (1988) Histocompatibility and liver transplant outcome: does HLA exert a dualistic effect? Transplantation 46: 372–377
5. Nikaein A, Backman L, Jennings L, Levy MF, Goldstein R, Gonwa T, Stone MJ, Klintmalm G (1994) HLA compatibility and liver transplant outcome: improved patient survival by HLA and cross-matching. Transplantation 58: 786–792
6. Opelz G, for the Collaborative Transplant Study (1993) Preliminary analysis of HLA matching in pancreas and liver transplantation. Transplant Proc 25: 2652–2653
7. Opelz G, Mytilineos J, Scherer S, Dunckley H, Trejaut J, Chapman J, Middleton D, Savage D, Fischer O, Bignon JD, Bensa JC, Albert E, Noreen H (1991) Survival of DNA HLA-DR typed and matched cadaver kidney transplants. Lancet 338: 461–463
8. Poli F, Nocco A, Crespiatico L, Cattaneo R, Lecchi L, Scalamogna M, Sirchia G (1994) A retrospective evaluation of HLA-A, B, and genomic HLA-DR compatibility in orthotopic liver transplantation. Transplant Proc 26: 3614–3615
9. Poli F, Scalamogna M, Mascaretti L, Pappalettera M, Nocco A, Crespiatico L, Cattaneo R, Lecchi L, Sirchia G (1995) Genomic HLA-DR compatibility in solid organ transplantation: a retrospective analysis of 1209 cases. Transplant Proc 27: 647–650
10. Sirchia G, Scalamogna M, Mascaretti L, Poli F, Pizzi C, Bossi G (1989) The North Italy Transplant program's organization, policies and activity: problems and proposals for 1990s. Tissue Antigens 34: 78–83
11. Thorogood J, for the l'ESPRIT study group (1993) Relationship between HLA compatibility and first liver allograft survival. Transplant Proc 25: 2655–2656
12. Yagihashi A, Kobayashi M, Noguchi K, Konno A, Yoshida Y, Terasawa K, Starzl TE, Iwaki Y (1992) HLA matching effect in liver transplantation. Transplant Proc 24: 2432–2433