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T. Leivestad
A. Foerster
S. Simonsen
A. Bratlie
E. Thorsby
O. Geiran

HLA-DR matching reduces rejection rate in heart transplantation

T. Leivestad (✉) · A. Bratlie · E. Thorsby
Institute of Transplantation Immunology, Rikshospitalet, N-0027 Oslo, Norway

A. Foerster
Institute of Pathology, The National Hospital, Oslo, Norway

S. Simonsen
Medical Department B, The National Hospital, Oslo, Norway

O. Geiran
Surgical Department A, The National Hospital, Oslo, Norway

Abstract We have studied the influence of serological matching for ten HLA-DR antigens on the occurrence of acute cellular rejection in heart transplantation by correlating the findings in routine endomyocardial biopsies taken during the first posttransplant year with the results of HLA typing of all recipients of a first cardiac graft and their donors during 1983–1994 at our center. We found that recipients of HLA-DR matched hearts had a lower frequency of acute cellular rejection, especially so for the moderate/severe rejection grades. Also, rejection appeared earlier in the DR-mismatched combinations. Whether the mismatch was for one or two DR antigens did not make a significant difference, neither could we demonstrate any influence of HLA-A or -B mismatches. The survival of DR-matched cardiac grafts tended to be higher at 1 year than DR-mismatched grafts, but the difference did not reach statistical significance.

Key words Cardiac transplantation · Rejection · HLA matching

Introduction

Donor hearts are usually allocated to recipients based on ABO and size match, while matching for HLA is seldom attempted. Due to the polymorphism of the HLA system, and to the logistical problems, only a few recipients obtain a graft fully matched for HLA. Large patient series, as in the Collaborative Transplant Study [7], are required to establish the influence of HLA matching on cardiac graft survival.

Cardiac grafts are usually monitored for rejection by routine endomyocardial biopsies at fixed intervals. The classification systems for the histological diagnosis of rejection have been several, but an international standard was established in 1990 [1]. Several centers including our own [2–4, 8, 9] have earlier reported a correlation between HLA mismatch and the occurrence of early rejection episodes. The present study presents data from 1983–1994, correlating the findings in routine endomyocardial biopsies, revised according to the international standards, to the prospective serological HLA typing of all first cardiac graft recipients and their donors.

Patients and methods

HLA typing

Serological HLA typing and cross-matching based on the immunomagnetic (IM) technique [10] have been used since 1986, some DR typings have also been confirmed genomically. Recipients were typed for "broad" HLA-A and -B specificities and for the HLA-DR antigens 1–10, and tested for the presence of panel-reactive antibodies (PRA) before waiting-list notification. The donors were similarly HLA typed and a microlymphocytotoxic cross-match was performed, in most instances previous to organ harvesting. The transplant was said to be HLA-A, -B, or -DR compatible if there were no detectable mismatches between the donor and recipient in the HLA-A (n = 10), -B (n = 25), or -DR (n = 10) antigens. Organ allocation was, however, mainly based on blood group and body size match. A negative T cell cross-match was required, although sometimes anticipated for logistical reasons in PRA negative patients.

Patients

During 1983–1994, a total of 208 patients received a first cardiac graft from an HLA-typed donor. Median age was 52 years (range 1–62). In 20 patients there was no demonstrable DR mismatch, in

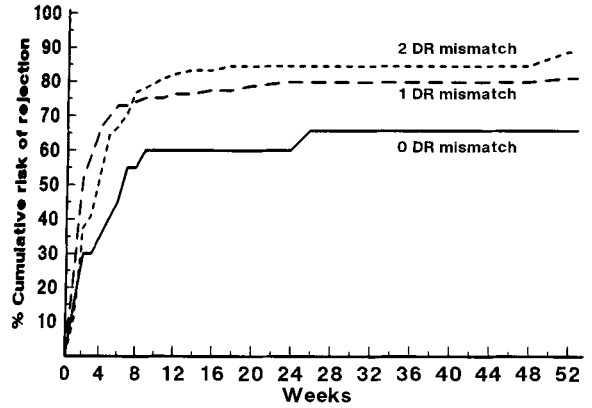

Fig. 1 Cumulative risk of acute cellular rejection (grade 1A–4) during the first posttransplant year in first cardiac graft recipients according to the number of demonstrable HLA-DR mismatches between donor and recipient (Mantel-Haenszel: no DR mismatches vs 1–2 DR mismatches, $P = 0.0389$)

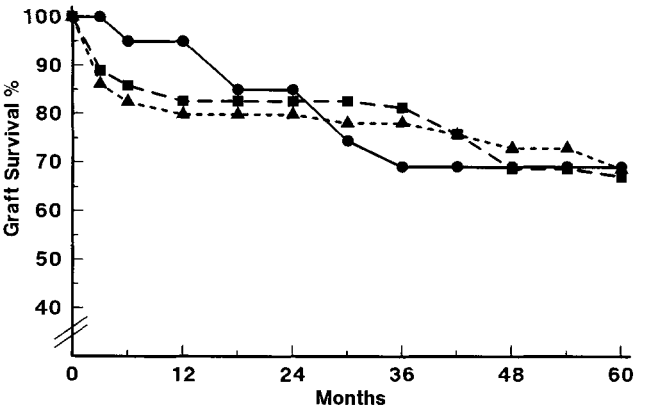

Fig. 3 Survival of first heart grafts according to number of HLA-DR mismatches between donor and recipient (● no DR mismatches, $n = 20$; ■ 1 DR mismatch, $n = 101$; ▲ 2 DR mismatches, $n = 87$)

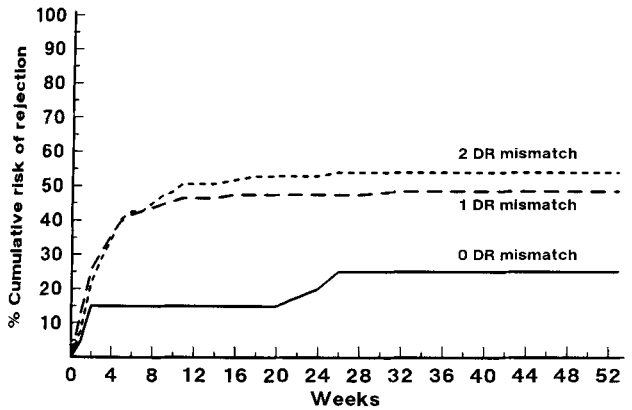

Fig. 2 Cumulative risk of moderate/severe acute cellular rejection (grade 2–4) during the first posttransplant year in first cardiac graft recipients according to the number of demonstrable HLA-DR mismatches between donor and recipient (Mantel-Haenszel: no DR mismatches vs 1–2 DR mismatches, $P = 0.0366$)

101 the donor had one, and in 87 the donor had two mismatched DR antigens. Age distribution was equal in these three groups.

Immunosuppression

Cyclosporine and azathioprine treatment was started preoperatively and corticosteroids peroperatively. Antibodies were not used for basal immunosuppression. Rejection episodes were primarily treated with corticosteroids alone if low grade, or in combination with antithymocyte globulin if moderate or severe.

Biopsies

Transvenous endomyocardial biopsies were taken weekly during the first 2 months after transplantation, then at 2-week intervals until 3 months, at 6 months, and later at each yearly control. Additional biopsies were taken when clinically indicated. All biopsies were classified according to the international classification: 0 = normal; 1A, 1B = degrees of mild rejection; 2, 3A, 3B = degrees of moderate rejection; 4 = severe rejection [1].

Statistics

Group comparisons were done with Fisher's exact test, chi-squared test, or Student's t-test as appropriate. Graft survival, counting death from any cause as graft failure, and time-related risk of rejection were estimated by the Kaplan-Meier method, comparing curves for equality using the Mantel-Haenzsel test and testing for the separate influence of HLA-A, -B and, -DR mismatch by the Cox regression.

Results

Incidence of rejection during the first year

Acute cellular rejection (grade 1A–4) was diagnosed in 163 out of 208 patients during the first year. This was observed in 13 (65 %) recipients of DR-compatible grafts, in 77 (76 %) recipients of grafts mismatched for one DR antigen, and 73 (84 %) mismatched for two DR antigens. These differences do not reach statistical significance. Figure 1 shows, however, that acute rejection occurred earlier in recipients of DR-mismatched compared to DR-compatible grafts. The time-related cumulative risk of acute cellular rejection during the first year was significantly lower in recipients of DR-matched grafts.

Risk of moderate/severe acute rejection

Moderate to severe acute rejection (grades 2, 3A, 3B, or 4) was diagnosed in 101 patients during the first year. This was observed in five (25 %) recipients of DR-matched grafts, 49 (49 %) recipients of grafts mismatch-

ed for one DR antigen, and 47 (54 %) recipients of grafts mismatched for two DR antigens (DR-matched vs DR-mismatched grafts: $P < 0.05$). Figure 2 shows the time-related cumulative risk of such rejection during the first year, confirming a significantly lower risk of moderate to severe acute cellular rejection in recipients of HLA-DR-matched grafts. No further effect of matching for HLA-A, or -B could be detected (data not shown).

Graft survival

There was a trend toward higher graft survival at 1 year for DR-matched grafts, as seen in Fig. 3, but the difference did not reach statistical significance. Nine patients died from acute rejection during the first year, three of these were recipients of a graft mismatched for one DR antigen and six of a graft mismatched for two DR antigens. At 5 years, the survival rate was similar for all groups, but the numbers were quite small.

Discussion

This study confirms that HLA matching influences the posttransplant course in cardiac transplantation. The main difference was seen when comparing the DR-matched grafts with the DR-mismatched grafts. Whether the incompatibility involved one or both DR antigens played a minor role.

Due to short waiting lists and a limited collaboration with other centers, the proportion of HLA well-matched grafts in low. A proportion of nearly 10 % DR-matched combinations, as in our material, is higher than would be expected, even within such a relatively homogeneous population as the Norwegians. We find that the negative influence of a single DR-antigen mismatch, together with the lack of influence by HLA-A, -B mismatch, gives an argument against comparisons using, e.g., 0–2 ABDR mismatch as the "well-matched" group. In our material, such a group will include a number of fully DR-mismatches grafts and exclude most of the DR-matched ones. If analyzed in that way, no significant HLA effect can be found.

Restricting HLA matching to take into account only the "broad" DR1–10 specificities increases the chance of obtaining HLA "matched" combinations. Our results indicate that such a selection would help to avoid acute cellular rejection episodes compared to random allocation. Whether matching for the DR subtypes, such as the serologically definable DR 11–18 antigens or the even more numerous DNA-based DRB1 variants, may add further advantages is still unclear. In renal transplantation we were unable to detect any pronounced effect of genomic DRB1 matching additional to that obtained by Serological matching for the DR antigens 1–10 [5].

A reduced rejection rate would be expected to result in improved long-term graft survival. A trend during the first year was seen (Fig. 3), but the difference did not reach statistical significance. More transplants may be needed to observe an effect. Further, since mortality, especially over long time, will be influenced by many immunological as well as non-immunological factors, a more detailed analysis of such factors is needed. However, a reduced rejection rate alone is valuable since it saves costs in terms of rejection treatment and hospitalization.

To take advantage of the DR-matching effect, a fast and reliable HLA typing technique that can be applied to blood samples drawn prior to organ harvesting is required. With the immunomagnetic technique all necessary typings and cross-matches may be safely performed on peripheral blood samples in less than 2 hours [10]. Compared to results from DNA typing, our routine serological typing has a discrepancy rate of approximately 5 % [5]. With the exception of grafts imported from outside our country, HLA typing and cross-matching have always been completed prior to heart transplantation, even with donors residing 2000 km away. Thus, even with the present 4-h limit to ischemia time, optimalization of HLA typing service and logistics could allow HLA-based organ exchange between centers leading to an increased number of well-matched heart grafts [5, 6]. However, better preservation methods are needed before the potential benefits of HLA matching can be fully utilized.

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