Preformed IgG Antibodies Against Major Histocompatibility Complex Class II Antigens Are Major Risk Factors for High-grade Cellular Rejection in Recipients of Heart Transplantation

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Background—Preformed anti-HLA antibodies reacting specifically with donor lymphocytes have been associated with acute vascular rejection and early cardiac allograft failure. However, the effect of preformed anti-HLA antibodies directed against allogeneic major histocompatibility complex (MHC) class I or II antigens of a donor panel on heart transplantation outcome has not been extensively studied.

Methods and Results—The study group consisted of 68 patients who received cardiac transplants between 1989 and 1996 and who were at high risk for developing anti-HLA antibodies before transplantation. The effect of preformed antibodies against allogeneic MHC class I or class II antigens on the development of early high-grade cellular rejection and on cumulative annual rejection frequency was determined. Both patients with left ventricular assist devices and retransplantation candidates had a similar increase in the frequency of IgG anti-MHC class II antibodies (IgG anti-II) compared with control subjects (P < 0.0001), whereas the frequency of IgG anti-MHC class I antibodies (IgG anti-I) was elevated only in patients with left ventricular assist devices. Pretransplantation IgG anti-II predicted early development of high-grade cellular rejection (P = 0.006) and higher cumulative annual rejection frequency (P < 0.001) in both of these sensitized patient groups. Among retransplantation recipients, a match between donors 1 and 2 at HLA-A additionally predicted an earlier time to a high-grade cellular rejection.

Conclusions—These results emphasize the importance of specifically screening heart transplantation candidates for the presence of IgG antibodies directed against MHC class II molecules and suggest that strategies aimed at their reduction may have an impact on the onset and frequency of high-grade cellular rejections after transplantation. (Circulation. 1998;98:786-793.)

Key Words: transplantation ■ risk factors ■ antibodies

The presence of preformed lymphocytotoxic antibodies reactive against donor lymphocytes in recipient serum, detected in a routine cross-match, is considered a contraindication to solid organ transplantation because of the high incidence of humoral allograft rejection, early graft failure, and poorer patient survival. These antibodies are primarily directed against donor major histocompatibility complex (MHC) class I HLA antigens constitutively expressed by the allograft endothelium, since nonactivated endothelium does not express MHC class II HLA antigens. Consequently, the risk for early graft failure (ie, within the first 24 to 48 hours) is significantly higher in the presence of a positive cross match with donor T lymphocytes, which, in the absence of activation, express only MHC class I antigens, than with donor B lymphocytes, which strongly express both MHC class I and II antigens. In addition, the real risk for early graft failure after a positive cross-match appears to reside in the IgG fraction of donor-specific antibodies. An IgM-positive cross-match can result from the presence of antilymphocytic autoantibodies, which do not specifically react with donor HLA allotypes, and their presence may not lead to early graft failure.

To identify patients at high risk of having a positive cross-match with a potential donor, heart transplantation candidates are prospectively tested for lymphocytotoxic antibodies against lymphocytes from a donor panel representative of all established HLA specificities, collectively referred to as measurements of panel-reactive antibodies (PRA). In addition to predicting an increased likelihood of donor-reactive anti-HLA antibodies and a consequent risk of early graft failure related to humoral rejection, several studies have shown that high levels of pretransplantation PRA in cardiac allograft recipients are associated with adverse posttransplantation outcome when compared with patients with low or negative reactivity. High PRA levels have been associated, in some studies, with increased...
frequency of acute cellular rejections, decreased long-term graft survival, and increased mortality rates. Moreover, the onset of accelerated coronary artery disease (CAD) in heart transplantation recipients, the major limitation to long-term graft survival, has been associated with the presence of anti-HLA antibodies. Since accelerated CAD in these patients may be a consequence of cumulative episodes of high-grade cellular rejections, it is possible that this association may actually reflect a relation between anti-HLA antibodies and acute cellular rejection.

In most published series no differentiation has been made between antibodies reacting with a T-cell and B-cell panel. Because these lymphoid lineage cells differ with respect to MHC class II HLA expression, and many centers only screen for antibodies reactive with T-cell panels, reports regarding the influence of pretransplantation anti-HLA antibodies on posttransplantation outcome may have significantly underestimated the significance of antibodies reactive with MHC class II antigens. In this study, we examined the separate effects on posttransplantation clinical outcome of preexisting anti-HLA antibodies with specificity for either allogeneic MHC class I or class II antigens. The influence of these antibody types on clinical outcome was then compared with that predicted by a standard T-cell PRA. The patients selected for study consisted of 2 groups considered to be at increased risk for the development of anti-HLA lymphocytotoxic antibodies: recipients receiving a second cardiac allograft and those on LVAD support before transplantation.

Methods

Patient Population

Sixty-eight patients at high risk of having elevated levels of anti-HLA antibodies were studied. These consisted of 2 distinct patient populations awaiting heart transplantation: 45 primary heart transplantation recipients, the major limitation to long-term graft survival, has been associated with the presence of anti-HLA antibodies. Since accelerated CAD in these patients may be a consequence of cumulative episodes of high-grade cellular rejections, it is possible that this association may actually reflect a relation between anti-HLA antibodies and acute cellular rejection.

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Detection of Anti-HLA Antibodies

Sera were obtained from all patients on the day of transplantation and screened for the presence of lymphocytotoxic antibodies against separated T lymphocytes and B lymphocytes obtained from a panel of 100 individuals representative of all HLA class I and class II antigens found in the North American population. Sera were screened for complement-mediated lytic activity in the presence or absence of dithiothreitol (DTT). Total T-cell PRA was considered positive if serum, in the absence of DTE, reacted against >10% of the T-cell reference panel.

Determination of Anti-HLA Antibody Specificity for MHC Class I or Class II Antigens

Working definitions for IgG antibodies against HLA class I molecules (IgG anti-I) or class II molecules (IgG anti-II) were established in our laboratory using, as reference, sera from 28 heart transplantation recipients with PRA values >10% and with anti-HLA class I and class II specificities defined by standard tail analysis. Because MHC class I antigens are constitutively expressed by both T cells and B cells, IgG antibodies against HLA class I molecules (IgG anti-I) were considered present in our analysis when the DTT-treated serum reacted with >10% of both the T-cell reference panel and the B-cell panel. This working definition for IgG anti-I correlated in 100% (20/20) of cases with the presence in patient sera of antibodies with defined HLA class I specificities.

To concomitantly identify and discriminate IgG antibodies against HLA class II molecules (IgG anti-II) in the presence of IgG anti-I, we established an algorithm that used the ratio of serum reactivity to B cells versus T cells because MHC class II antigens are constitutively expressed by B cells but not T cells. To confirm this working definition using sera with defined IgG anti-HLA class II specificities, a logistic regression analysis was performed by a maximum likelihood procedure using Biological Management Database Program statistical software to calculate the IgG anti-II predictive value for the ratios of B-cell serum reactivity/T-cell serum reactivity of 1.25, 1.50, 1.75, 2.00, and 3.00. Maximal sensitivity (91%) for identifying sera with reactivity against defined HLA class II antigens was obtained with a ratio of B-cell/T-cell serum reactivity of 2.00 (model coefficient −3.481, SE 1.19, P = 0.0002). Therefore, IgG antibodies against both MHC class I and class II molecules were considered present if DTE-treated serum reacted against >10% of both the T- and B-cell reference panels, and the B-cell reactivity exceeded the T-cell reactivity by at least 2-fold. IgG anti-II were also considered present if the DTT-treated serum reacted against >10% of...
the B-cell but not the T-cell reference panel. Testing the validity of this approach with the use of sera analyzed by tail analysis confirmed that 100% of the samples that reacted only with B cells (n=11) contained antibodies with anti-HLA class II specificities. Overall, the use of these combined criteria for identifying IgG anti-II (ie, reactivity only with B cells or at least 2-fold higher reactivity with B cells than T cells) correctly identified patients with MHC class II serum reactivity with 94% sensitivity and 88% specificity.

### Study Design and Statistical Analysis

The frequency of serum reactivity for IgG anti-I, IgG anti-II, or total T-cell PRA was compared between New York Heart Association class IV control subjects awaiting heart transplantation (n=66) and either LVAD recipients (n=45) or retransplantation candidates (n=23). For each variable tested, a 2x2 table was constructed to compare the frequencies in the study population with the frequencies in control subjects with heart failure. Odds ratios were calculated by dividing the product of A×C by the product of B×D, where A and B are individuals in each group positive for the variable tested, and C and D are individuals in the groups negative for the variable. \( \chi^2 \) analysis was used to determine the P value. Group differences for continuous variables, for example, waiting time to transplantation, were analyzed by Student’s \( t \) test.

The influence of various potential immunologic risk factors on the time to the first high-grade (3A/3B) cellular rejection after transplantation was determined by Kaplan-Meier actuarial analysis, with \( P \) values calculated by log rank statistics.

The Cox proportional hazards regression model was used for the multivariate analysis of time to first high-grade rejection. This is a multiple regression analysis for examining time-dependent outcomes and their potential associated risk factors by modeling a linearized function of a set of \( p \) covariates. The model may be written as

\[
\lambda(t) = \lambda_0(t)e^{\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p}
\]

where \( \lambda(t) \) is the baseline hazard when all the \( x \) variables (covariates) equal 0. The effect of a particular risk factor is equal to \( e^\beta \) for each unit of \( x \).

The interpretation of a risk factor allowed into the model with a value of \( P<0.05 \) is that it is an independent risk factor associated with the event, over and above other potential risk factors included in the equation. The risk ratio is the ratio of the estimated hazard for those with the characteristic variable in question to the estimated hazard for those without, controlling for other variables (or covariates). Any possible grouping effects (ie, LVAD recipients versus retransplantation recipients) were corrected by stratification in the Cox model. The variables analyzed included the presence or absence of each antibody type before transplantation (total T-cell PRA, IgG anti-I, IgG anti-II, IgM anti-I, IgM anti-II); donor and recipient age, sex, and race; donor-recipient matching at the HLA-A, B, and DR loci; and ischemic time.

Because nonfatal morbid events such as cellular rejections can occur repeatedly in the same patient, cumulative high-grade (3A/3B) rejections were modeled by the method of Wei et al by taking into account the correlation of repeated episodes within each patient. This method computes robust variance estimates that allow for the dependence among multiple event times.

For all statistical analyses, data were analyzed with the SAS System software.

### Results

**Anti-HLA Antibodies in Sensitized Individuals**

As shown in Table 1, compared with NYHA class IV control subjects awaiting heart transplantation, the frequencies of anti-MHC class I IgG antibodies and total T-cell PRA were increased only among LVAD recipients In contrast, the frequency of anti-MHC class II IgG antibodies was significantly higher in both LVAD recipients and retransplantation candidates than in NYHA class IV heart failure control subjects (33% and 29% versus 3%, respectively, \( P<0.0001 \)).

We next sought to determine whether the production of either IgG anti-I or anti-II was influenced by perioperative transfusion of blood products. Among the LVAD recipients who developed anti-HLA antibodies as defined by a positive T-cell PRA, 90% had received perioperative blood products, with a mean of 16 U of red blood cell transfusions (range 0 to 88) and 12 U of platelets (range 0 to 36). By Kaplan-Meier univariate analysis, at the median duration of LVAD implantation of 4 months, 8% of patients who received <6 platelet units developed IgG anti-I antibodies compared with 63% who received >6 U (\( P=0.002 \)). In contrast, perioperative red blood cell transfusions did not influence the production of IgG anti-II in these analyses. The development of IgG anti-II was not influenced by either the number of perioperative red blood cell or platelet transfusions.

**Presence of IgG Anti-MHC Class I Antibodies Increases Waiting Time to Heart Transplantation**

At our institution a positive prospective donor-specific cross-match is considered a contraindication to heart transplantation, and none of the patients in this study were given transplantation across a positive cross-match. Therefore, individuals whose sera are repeatedly positive in cross-match reactions have longer waiting times until a cross-match negative donor is found. Because prospective cross-matches are only performed with unseparated donor lymphocytes, which are predominantly T cells expressing MHC class I antigens, we investigated the effects of IgG anti-I on waiting time to heart transplantation. As expected, LVAD recipients with IgG anti-I had a significantly longer waiting time than those without these antibodies (175 vs 90 days, \( P=0.009 \)). Similarly, LVAD recipients with a total T-cell PRA also had
a longer waiting time than those without these antibodies (190 vs 87 days, \(P=0.015\)). The presence of IgG anti-II did not affect the waiting time to transplantation (LVAD 139 vs 114 days, \(P=0.50\)) as these antibodies were not identified when donor-specific cross-matching was performed on unseparated peripheral blood mononuclear cells.

**Presence of IgG Anti-MHC Class II Antibodies at Time of Transplantation Predicts Shorter Duration to First High-grade Cellular Rejection for LVAD and Retransplantation Recipients**

As shown in Figure 1, the time intervals between transplantation and the first high-grade cellular rejection were similar for both LVAD recipients and retransplantation recipients, with one quarter of both populations rejecting by 80 days. For this reason, the influence of each antibody type on this outcome was examined not just in each group separately but on the combined group of all patients at high risk.

As shown in Figure 2, IgG anti-II detected at the time of transplantation was highly predictive of early high-grade cellular rejection in the posttransplantation period for the combined group of patients receiving a second graft or previously receiving LVAD support. This observation held when each group was studied separately (data not shown). The median time for a high-grade rejection was 70 days for patients positive for IgG anti-II. In contrast, the actuarial freedom from rejection never fell <50% in >1700 days of follow-up for patients without IgG anti-II (odds ratio=24.3, \(P=0.006\)). As shown in Figure 3, the presence of IgG anti-I was also a moderate risk factor for a high-grade rejection; however, this did not reach statistical significance (\(P=0.08\)). Finally, the presence of a positive total T-cell PRA at the time of transplantation was not at all predictive of early high-grade rejection (Figure 4). Additionally, neither the presence of IgM anti-I nor IgM anti-II at the time of transplantation influenced the time to a high-grade cellular rejection (\(P=0.94\) and \(P=0.79\), respectively).

**Presence of IgG Anti-MHC Class II Antibodies Is a Major Risk Factor for Posttransplantation Cellular Rejections**

By Cox proportional hazard modeling for multivariate analysis, the only risk factors identified to predict an early high-grade cellular rejection were the presence of pretransplantation IgG anti-II (\(P=0.018\)) and, to a lesser extent, IgG anti-I (\(P=0.086\)) (see Table 2). These observations held for both LVAD and retransplantation recipients. None of the other variables tested in this analysis were predictive of
rejection in this group of sensitized individuals, including T-cell PRA; matching at the HLA-DR, -B, or -A loci; ischemic time; or donor age.

**Presence of Pretransplantation IgG Anti-MHC Class II Antibodies Is Associated With Higher Cumulative Annual Rejection Frequencies**

As shown in Table 3, those patients with IgG anti-II detected at the time of transplantation had higher cumulative annual rejection frequencies than those without these antibodies (0.846 vs 0.169 high-grade rejections per patient year of follow-up). Among the demographic and immunologic variables examined, including the other antibody types, only pretransplantation IgG anti-II was predictive of a higher cumulative annual rejection frequency ($P<0.001$). Neither the presence of IgG anti-I nor total T-cell PRA significantly influenced the cumulative annual rejection frequencies.

**Matching Between First and Second Donor at HLA-A Locus Predicts Early High-grade Cellular Rejection for Recipients of Second Cardiac Allograft**

As shown in Figure 5, among retransplantation recipients, those who received a second allograft that shared one or more HLA-A locus antigens with the first donor had a significantly shorter time to a first high-grade cellular rejection. This difference was most notable in the first posttransplantation month, in which 67% of retransplantation recipients of a donor 1–donor 2 HLA-A match had a high-grade cellular rejection compared with only 5% of those not receiving a heart from a second donor matched at HLA-A with the first donor ($P=0.0026$, odds ratio 30.0). This risk factor was independent of any anti-HLA IgG antibody effect, since only 1 of 6 patients with donor 1–donor 2 HLA-A match had IgG anti-II pretransplantation. Matching of the first and second donors at the HLA-B and DR loci did not influence the duration to early rejections among the retransplantation recipients.

**Discussion**

In this study, we investigated the effects of anti-HLA antibodies present in 2 populations of sensitized individuals awaiting heart transplantation. IgG antibodies against non–donor-specific MHC class II molecules were detected at increased frequency among both LVAD recipients and retransplantation candidates. The presence of IgG antibodies against MHC class II molecules detected in recipient serum at the time of transplantation was found to be a major risk factor both for the development of early high-grade cellular rejections and for significantly increased cumulative annual rejection frequencies. These observations were independently

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**Figure 3.** Among a combined group of patients at high risk for sensitization (n=68), pretransplantation IgG against MHC class I molecules (IgG anti-I) is a weaker predictor for a first high-grade cellular rejection than IgG anti-II.

**Figure 4.** Positive total T-cell PRA before transplantation has no effect on time to a first high-grade cellular rejection.
confirmed in both populations of sensitized individuals. Neither anti-MHC class I IgG antibodies nor lymphocytotoxic antibodies detected in a conventional PRA assay were found to be predictive of earlier cellular rejections or increased cumulative annual rejection frequencies. Because both anti-HLA antibodies and early cellular rejections have been associated with accelerated graft vasculopathy in heart transplantation,\(^{6–8,14,15}\) these results emphasize the importance of specifically screening heart transplantation candidates for the presence of IgG antibodies against MHC class II molecules and suggest that strategies aimed at their reduction may have an impact on the long-term outcome of cardiac allograft recipients.

Although previous studies have identified adverse effects of anti-HLA IgG antibodies on early posttransplantation graft rejection and survival, especially in instances of a positive donor-specific cross-match with unseparated donor mononuclear cells,\(^ {1–3}\) in none of these studies was a distinction made of anti-HLA IgG antibodies on early posttransplantation graft rejection of recipients developing accelerated transplantation-related CAD.\(^ {18}\) This diversification of the immune response has been postulated to be driven by sensitized B cells that bind soluble HLA-DR molecules by using specific surface Ig receptors, endocytose these molecules, and subsequently present multiple HLA-DR allopeptides to CD4 T cells.\(^ {19–21}\)

Therefore, the relation between recurrent high-grade cellular rejections and preexisting IgG anti-MHC class II antibodies documented in this study may be secondary to the presence in allosensitized patients of circulating pre-sensitized memory B cells capable of reacting with HLA-DR molecules and presenting cryptic epitopes to helper CD4 T cells. The presence of alloreactive B cells in sensitized candidates may reflect either exposure to alloantigens after administration of blood products, pregnancy, or prior transplantation or induction of a broad state of B-cell hyperreactivity caused by an abnormal cytokine milieu in LVAD recipients.\(^ {22}\)

In our study, an additional risk factor for early high-grade cellular rejection of the second allograft in retransplantation recipients was a match at the HLA-A MHC class I locus between the first and second donors. Because this study was relatively small, the association between donor 1–donor 2 HLA-A locus match and cellular rejection needs further confirmation. However, the fact that only 1 of 6 patients with a donor 1–donor 2 match also had IgG anti-II indicates that for retransplantation recipients, matching between donors at the HLA-A locus and preformed IgG anti-II may be independent risk factors for high-grade cellular rejection.

Because the presence of IgG anti-MHC class I or II antibodies in sensitized patients leads to a prolonged waiting time to heart transplantation because of repeated instances of positive cross-matches with potential donors.

The mechanism by which the presence of pretransplantation IgG antibodies against HLA class II antigens relates to the posttransplantation development of earlier and more frequent high-grade cellular rejections remains conjectural at present. Recent cumulative evidence has emerged that the indirect pathway of CD4 T-cell activation plays a major role in acute and chronic cardiac allograft rejection caused by reactivity against donor alloantigenic HLA peptides processed by host antigen-presenting cells such as macrophages, dendritic cells, and B cells. In previous studies, we have shown that acute cellular rejection of cardiac allografts is accompanied by the appearance both in the circulation and in the allograft of recipient T cells, which react with donor HLA-DR peptides presented by self–antigen-presenting cells.\(^ {10}\) Primary rejections appear to be invariably accompanied by indirect recognition of a dominant HLA-DR allopeptide,\(^ {16,17}\) whereas recurrent rejections appear to be accompanied by intermolecular spreading and T-cell recognition of multiple donor HLA-DR alloantigenic determinants.\(^ {12}\) Similar patterns of progressive intramolecular and intermolecular HLA-DR epitope spreading can be detected in heart transplantation recipients developing accelerated transplantation-related CAD.\(^ {18}\) This diversification of the immune response has been postulated to be driven by sensitized B cells that bind soluble HLA-DR molecules by using specific surface Ig receptors, endocytose these molecules, and subsequently present multiple HLA-DR allopeptides to CD4 T cells.\(^ {19–21}\)

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Because the presence of IgG anti-MHC class I or II antibodies in sensitized patients leads to a prolonged waiting time for transplantation, early posttransplantation humoral rejection, and earlier and more frequent posttrans-

### TABLE 2. Multivariate Analysis of Risk Factors for First High-grade Cellular Rejection After Transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient ± SE</th>
<th>P</th>
<th>Risk Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG anti-II</td>
<td>1.035 ± 0.4393</td>
<td>0.0184</td>
<td>2.816</td>
<td>(1.19, 6.66)</td>
</tr>
<tr>
<td>IgG anti-I</td>
<td>0.908 ± 0.5295</td>
<td>0.0863</td>
<td>2.480</td>
<td>(0.88, 7.00)</td>
</tr>
</tbody>
</table>

By multivariate analysis, with Cox proportional hazards model, pretransplantation IgG anti-II, and to a lesser extent IgG anti-I, is predictive of earlier first high-grade cellular rejection after heart transplantation in highly sensitized individuals (n=68).

### TABLE 3. Influence of Pretransplantation Anti-HLA Antibodies in Sensitized Patients (n=68) on Cumulative Annual Rejection Frequencies of Subsequent Heart Transplantation

<table>
<thead>
<tr>
<th>Cumulative Annual Rejection Frequency (No. of 3A or 3B Rejections/yr)</th>
<th>Positive</th>
<th>Negative</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG anti-II</td>
<td>0.846</td>
<td>0.169</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IgG anti-I</td>
<td>0.611</td>
<td>0.291</td>
<td>0.09</td>
</tr>
<tr>
<td>T-cell PRA</td>
<td>0.468</td>
<td>0.328</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Cumulative high-grade (3A/3B) rejections were modeled by the method of Wei, Lin, and Weissfeld.\(^ {13}\)
plantation cellular rejections, strategies to reduce the levels of these antibodies before transplantation are needed for this rapidly enlarging pool of patients awaiting heart transplantation. Prior experience with sensitized patients has focused on immunosuppressive therapies initiated after transplantation, including plasmapheresis, \(^3\) and photopheresis, \(^2\) to avoid the negative consequences of these pretransplantation antibodies. We emphasize the need to carefully screen all patients at risk for sensitization before transplantation and to identify the presence, isotype, and specificity of anti-HLA antibodies that portend heightened risk for adverse posttransplantation outcomes. Moreover, our results show that whereas a T-cell PRA may be useful for identifying individuals at risk of having a positive donor-specific cross-match and, potentially, of vascular allograft rejection, it has no predictive value for subsequent cellular rejection. We therefore advocate that all patients before transplantation should be specifically screened for the presence of antibodies against both MHC class I and class II antigens and that immunosuppressive strategies be instituted. These strategies will need to be tailored to the antibody specificity detected in any given patient and the clinical complication it portends. Such strategies might include the use of intravenous immunoglobulin, \(^2\) plasmapheresis, \(^2\) or Protein A column immunoabsorption to deplete circulating antibody levels or B-cell immunosuppression with agents such as cyclophosphamide to interrupt pathways of B-cell alloantigenic presentation. \(^2\) In view of the increasing use of LVAD support and the growing numbers of patients awaiting retransplantation, high priority should be given to evaluation of therapeutic protocols aimed at reducing anti-HLA antibodies before heart transplantation.

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