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The long-term outcome of treated sensitized patients who undergo heart transplantation

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Abstract

Background—Sensitized patients prior to heart transplantation are reportedly at risk for hyperacute rejection and for poor outcome after heart transplantation. It is not known whether the reduction of circulating antibodies pre-transplant alters post-transplant outcome.

Methods and Results—Between July 1993 and July 2003, we reviewed 523 heart transplant patients of which 95 had pre-transplant panel reactive antibody (PRAs) >10%; 21/95 were treated pre-transplant for circulating antibodies. These 21 patients had PRAs > 10% (majority 50–100%) and were treated with combination therapy including plasmapheresis, intravenous gamma globulin and rituximab to reduce antibody counts. The 74 untreated patients with PRAs > 10% (untreated sensitized group) and those patients with PRAs < 10% (control group) were used for comparison. Routine post-transplant immunosuppression included triple-drug therapy. After desensitization therapy, circulating antibody levels pre-transplant decreased from a mean of 70.5 to 30.2%, which resulted in a negative prospective donor-specific crossmatch and successful heart transplantation. Compared to the untreated sensitized group and the control group, the treated sensitized group had similar five-yr survival (81.1% and 75.7% vs. 71.4%, respectively, $p = 0.523$) and freedom from cardiac allograft vasculopathy (74.3% and 72.7% vs. 76.2%, respectively, $p = 0.850$).

Conclusion—Treatment of sensitized patients pre-transplant appears to result in acceptable long-term outcome after heart transplantation.

Keywords

circulating antibodies; heart transplant; outcome; sensitization; treatment

Circulating antibodies against human leukocyte antigens (HLA) can occur in patients awaiting heart transplantation. This process by which antibodies are formed is called sensitization. Sensitization occurs from exposure of foreign white blood cells to the patient via blood transfusions, pregnancy, previous organ transplant, or the placement of a

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ventricular assist device. A major concern of sensitization in patients undergoing heart transplantation is the development of hyperacute rejection where these circulating antibodies are coincidentally targeted against the donor heart HLA antigens. This results in sudden, irreversible cessation of graft function minutes to hours after revascularization. Autopsy findings include diffuse interstitial edema; focal hemorrhage; small arteries, arterioles, capillaries, and venules plugged with platelet aggregates; and intravascular fibrin and polymorphonuclear neutrophils present within capillaries and venules.

Several reports have demonstrated that pre-transplant sensitization leads to decreased survival, increased rejection, and development of cardiac allograft vasculopathy (CAV) after heart transplantation. Initial studies have shown that panel reactive antibody (PRA) tests >10% are associated with lower survival (1–5). In a previous retrospective study conducted at our institution, we reported on survival and rejection rates in 311 cardiac transplant recipients. Despite negative donor-specific crossmatches at the time of transplant, patients with PRA ≥ 11% had significantly lower three-yr survival than patients with PRA < 11%. Furthermore, these sensitized patients had rejection episodes that tended to occur earlier and were more clinically severe (required OKT3 therapy) than patients with PRA < 11% (2). Other groups have reported that a higher percentage of PRA-positive results are associated with poor outcome. A recent large registry has shown that only PRA > 25% is associated with poor survival after heart transplantation (6).

The PRA test (lymphocytotoxic assay) informs one of the presence of circulating anti-HLA antibody but not the quantity of antibody. Results that reveal a high percentage of PRA reactivity refer to more individual anti-HLA antibody being detected. However, in general, the more circulating antibodies detected the more likely that some of these antibodies have significant quantity to cause immunologic injury to the donor heart. In addition, these patients who produce multiple anti-HLA antibodies prior to transplant appear to be more immuno-responsive, which may increase their risk to mount an immunologic response (rejection) against the donor heart after transplantation (7). The clinical observations correlating high pre-transplant PRA results to lower survival after transplant corroborate these generalizations (1–5).

There are other antibodies besides anti-HLA antibody that may damage the donor heart (8–10). These non-HLA antibodies that may have clinical relevance include autoantibodies (IgM non-HLA, vimentin, and anti-heart antibodies) and antibodies to major histocompatibility complex class I chain A, major histocompatibility complex class I chain B, and undefined endothelial antigens. Antibodies to non-HLA antigens expressed on donor endothelial cells constitute the largest unknown group of potentially clinically relevant non-HLA antibodies. They may be polymorphic cell surface antigens or autoantigens exposed as a result of damage to the endothelial cell (10). The ability to test for non-HLA antibodies is far behind the refined and sensitive methods currently available to detect HLA antibodies. Further work is necessary to define the most important non-HLA antigens. Detection of non-HLA antibodies and their avoidance or removal is likely to lead to improved graft survival.

Treatment to reduce circulating antibodies prior to transplant has had mixed results. The use of plasmapheresis, intravenous gammaglobulin (IVIG), rituximab (anti-B cell antibody), and high dose cyclophosphamide have been demonstrated to successfully reduce circulating antibodies (11–14). These therapies have allowed heart transplantation to proceed with a negative prospective donor-specific crossmatch and low risk of hyperacute rejection. However, it has not been established whether these successfully treated pre-transplant sensitized patients have acceptable outcome after heart transplantation. We now report our experience in regard to these patients.

Methods

Between July 1993 and July 2003, 523 heart transplant patients were retrospectively reviewed for elevated peak PRAs of which 95 patients were found to have pre-transplant peak PRAs > 10%. Of these 95 patients, 21 were treated prior to transplant for circulating antibodies. Only five of these 21 treated sensitized patients were a part of the previous retrospective study conducted at our institution. Patients with circulating antibodies were treated when they had two prospective positive crossmatches against potential donors or if PRAs were >80% in which prospective cross-matches were performed on only the most recent pre-transplant sera. Based on this information, the patients were stratified into three different groups: treated sensitized group, 21 (4.0%) patients with peak PRA level >10% requiring treatment; untreated sensitized group, 74 (14.2%) patients with peak PRA level >10% without treatment; and a control group, 428 (81.8%) patients with peak PRA level 0–10% without treatment. PRA levels for each patient were analyzed using complement-dependent cytotoxicity (CDC) and flow cytometry (routinely after 1999). All patients were started on triple-drug therapy immunosuppression following transplant. Patients were routinely started on either tacrolimus (after 1999) or cyclosporine, either mycophenolate mofetil (after 1998) or azathioprine, and corticosteroids. No routine induction therapy was administered.

Baseline assessments were completed using all demographic data. The primary end points include five-yr post-transplantation survival, five-yr freedom from CAV, five-yr freedom from non-fatal major adverse cardiac events (NF-MACE, defined as myocardial infarction, congestive heart failure, percutaneous coronary intervention, implantable cardioverter-defibrillator implantation, or stroke), five-yr freedom from any treated infection, and first-yr freedom from any treated rejection. Rejection grades of endomyocardial biopsies were determined according to the International Society for Heart and Lung Transplantation (ISHLT) cardiac allograft biopsy scale. ISHLT Grades 1A, 1B, and 2 were not treated. Grade 3A was treated with an oral prednisone bolus and taper (50 mg orally twice a day for three d with gradual taper over two wk to 10 mg orally twice a day). ISHLT Grades 3B and 4 (plus any ISHLT grade with hemodynamic compromise defined as ejection fraction <40%, cardiac index <2, and on inotropic support) were treated with OKT3 5 mg intravenously daily for 14 d. These rejection results depict grades of the former (1990) ISHLT biopsy grading system that was in use during the time period of this study.

Coronary angiography was performed between four and six wk after heart transplant and thereafter, annually. A diagnosis of CAV was made if there was any new luminal stenosis ≥30%, or significant distal pruning of the coronary arteries at annual angiograms compared with the baseline angiogram.

Statistical analysis

Two-tailed *t*-tests, chi-square tests, and Fisher's exact tests were utilized to assess the variation between group 1 and groups 2 and 3. The Wilcoxon log-rank statistic was used to compare Kaplan–Meier survival curves. $p < 0.05$ was considered statistically significant.

Results

Among the three study groups, there were no significant differences in such baseline demographics as mean recipient age, mean donor age, reason for transplantation, ischemic time, and CMV mismatch (Table 1). However, there were significantly more women in the treated group when compared to the control group (Table 1), although there was no statistical difference between the treated group and the untreated group in terms of percentage of women. In terms of HLA matching, 19/21 patients in the treated sensitized

group exhibited six HLA mismatches, while the other two patients exhibited five HLA mismatches. These HLA mismatch findings are similar to the untreated and control groups (data not shown).

The 21 patients of the treated sensitized group had mean peak PRA of 70.5% with a range of 28–100% (majority 50–100%). The 74 patients of the untreated group exhibited a mean peak PRA of 18.8% with a range of 11–48%, while the 428 patients of the control group demonstrated a mean peak PRA of 0.9% with a range of 0–10%. Patients in the treated sensitized group were treated with 1–6 courses of combination therapy, including plasmapheresis (daily for five d) and/or IVIG administered at 2 g/kg in divided dose over two d and/or rituximab administered at 375 mg/m² to reduce antibody counts. Therapy was administered according to treating physician choice. In general, plasmapheresis and IVIG were first choice of therapy with rituximab being administered for refractory elevated circulating antibodies. Specifically, five of these patients were treated with combination therapy of plasmapheresis, IVIG, and rituximab; four with plasmapheresis and IVIG; and 12 patients with solely plasmapheresis. Of the 21 patients with significantly elevated PRAs, all patients were successfully treated, with PRAs decreasing from a mean of 70.5% to 30.9%. Mean peak PRA reductions can be seen in Fig. 1. This treatment allowed for successful heart transplantations with negative prospective donor-specific crossmatches and no episodes of hyperacute rejection. The prospective crossmatches were negative by CDC. Of note is that this study included only sensitized patients who underwent heart transplantation. It is not a true assessment of desensitization therapy but rather an evaluation of the outcome of transplant patients who were desensitized prior to transplant.

Immediately post-transplant, further immunosuppression was administered to select patients because of concerns of persistent circulating antibody levels (physician choice). Patients with persistently elevated PRAs despite desensitization therapy were given thymoglobulin immediately post-operative. In addition, plasmapheresis and IVIG were initiated if a rise in circulating antibody was detected. Donor-specific antibodies were routinely checked every other day for the first week after transplant in patients with pre-transplant circulating antibodies. Thereafter, circulating antibodies were checked for those patients with persistent circulating antibodies. Routine inspection for circulating antibodies was not carried out in all patients. Specifically, six patients in the treated sensitized group were administered thymoglobulin 1.5 mg/kg qd × 5 followed by IVIG 2 g/kg in divided dose over two d. Additionally, 11 patients from the sensitized group received plasmapheresis therapy for five d immediately following their transplant. Conversely, 10 patients (13.5%) from the untreated group and 34 patients (7.9%) from the control group received cytolytic induction therapy for renal insufficiency to allow delayed initiation of calcineurin inhibitor.

There was similar five-yr survival among the untreated sensitized group and the control group vs. the treated sensitized group (81.1% and 75.7% vs. 71.4%, respectively, $p = 0.52$) (Fig. 2). There was also similar five-yr freedom from CAV among the untreated and control groups vs. the treated group (72.7% and 76.2% vs. 74.3%, respectively, $p = 0.85$) (Fig. 3). The three groups were also not found to be significantly different in terms of five-yr freedom from NF-MACE (90.9% and 90.5% vs. 95.2%, $p = 0.77$) (Fig. 4) and five-yr freedom from any treated infection (73.8% and 71.6% vs. 71.4%, $p = 0.75$) (Fig. 5). However, first-yr freedom from any treated rejection was significantly less in the treated group compared with the untreated group (57.1% vs. 85.1%, $p = 0.013$) and compared to the control group (57.1% vs. 87.4%, $p < 0.001$) (Fig. 6). The treated group was found to have significantly less first-yr freedom from antibody-mediated rejection when compared to the untreated group (66.7% vs. 89.2%, $p = 0.01$) and control group (66.7% vs. 96.5%, $p < 0.001$). However, first-yr freedom from cellular rejection was found to be comparable in the treated group compared to the untreated group (90% vs. 95%, $p = 0.90$) and the control

group (90% vs. 91%, $p = 0.74$). In addition, hemodynamic compromise rejection was not found to be significantly different when comparing the treated sensitized group to the untreated group (4.8% vs. 1.4%, $p = 0.22$) and the control group (4.8% vs. 1.6%, $p = 0.43$). There was no significant difference in all outcomes between patients that utilized different combinations of post-transplant therapies in the treated sensitized patient group.

Six of 21 (29%) patients were found to have retrospective crossmatches that were CDC negative, but Flow positive. These patients were found to have similar outcomes including five-yr survival, five-yr freedom from CAV, five-yr freedom from NF-MACE, and one-yr freedom from any treated rejection compared to CDC-negative/Flow-negative retrospective crossmatch recipients (data not shown).

Discussion

This study suggests that the successful treatment of the highly sensitized patient pre-transplant can safely undergo heart transplantation with comparable post-transplant outcomes compared to low-or non-sensitized patients. This is important as many studies have reported lower survival and increased incidence of CAV in patients that are highly sensitized prior to heart transplantation.

A large retrospective cohort study of 8160 heart transplant recipients was conducted by Nwakanma et al. (6) to determine the association between PRA at transplant and survival and rejection. Patients were divided into four groups based on PRA levels: 0%, group 1 ($n = 6481$); 1–10%, group 2 ($n = 930$); 11–25%, group 3 ($n = 309$); and >25%, group 4 ($n = 440$). First-yr rejection rates were significantly increased with higher PRA levels. Actuarial survival was significantly different among the four groups, and increasing PRA was a significant predictor of mortality. However, multivariate analysis showed that only group 4 (PRA > 25%) had worse survival than group 1. These observations appeared somewhat similar in our study. The untreated sensitized patients mostly had PRAs < 25% and had comparable survival to the control group. In the Nwakanma study, the treated sensitized patients exhibited a lower survival immediately following transplant. However, in the current study, the successful treatment of our highly sensitized patients before transplant (use of desensitization therapies) and after transplant (increased immunosuppression) allowed for comparable five-yr survival after heart transplantation. In addition, the comparable survival that was observed in the treated sensitized patient group occurred despite these patients having more first-year rejection episodes. Importantly, although there were more antibody-mediated rejections in the treated sensitized group, there was no increase in rejection with hemodynamic compromise (which is associated with high mortality).

The reported (from the literature) reduced survival in sensitized patients appears to be because of a higher incidence of hemodynamic compromise rejection after heart transplantation. Holt et al. (12) reviewed 17 pediatric patients with PRAs > 10% to compare post-transplant rejection and survival outcomes between patients who were transplanted with a CDC-positive crossmatch and patients transplanted with a negative crossmatch. All patients underwent peri-operative plasmapheresis, thymoglobulin, and cyclophosphamide. Thirteen of the 17 patients had a CDC-positive crossmatch. Within the first six months post-transplant, the frequency of rejection in these patients was significantly greater than in patients with a negative crossmatch. Rejection in CDC-positive crossmatch patients was associated with hemodynamic compromise in 58% of first rejection episodes and 67% of recurrent rejection episodes.

The present study also demonstrated that highly sensitized pre-transplant patients can have circulating antibodies significantly reduced to allow heart transplantation to proceed with a negative prospective donor-specific crossmatch. Although not a uniform finding, pre-transplant plasmapheresis followed by IVIG has been shown to possibly be an effective therapy in sensitized patients. Pisani et al. (11) examined 118 heart transplant recipients, of which 16 were sensitized (PRA > 10%) and were treated with plasmapheresis and IVIG immediately pre-transplant. In this small study, the treated sensitized group had more positive cross-matches, pulmonary hypertension, and need for mechanical circulatory support prior to transplant. However, there was no statistically significant difference in length of stay or mortality at the mean follow-up of 21.6 + 15.0 months after heart transplantation. Interestingly, there was no reported difference in the occurrence of rejection episodes between the two groups.

Historically, the pre-transplant highly sensitized patient has poor outcome after heart transplantation. In the present study, there may be several reasons for the comparable five-yr post-transplant survival in the treated highly sensitized patients compared to the untreated and control groups. Treatment with plasmapheresis/IVIG/rituximab (pre-/post-transplant) and thymoglobulin (post-transplant) may immunomodulate the immune system preventing severe (hemodynamic compromise) rejection after transplant. The use of mycophenolate mofetil in our post-transplant immunosuppression regimens may also have improved outcome in our patients. Results from a large randomized trial reported that mycophenolate (compared to azathioprine) reduced hemodynamic compromise rejection and antibody production (15, 16).

Donor-specific antibody production after heart transplantation has been associated with rejection. In a study by Tambur et al. (17), 71 heart transplant recipients were evaluated for the presence of new HLA-directed antibodies during their first-year post-transplant. Twenty-five patients had newly detected HLA antibodies, with 18 patients expressing HLA class I and 11 patients expressing HLA class II antibodies. Outcome analysis revealed a significant correlation between de novo HLA-directed antibodies and cellular rejection ($p = 0.0002$). HLA class II antibodies were also significantly correlated with CAV ($p < 0.002$) and allograft failure ($p = 0.008$).

A limitation of this study was that it did not assess for the development of donor-specific antibodies after heart transplantation. It is likely that despite aggressive immunotherapy in the immediate post-operative period, donor-specific antibodies were produced by the treated highly sensitized patients. Nevertheless, survival and the development of CAV are hard end points and did not appear to be affected by the presumed development of post-transplant donor-specific antibodies.

In conclusion, treatment of highly sensitized patients pre-transplant appears to result in successful heart transplant surgery (without hyperacute rejection) and acceptable long-term outcomes. The previously reported poor outcome of these highly sensitized patients after heart transplantation appears to be ameliorated by current treatment modalities pre-/post-transplant surgery.

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Fig. 1. Individual reductions in mean panel reactive antibody levels of all 21 treated sensitized patients.

Fig. 2.
There were no significant differences in five-yr survival among the three study groups ($p = 0.523$).

Fig. 3.
There were no significant differences in five-yr freedom from cardiac allograft vasculopathy among the three groups ($p = 0.850$).

Fig. 4. There were no significant differences in five-yr freedom from NF-MACE among the three groups ($p = 0.771$).

Fig. 5.

There were no significant differences in five-yr freedom from any treated infection among the three groups ($p = 0.752$).

Fig. 6.

First-yr freedom from any treated rejection was significantly lower in the treated group vs. the untreated group ($p = 0.013$) and the treated group vs. the control group ($p < 0.001$). Hemodynamic compromise rejection (HDC) was not significantly different among the three groups.

Table 1

Clinical characteristics of the adult heart transplant patients included in the study

	PRA > 10% treated	PRA > 10% untreated	PRA < 10% control
N	21	74	428
Mean pre-transplant peak PRA (%)	70.5 ± 28.9 *	18.8 ± 8.5	0.9 ± 2.2
Mean PRA at transplant (%)	56.9 ± 39.1 *	18.2 ± 8.5	0.5 ± 1.8
Mean recipient age (yr)	54.2 ± 9.6	52.5 ± 13.1	55.0 ± 12.2
Gender (% female)	52.4 **	32.40	27.30
Mean donor age (yr)	30.1 ± 14.1	32.0 ± 13.0	26.5 ± 13.8
Reason for transplant			
Ischemic cardiomyopathy (%)	52.40	43.30	52.10
Idiopathic cardiomyopathy (%)	33.30	27.00	29.40
Other (%)	14.30	29.70	17.50
Mean ischemic time (min)	213.0 ± 70.4	218.6 ± 59.7	197.4 ± 65.9
CMV mismatch (%)	19.00	21.60	20.30

PRA, panel reactive antibody.

* There was a significant difference in mean pre-transplant peak PRA (%) and mean peak PRA at transplant (%) between the treated and untreated group and the treated and control group ($p < 0.001$).

** There was a significant difference in percentage of females between the treated and control group ($p = 0.013$).