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Cardiac transplantation

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Cardiac transplantation is an important therapeutic modality for the treatment of the morbidity and reduced survival associated with end-stage congestive heart failure. Cardiac transplant has evolved and matured and is often used as a gold standard to compare novel medical and surgical therapies for advanced heart failure. This issue of *Cardiology Rounds* will provide an update on current national standards and present some aspects of cardiac transplantation management used at Brigham and Women's Hospital. Although cardiac transplantation has emerged as a sub-subspecialist career path, this discussion of the unique clinical challenges encountered with this particular patient population is directed to the general cardiologist.

General characteristics

The finite number of donors in any geographic area limits the overall size of any cardiac transplantation program. Because of such limited single center volume, virtually all large transplant centers have had to form collaborative relationships to accumulate sufficient patient populations for clinical investigative protocols, to establish national outcome standards, and to provide more meaningful insight into demographic information of this patient population. There are three such databases in the United States:

• UNOS (United Network of Organ Sharing) provides national oversight to the transplantation/organ donation process. The major role of UNOS is in developing the optimal and fairest allocation of the precious resource.

• The Registry of the International Society of Heart and Lung Transplantation records outcomes and general clinical characters for all programs.

• The Cardiac Transplant Registry Database (CTRD) compiles demographic treatment and outcome data from high volume programs.

By constructing collective outcome data, these organizations have established international and national standards and expectations. The number of yearly cardiac transplantations performed worldwide peaked at 4068 procedures in 1995 and declined to 2961 in 1998, primarily because of limited donor availability.[1] Approximately 2300 transplantations will be done each year in the United States. Such decline has occurred despite broadening the acceptance age of donors, increased public education, and other measures to expand donor availability. Concurrent with this diminished pool, the need has expanded. Currently, approximately twice as many potential recipients will be listed as will be transplanted. This simple inequity translates to more patients on waiting lists and continuing pressure as transplant cardiologists to re-evaluate each patient's priority status.

In the early years of cardiac transplantation, approximately 60% of all transplants were done for dilated cardiomyopathy, the balance for ischemic heart disease. At the present time, however, approximately 45% of patients are transplanted for non-ischemic cardiomyopathy, 45% for ischemic cardiomyopathy, with approximately 3.5% for valvular heart disease, 2.5 % for retransplantation, 2% for congenital heart disease, and another 2% for other conditions,[1] such as sarcoid, hypertrophic cardiomyopathy, amyloid, Chagas, chemotherapeutic, and other myopathies.

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Survival following transplantation

There has been a difference in survival in the four different eras of immunosuppression. The early clinical experience between 1980 and 1985 was associated with lower survival rates than those achieved between 1986 to 1990. Improvement was also noted in the years between 1991 and 1998. But in the past 9 years, there has been no detectable difference in survival characteristics (1991-1994 and 1995-1998). This underscores an obvious clinical point, that immunosuppressive protocols have been generally standardized to triple immunosuppressive therapy that includes prednisone, cyclosporine or tacrolimus, and azathioprine or mycophenolate mofetil; that immunosuppressive protocols for rejections are similar; and that longevity standards have been set very high and are consistently achieved across the nation.

The current overall national standards for one- and five-year survival are 79% and 63%, respectively.[1] These data, taken from the Registry of the International Society of Heart and Lung Transplantation, suggest that median survival is approximately 8.8 years when one takes into account early post-operative mortality. For those surviving the first year of transplantation, subsequent projected median survival increases to 11.5 years.[1] After the first year, the average annual mortality rate is about 4%.

Risk factors for poor outcome following cardiac transplantation

There are a number of recipient risk factors for cardiac transplantation that have consistently demonstrated an adverse prognosis after transplantation. These variables include the need for mechanical support with left ventricular assist devices, respiratory ventilator support at the time of transplant, retransplantation, and most importantly, increasing recipient age.[1] There is some evidence that suggests that female recipients and the initial diagnosis of CAD become additional risk factors for reduced long-term success. Donor risk factors that have been consistently identified include longer ischemic time of the donated organ, an increasing donor's age, and donor's gender; a female heart transplanted into a female recipient may perhaps have an adverse long-term prognosis.[1]

Post-transplantation morbidity

Major morbidities following cardiac transplantation include infection, hypertension, and renal dysfunction, all often the consequence of immunosuppressive therapies. Hypertension often requires multiple pharmacologic therapies, and renal dysfunction is clinically significant in approximately 25% of patients, with 2 to 5% of patients ultimately requiring dialysis. Hyperlipidemia and glucose intolerance are significant medical problems that require ongoing medical care.[1]

Post-transplant malignancies represent a significant ongoing risk to all patients following heart transplantation. Approximately 38% of these neoplasms will be a traditional post-transplant lymphoproliferative disease, a B-cell lymphoma. Other post-transplant malignancies include lung and colonic cancers, as well as skin neoplasm. Malignant melanoma is relatively infrequent in this group.

Cardiac rejection

There are three forms of cardiac rejection that are clinically recognized:

• Acute cellular rejection is diagnosed by endomyocardial biopsy, with lymphocytic infiltrate and myocyte necrosis. There is a standardized grading system to these histological changes, and therapeutic response is guided by both histology and clinical presentation.

• A chronic rejection process is often manifest by the development of allograft coronary artery disease. Patients will develop a progressive and diffuse arteriopathy, usually manifest by the development of new regional wall motion abnormalities; angina is not a usual clinical presentation because of the denervated heart.

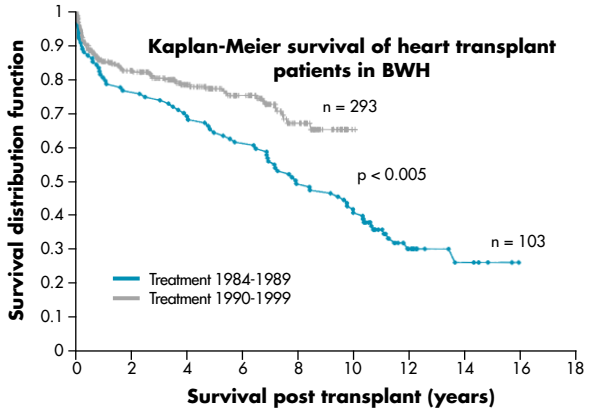
• Finally, an occasional patient will present with advanced graft failure, no coronary disease, and absent histological changes. The etiology of such rejection remains controversial, but is termed "acute humoral" or "acute vascular" rejection.

Cardiac transplantation at Brigham and Women's Hospital

The overall results of cardiac transplantation at Brigham and Women's Hospital are shown in Figure 1. These compare favorably to the national standards. The one-year survival is 85.5%; three-year survival is 80.5%. Figure 1 also demonstrates improved survival with newer immunosuppressive protocols paralleling national outcomes data. The incidence of post-transplant morbidities at BWH is similar to national standards.

Despite similar outcomes, same selection techniques for donor and recipient, and virtually identical immunosuppressive regimens when compared to other large programs, the incidence of both rejection and infectious complications following cardiac transplantation at BWH is significantly less than projected by analysis of CTRD data. This is summarized in Figure 2. The overall incidence of rejection is one-half that of national standards. With less treated rejection and hence less immunosuppression, it follows that there will be fewer infectious complications. We suspect that the primary explanation for the lower reduced rate of rejection and subsequent infection complications relates to the expertise of our pathology colleagues in differentiating between ischemic injury and acute cellular rejection. Such differentiation is often subtle, and many times missed by less experienced pathologists. Believing that much of the early histologic changes are related more to ischemic injury rather than to acute cellular rejection, the program at BWH has been generally reluctant to provide "over immunosuppression" to its patient population. Survival has not been compromised by this more conservative approach, and long-term morbidity seems the same. However,

Figure 1: Survival following cardiac transplantation in two different eras of immunosuppression.



this conservative approach to biopsy interpretation and immunosuppression seems justified, with fewer infectious complications encountered. This variance in the incidence of rejection also implies that other transplantation programs may "over-immunosuppress" their patients in the early years following surgery, predisposing them to infectious complications.

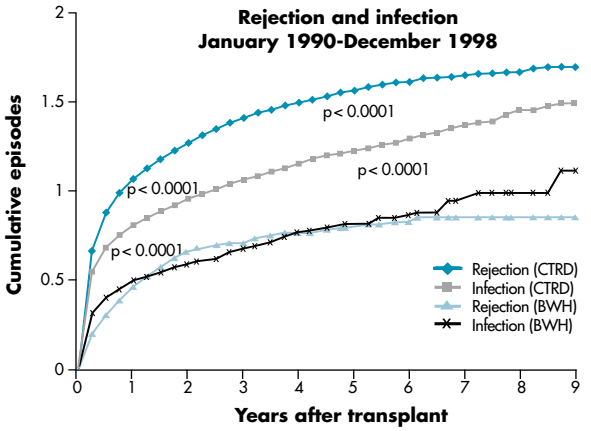
Clinical dilemmas of heart transplantation

HLA matching

Matching for the HLA locus is well-established in cadaver renal transplantation and serves as one means of allocating kidney donations. In the heart transplant population, three or more HLA mismatches is associated with more rejection, the primary benefit to an HLA match may be at the A and DR loci.[2, 3] However, as opposed to renal transplantation, prospective HLA crossmatching continues to be impossible in the heart transplant community, primarily because of the very limited donor supply, the acuity of the recipient's illness, and limited geographic distribution for organs imposed by current tissue preservation techniques.

The panel reactive antibody screen (PRA) is used to determine humoral sensitization to a common panel of HLA antigens. Such PRA screening, conducted prior to listing for transplantation and during the waiting period, begins to define the immunologic status of the recipient. For example, a potential recipient with a PRA greater than 25% is an individual who has been sensitized to greater than 25% of HLA antigens in a randomly selected population. This individual will need a cross-match with any identified donor before transplantation can be performed. Positive cross-matches are to be avoided, as they are associated with a high likelihood for acute rejection. The presence of a retrospective positive cross-match is a predictor for hyperacute rejection, although such a rejection process is not always related to PRA activity.[4,5] Perhaps most importantly, patients who develop new anti-donor HLA antibodies after transplantation are patients who are predisposed to hyperacute rejection and may require intensive immunosuppressive therapy. A high degree of PRA sensitization is

Figure 2: Comparison of incidence of rejection and infectious complications between BWH program and national standards.



common with prior pregnancy, multiple transfusions, or prior transplantation.

In the new era of left ventricular assist devices (LVAD), HLA sensitization may emerge as a significant clinical dilemma.[6] Because LVAD patients often require multiple blood transfusions that will include platelets as well as plasma, these patients often develop high PRA activities while subsequently awaiting transplantation. Moreover, LVADs may generate cross-reactive antibodies to HLA molecules by activation of the inflammatory response.[6] Fifteen per cent of patients who required LVAD prior to transplantation at BWH needed prospective cross-matching because of high PRA, compared to only 2% of the patients who did not require such support; 2 of the patients with LVADs were nearly 100% sensitized. The dilemma is obvious; growing numbers of patients with an LVAD will generate a large group of sensitized patients that will have more limited opportunities for finding suitable donors despite their dependence on the LVAD for survival.

Therapeutic modalities to reduce pretransplant PRA levels remain speculative.[7] Some studies have utilized preoperative immunosuppression, including cyclophosphamide or steroids, as a means of lowering PRA activity. Other investigators have incorporated low dose total body lymphoid radiation, plasmapheresis, or gamma globulin. The long-term outcomes with such approaches are unknown.

Nuances of immunosuppressive therapy

It is beyond the scope of this limited review to provide all the clinical nuances of immunosuppressive therapy. However, there are several important clinical considerations regarding induction and maintenance therapy that are deserving of mention.

Induction therapy: The choices of induction therapy in the year 2000 include steroid therapy, OKT3 antibody directed against the CD3 T-cell complex, the use of an antithymocyte (polyclonal), antilymphocyte serum, or an Interleukin-2 receptor antibody. Solumedrol induction therapy is standard, and the rationale for the addition of other induction therapy is

that both the number of rejections and complications of immunosuppressive therapy will be reduced. But such additional induction therapy has many drawbacks that have to be balanced in any final decision.

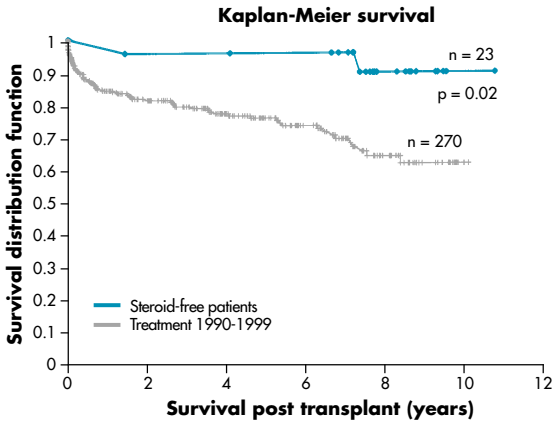
The use of OKT3 monoclonal therapy is associated with a cytokine release syndrome, manifested by fever, chills, and non-cardiogenic pulmonary edema that may appear very early following its administration. This requires pretreatment with high-dose steroids, as well as antihistamines. In addition, induction therapy with OKT3 monoclonal therapy may induce antimurine antibodies that precludes or limits the use of OKT3 for severe rejections in the future. Finally, the incidence of post-transplant lymphoproliferative disease may be higher in patients who receive OKT3 induction therapy,[8] the incidence of acute "vascular" rejection may be higher, and the incidence of significant CMV infection is certainly enhanced. Because of this, induction therapy with OKT3 is usually only considered in patients who have significant contraindications to conventional immunosuppressive therapy; renal dysfunction that limits the ability to start cyclosporine is perhaps the single most important indication for a brief course of OKT3 induction therapy.[9]

Experience with IL2 receptor antibodies and monoclonal therapy directed against various T-cell ligands are much more limited in the heart transplant population, but the initial results are promising.[10]

Chronic rejection therapy: There are general clinical characteristics that define the recipient population predisposed to higher risk for acute cellular rejection. These characteristics include the younger patient, the multiparous female, patients with active myocarditis, individuals with positive cross-match, and the rare patient following retransplantation. With each individual recipient, immunosuppressive regimens are tailored to their needs. The predisposition to acute rejection, the patient's serial endomyocardial biopsy, response to therapy, and the morbidity of such therapy, are all taken into account in developing an individual long-term maintenance program.

Corticosteroids*:* The administration of solumedrol therapy at the time of surgery remains the cornerstone of initial immunosuppression following heart transplantation, and is tapered rapidly over the subsequent six months to low maintenance dose, prednisone 0.1 mg/kg. In the past 5 years, many centers have developed protocols to wean patients from corticosteroid administration completely. Justification for this includes avoidance of steroid-induced morbidities, hypertension, diabetes, osteoporosis, obesity and infectious complications that are the most common side effects. Disadvantages of a steroid-free regimen might include more risk of rejections, the need for more biopsies, meticulous compliance with the remaining immunosuppressive

Figure 3: Comparison of survival of patients withdrawn from steroid immunosuppression to those on conventional triple drug therapy.



agents, and unknown effect on allograft coronary artery disease.

For patients deemed at low risk for rejection, approximately one-half should be successfully weaned from daily prednisone therapy. It is interesting to note that the subsequent survival of such selected patients may be superior to patients who require triple therapy.[11] The survival of patients at BWH with and without steroids is shown in Figure 3. Individuals who have been successfully weaned from steroids may be an "immunologically" preferred patient population, predisposed to fewer rejection episodes and hence, a better survival. The improved survival in these patients may have less to do with their immunosuppressive regimen (ie, less steroid-related morbidities) and more to do with their own intrinsic ability to accept a transplanted organ.

Cyclosporine: Cyclosporine remains an important immunosuppressive agent in virtually all patients following heart translation. The mechanisms of action of cyclosporine are multiple and complicated. Much clinical data suggests that cyclosporine primarily reduces the severity of rejection episodes rather than preventing the rejection process. Patients who reject on cyclosporine therapy usually have early histologic changes that are not associated with hemodynamic compromise. These changes can usually be addressed with modest changes in immunosuppressive regimens. The primary toxicity of cyclosporine includes nephrotoxicity, neurotoxicity, gingival hyperplasia, and hirsutism.

Azathioprine: Azathioprine is the third component to conventional triple immunosuppressive therapy. By inhibiting DNA synthesis, it suppresses activated T and B cells. It is usually adjusted to reduce the white count to 3000-5000 cells/mm.[3] Hepatotoxicity is rarely encountered with its judicious use.

Mycophenolate mofetil: Mycophenolate mofetil inhibits guanine synthesis, with subsequent depletion of guanine molecules. Since proliferating lymphocytes are

fully dependent upon such synthesis, mycophenolate mofetil is a specific lymphocyte inhibitor. A recent, large, randomized study reports that mycophenolate mofetil can be substituted for azathioprine, with reduced rejection rates, perhaps improved survival, but a slightly higher incidence of a CMV infectious complications.[12] Because of this, mycophenolate mofetil is currently used as a replacement drug for azathioprine in patients who are intolerant of azathioprine or have persistent rejection.

Tacrolimus: Tacrolimus likewise inhibits T-cell proliferation and suppresses the antibody response to T-cell mediated antigens. There is some clinical evidence to suggest that it is superior to cyclosporine in the pediatric population, with fewer long-term side effects in this population. In the adult population, it is currently utilized in those patients who have persistent rejection or have intolerable side effects (ie, gingival hyperplasia) to cyclosporine therapy.[13, 14] Nephrotoxicity to tacrolimus continues to be an ongoing dilemma, and is comparable to cyclosporine.

Rapamycin: Rapamycin is a newer immunosuppressive agent of great promise. It inhibits cyclosporine resistant T-cell and B-cell stimulation. It inhibits B-cell immunoglobulin synthesis, and also inhibits fibroblast growth factors. It is this action that may define the role of rapamycin in the prevention of allograft coronary artery disease. Comparative clinical studies are currently underway.

Biopsy interpretation: There are many considerations in the decision to treat histological rejection. The clinician must take into account not only the histologic grade of rejection, but also how many biopsy samples showed such rejection, the levels of histologic change through each sample, objective changes in cardiac function, and responses to prior therapy.

Acute vascular rejection: Perhaps the greatest challenge to treating rejection is seen in patients who have minimal or absent histologic changes, but unexplained low cardiac output, unexplained increase in left ventricular wall thickness, new regional wall motion abnormalities, all occurring in the absence of allograft coronary artery disease. This acute rejection process has been termed “acute vascular rejection,” for traditional histological markers of lymphocytic infiltrate and myocyte necrosis are absent. It is hypothesized that this rejection process is secondary to antibodies to the donor HLA class II antigens,[15] and may be more frequently observed in patients who have received OKT3 induction therapy.[16] Fortunately, such rejection is relatively rare, occurring in 2-4% of transplant recipients. Treatment of acute vascular rejection remains problematic. It may well respond to monoclonal or polyclonal therapy, plasmapheresis, total body lymphoid radiation, or photopheresis. Randomized, multicenter studies assessing the therapeutic efficacy of each of these forms of therapy remains difficult to organize given its rare presentation and rapid clinical decline.

Allograft coronary artery disease

Allograft coronary artery disease remains one of the major dilemmas following cardiac transplantation. This diffuse arteriopathy represents the major morbidity to over 35% of patients following heart transplantation. Its clinical presentation is often subtle, for high-grade proximal obstructive disease is often not visualized on conventional arteriograms until it is far advanced. Rarely, occlusive arterial damage may be visualized on endomyocardial biopsy. Scintographic studies are usually of little incremental help given the global nature of the arterial process and the absence of regional variation to coronary blood flow. Moreover, in patients who have advanced allograft coronary artery disease, systolic function may be well-preserved until the final stages of advanced disease; its clinical presentation is often explained by diastolic abnormalities with symptoms of dyspnea, high right and left heart diastolic filling pressures, but normal systolic function. High dose nitrates are often effective therapy for this population.

Recent clinical observations suggest that the use of HMG-CoA reductase inhibitors may prevent or delay the evolution of allograft coronary artery disease. Initial studies with pravastatin reported a reduction in both intimal thickness and intimal index as determined by intravascular ultrasound when compared to control patients.[17] A more recent study not only confirms a reduction in intimal thickening and index with HMG CoA reductase inhibitors, but also suggests that survival of patients is improved and that this therapy is associated with less angiographic coronary artery disease and a trend towards reduced episodes of histologic rejection.[18] These preliminary observations suggest that HMG-CoA reductase inhibitors have profound and multiple effects following heart transplantation. There are several potential explanations for such pharmacologic effect, including their impact on LDL, anti-inflammatory actions, potentiation of cyclosporine effect by increasing levels, and blocking Interleukin 2 synthesis. These preliminary clinical observations are fertile ground for additional translational research between basic investigative protocols and clinical outcomes.

Retransplantation

Heart transplant specialists continue to be reluctant to consider retransplantation in a group of patients who redevelop severe heart failure, usually as a consequence of chronic rejection. Such patients have traditionally been considered to have a more limited prognosis with retransplantation, prone to more rejections, infection, and a higher incidence of allograft coronary artery disease. They pose an additional ethical dilemma since they have already been the recipient of a donor organ. Given the limitations to the number of donated organs, reluctance to retransplant has been considered reasonable.

However, more recent analysis suggests that the time between the first transplant and the consideration of a second transplant may be helpful in defining the outcome of retransplantation. Patients who survive more than 2 years after the first heart transplant have almost the same outcome with retransplantation as those with initial transplant procedures.[1] Such new information should be incorporated into the evaluation of any re-transplant candidate, but retransplantation will always be a limited option because of donor availability and expanding waiting lists.

Summary

In the clinical art of cardiac transplantation, outcomes have become more predictable and immunosuppressant protocols have become more standardized, leading to more reliable patient expectations. The future in heart transplantation will focus on new immunosuppressive regimens that have less associated morbidities. Cooperative research between transplant programs will continue to identify the causes of and reduce long-term consequences of allograft coronary artery disease.

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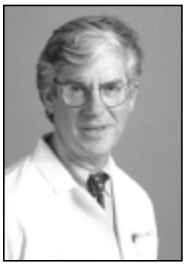

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