Heart Transplantation: New Realities, Challenges and Development- Demographics and Therapeutics

Abstract

Since the first heart transplant, refinement of donor and recipient selection methods, better donor heart management, and advances in immunosuppression have significantly improved survival. In this first of two articles, a perspective of the current realities of cardiac transplantation is shown, as well as the challenges to sustain services worldwide, and some of the new developments, both presently available and just beyond the horizon. Topics that will be covered in this first part include the donor and recipient demographics, as well as recent advances in transplantation immunology, allograft vasculopathy, and immune tolerance.

Keywords

Heart failure; Transplantation; Mechanical circulatory support; Immunosuppression

Abbreviations

CHD: Congenital Heart Disease; MCS: Mechanical Circulatory Support; HLA: Human Leukocyte Antigen; AMR: Antibody Mediated Rejection; CNIs: Calcineurin Inhibitors; CAV: Coronary Allograft Vasculopathy; LVADs: Left Ventricular Assist Devices; PTLD: Post Transplant Lymphoproliferative Disorder

Introduction

The first human heart transplant performed in South Africa in 1967 by Christiaan Barnard, took considerable advantage of the pioneering experimental work by Alexis Carrel, Frank Mann, Norman Shumway, and Richard Lower [1-4]. The first heart transplant recipient recovered well initially, but died of pneumonia 18 days later. Initial outcomes were poor, due to a limited understanding of early post-operative complications as well as limited measures to detect and treat rejection and opportunistic infections. The second recipient survived for 19 months, but surprisingly died of myocardial infarction. Cardiac allograft vasculopathy was eventually recognized as the cause of this death [3]. In the UK a moratorium on heart transplantation was declared in 1973 to 1980.

During this interval, cardiac transplantation continued in the US. It recovered due to refinement of donor and recipient selection methods, better donor heart management, and the introduction of cyclosporine. In excess of 88,000 total heart transplants have been performed worldwide [5]. The International Society of Heart and Lung Transplantation registry currently reports that 1-year survival after heart transplantation is 81%. The annual mortality thereafter is 4% per year. The half-life for survival is 10 years. Mortality is highest in the first year of transplant, after this the conditional half-life is 13 years. The causes of death within the first 6 months are mainly due to graft dysfunction and infection. Late attrition is due to chronic rejection, chronic allograft vasculopathy and malignancies. Heart transplantation is now the optimal treatment for selected patients with end-stage heart failure with 1-year survival is in the region of 90%, 5-year survival rate is approximately 70%, and a median survival in excess of 10 years [5]. The field of heart transplantation is in evolution. Advances in organ preservation, immune monitoring, and immunosuppressive regimens will lead to further improvement in the quality and the length of life of heart transplant recipients. In this article, the objective is to give a perspective of the current reality of cardiac transplantation as well as challenges to this and the new developments which may help to sustain cardiac transplantation in the future.

Patient Demographics

The patient demographics associated with cardiac transplantation are changing. In the USA, older age is now only a relative contraindication to heart transplantation. Rejection is usually less frequent in older recipients while the incidence of infection and allograft vasculopathy may be higher [6,7]. Outside of the US, greater proportion of younger patients with complex congenital heart disease (CHD) patients are being referred for evaluation [3,5]. More patients with CHD survive into adulthood and may develop heart failure later in life, despite adequate surgical repair or palliation [8,9]. CHD is one of the strongest risk factors for 1-year mortality after heart transplantation in adults [5,8]. This high initial attrition rate may be due to challenging anatomical arrangements of the heart and great vessels, adhesions from prior surgery, collateral vessels present in CHD; and importantly, a higher incidence of HLA sensitized patients due to multiple transusions [10]. More recently, cardiac transplantation has taken place with ABO- incompatible donors. This has increased the donor pool for infants and reduced the mortality rate among infant on the waiting list for transplantation [5,11]. This has been driven, particularly in the
UK, by the paucity of hearts for donation with the aim of buying time on the transplant waiting list. This is due to an increase in the numbers of non-heart beating donors (DCDs), whereby retrieval takes place in a circulation arrested donor, and the increased survival of head injury patients and those with intracranial bleeds who are treated by a decompressive craniotomy, reducing the pool of donors who have raised intracranial pressure and who have coned, resulting in brain stem death. The net result is a retrieval rate for heart transplantation of around 19%. MCS allows many severely ill adult and pediatric patients to survive until a suitable donor heart is available. Patients with MCS are at increased risk for rejection, infection, stroke, and bleeding. The need for transusions also increased the risk of pre-sensitization [5-7]. In patients with MCS who undergo transplantation, survival at 1 and 5 years is decreased compared to those transplanted without MCS, but is still higher than 80% and 70%, respectively [5].

As increasing number of patients are transplanted earlier in life, it is also expected that retransplantation will become more common in the future, retransplantation accounts for less than 3% of heart transplants [5]. Survival for retransplanted patients is significantly lower than for other transplant patients. This is due to allosensitisation and the consequence of years of immunosuppression. Risk factors for adverse outcomes after retransplantation are early retransplantation after primary transplantation (<6 months), retransplantation for acute rejection, and early allograft failure [12-14]. When selection criteria for retransplantation excluded these indications, 1-4 year survival is comparable to primary transplantation [12,13].

**Advances in donor allocation and selection**

Recipient criteria for heart transplantation include severe symptoms despite maximal medical management, the absence of reversible or surgically amenable heart disease, and where estimated 1-year survival is less than 50% [15]. An estimate of reversible or surgically amenable heart disease, and where symptoms despite maximal medical management, the absence criteria for retransplantation excluded these indications, 1-4 year rejection, and early allograft failure [12-14]. When selection criteria for retransplantation excluded these indications, 1-4 year survival is comparable to primary transplantation [12,13].

Recipient criteria for heart transplantation include severe symptoms despite maximal medical management, the absence of reversible or surgically amenable heart disease, and where estimated 1-year survival is less than 50% [15]. An estimate of functional capacity can be quantified by measurement of peak O₂ consumption (VO₂ max). Currently, VO₂ max remains the single best cardiopulmonary evaluation to predict mortality in heart failure. Patients with low VO₂ max (<12 ml/min/kg) have high mortality even if treated with beta blockers. International Society of Heart and Lung (ISHLT) guidelines suggest that transplantation should be considered for these patients. Heart failure prognosis scores to estimate survival, such as the Heart Failure Severity Score are useful. This calculates a survival probability on the basis of the presence of ischemic cardiomyopathy, resting heart rate, left ventricular ejection fraction, mean blood pressure, interventricular conduction delay, VO₂ max and serum sodium concentration [16].

The eligibility for transplantation is considered with regard to risk factors, notably pulmonary hypertension. Right heart catheterization should be performed in all potential candidates for heart transplantation to quantify pulmonary vascular resistance [16]. Right heart failure is a substantial cause of mortality as right ventricular failure is likely when post implant pulmonary artery pressures exceed 50 mmHg. Patients with chronic heart failure may develop pulmonary hypertension due to elevated left ventricular end diastolic pressure with elevated left atrial and pulmonary venous pressures. This is a reactive form of pulmonary hypertension and may fall when the cardiac output is increased with inotropes or unloaded with nitrate infusions [16]. The transpulmonary gradient is calculated by subtracting the left atrial filling pressure from the mean pulmonary artery pressure. A fixed transpulmonary gradient in excess of 14 mmHg is associated with greatly elevated risk, and thus this cut off is used in the UK [17].

**Preoperative preparation**

Donor-recipient matching takes place on the basis of urgency, blood group and size (80% or greater of recipient body weight). Organs are generally not used when the recipient has preexisting antibodies to the donor’s HLA antigens. Desensitization is possible in selected cases and will be discussed later in this article. The donor heart is assessed by measurement of filling pressures and cardiac output with a Swan Ganz catheter inserted by the organ retrieval team or by direct pressure measurements. Trans-esophageal echocardiography is sometimes used to support the retrieval assessment process. Conditions precluding use of a donor heart are summarized in Table 1. If the donor heart

| **Table 1: Exclusion criteria for donor hearts.** |
|-----------------|------------------|
| **1** | HIV positivity* |
| **2** | Significant ventricular arrhythmias |
| **3** | Echocardiographic abnormalities |
| **4** | Significant global hypokinesia |
| **5** | Significant valvular abnormality |
| **6** | Significant coronary artery disease |
| **7** | Any acute malignancy with the exclusion of primary brain cancer (unless craniotomy or ventricular shunt has been performed) |
| **8** | Inadequately treated systemic infection |
| **9** | Hepatitis B surface antigen positivity, unless recipient is positive |
| **10** | Significant left ventricular hypertrophy |
| **11** | Cardiac contusion |
| **12** | Death from carbon monoxide poisoning with carboxy hemoglobin level 20% |
| **13** | Intravenous drug abuse |

*USA, some cardiac and kidney transplant programs match HIV +ve donors to HIV +ve recipients |
is deemed to be satisfactory, the patient is prepared for surgery. Immunosuppression is given preoperatively, azathioprine and cyclosporine orally 24 h preoperatively as well as anesthetic premedication.

The United Network for Organ Sharing regulates donor heart allocation in the USA. It has a priority system based on the severity of cardiac illness, transportation distance, length of time on the waiting list, and ABO blood group compatibility [18]. There is a physiological limit of approximately 4 to 5 h of ischemia time for the retrieved heart. This prevents national sharing of donor hearts in the US, or matching donor hearts according to human leukocyte antigen (HLA) compatibility [19]. The allocation process was changed in 1999 to account for medical urgency and to reduce waiting times for blood type O recipients [18]. The number of waiting recipients is increasing and sadly the number of donors is falling. This has resulted in a trend to transplant urgent status recipients and to a relaxation of donor acceptance criteria. Post-transplant survival has remained constant despite these changes, due to advances in treatment [19]. The first step of donor heart acceptance is to rule out any contraindication to heart donation such as significant heart dysfunction, CHD, transmissible diseases, or malignancies (except primary tumors of the central nervous system with low metastatic potential) (Table 1).

The second step is to match a specific donor to a suitable transplant candidate. Matching is based on ABO blood group compatibility and body size. Although adult donor hearts must be ABO compatible with the recipient, this concept has been recently challenged in infants (age <12months) by the successful performance of ABO incompatible heart transplants [20]. Matching donor and recipient for size is especially important in pulmonary hypertension. In general, a height and weight difference of up to 20 percent is tolerated. In potential recipients with significant pulmonary hypertension, donor size equal or higher than the recipient is usually recommended. In pediatric patients the use of oversized donor hearts has been advocated by many centres with successful outcomes and this mitigates against the low numbers of suitably sized donors [11].

There are donor characteristics which are associated with adverse outcomes. The use of older donor hearts (>40 year old) is associated with higher peri operative mortality and a higher incidence of later cardiac allograft vasculopathy [5]. Donor left ventricular hypertrophy (left ventricular wall thickness greater than 14 mm) is associated with decreased long-term survival [21]. Gender mismatch with a female donor heart transplanted into a male is associated with worse 5 and 10 year survival [5]. Donor heart allocation from hepatic C positive patients is associated with higher peri operative mortality and a higher adverse outcomes. The use of older donor hearts (>40 year old) is associated with better post-transplant outcomes [5].

Advances in immunology

As understanding of the pathways involved in immune activation has evolved, there have been many breakthroughs in transplantation medicine, including the development of novel immunosuppressive agents. Signal 1 is provided when antigen-presenting cells and antigens activate the T cell receptor. Signal 2 (co stimulation) occurs when CD80 (B7-1) and CD86 (B7-2) on the antigen-presenting cells engage CD28. Both signals activate important signal transduction pathways (calcineurin, RAS-mitogen-activated protein kinase (MAP-K) pathway, and the nuclear factor-kappa B (NF-kB) pathway). These pathways lead to expression of many molecules, including interleukin (IL)-2 and IL-15. Interleukin-2 and other cytokines then activate the “target of rapamycin” pathway to provide the trigger for cell proliferation (signal3). AP-1 “activating protein 1; CDK” cyclins-dependent protein kinase; IKK “serine-threonine protein kinase; JAK3 “janus kinase 3; MHC “ myosin heavy chain; mRNA “messenger ribonucleic acid; mTOR” mammalian target of rapamycin; NFAT “ nuclear factor of activated T cells; PKC “protein kinase C; S1P-1 “sphingosine-1-phosphate; TCR” T cell receptor with permission, from Halloran. The alloimmune response starts with the activation of antigen-presenting cells of donor and host origin. Once activated, antigen presenting cells engage alloantigen-reactive naive T cells and central memory T cells [25-28]. Naive T cells and memory T cells re circulate in the secondary lymphoid organs or undergo clonal expansion and differentiate into effector cells when activated. Direct antigen presentation to alloreactive cells by graft endothelium may also occur [27,29]. T cell activation requires the stimulation of 3signal pathways (Figure 1) [27]. The first signal originates from the interaction between the major histocompatibility complex/peptide complex and the T cell receptor/CD3 complex. Antigen-presenting cells provide co-stimulation when the CD80 and CD86 (B7) interact with the CD28 on T cells. The second signal (co stimulation) occurs by the interaction of CD80 and CD86 with CD152 (CTLA-4) as well as the interaction of CD40 and CD154. These signals lead to the activation of the calcium-calmodulin pathway, mitogen-activated protein kinase pathway, and the nuclear factor-kappa B pathway [27,30]. This leads to the expression of interleukin-2 as well as molecules such as CD154 and CD25. The third signal of the alloimmune response occurs when interleukin-2 and other cytokines activate the target of rapamycin pathway that leads to cell proliferation and differentiation. B cells are also activated when antigens interact with B cell receptors in secondary lymphoid organs and in the transplanted organ. Complement and inflammatory mediators contribute to the alloimmune response [27].

Rejection takes place by cellular and antibody-mediated processes [31-33]. In cellular rejection (CMR), effector T cells mediate an inflammatory response leading to infiltration of the myocardium by activated macrophages, effector T cells, and plasma cells. The characteristic lesion of CMR consists of mononuclear cells invading the myocardium. CMR is classified
into 3 grades depending on the extent of cellular infiltration and myocyte damage. In the internationally accepted grading system for cellular rejection, ISHLT grade 2R or higher is considered clinically significant cellular rejection [34,35]. Antibody-mediated rejection (AMR) occurs when alloantibody against donor antigens targets capillary endothelium [31-33]. AMR is usually associated with hemodynamic compromise at presentation and a greater risk of allograft vasculopathy and mortality [32,33]. AMR is usually diagnosed histologically by demonstration of capillary injury with endothelial cell swelling and intravascular macrophage accumulation. Positive immuno fluorescence for CD68, C4d and C3d complement fragments may be associated with clinical allograft dysfunction [35,36].

**Advances in immunosuppression**

The success of heart transplantation was closely related to the discovery of effective immunosuppressive regimens. In the early 1980s, the introduction of cyclosporine was followed by a significant improvement in survival of heart transplant recipients. Immunosuppression prevents or treats rejection and minimizes the risk of infection or malignancy. Immunosuppression may block lymphocyte activation or response pathways, or by depleting lymphocytes, or diverting lymphocytic traffic [26,37]. Induction therapy is a period of intense immunosuppression in the initial days after transplantation. This provides intensive immunosuppression when the alloimmune response is also most intense. It may also be used to permit delayed initiation of calcineurin inhibitors (CNIs) in patients with significant renal failure. Induction immunosuppression may use depleting antibodies (e.g., polyclonal antibodies (horse or rabbit anti thymocyte globulin), anti-CD3 antibodies (OKT3), human monoclonal anti-CD52 (alemtuzumab)), or nondepleting antibodies (e.g., anti-CD25 antibodies (daclizumab, basiliximab) or fusion proteins (e.g., CTLA4-Ig (LEA29Y)) [38-40].

A survival benefit of induction therapy not been clearly established, however [38-40]. OKT3 use may be associated with a greater risk of lymphoproliferative disorders [38,41]. Induction agents are probably most useful in highly sensitized patients or patients with severe RF at the time of transplantation. Maintenance immunosuppression is usually triple therapy, comprising corticosteroids (usually prednisolone), a CNI (cyclosporine or tacrolimus), and an anti proliferative agent (usually mycophenolate mofetil). Prednisolone is used early after heart transplantation and tapered to low doses or withdrawn during the first year. Withdrawal of steroids may take place early within the first month after or later between 6 to 12 months post-transplant. Late steroid withdrawal may have the advantage of maintaining more intensive therapy in the first 6 months when the risk of rejection is still high [41-43]. There is a strong interest in minimising steroid use in children, as it impairs growth [9]. Tacrolimus is the most commonly used CNI [5,44]. It is associated with a decreased incidence of rejection episodes and is used instead of cyclosporine where rejection is more likely [45]. Tacrolimus may be used as monotherapy in heart transplantation and has shown to be safe [44]. Mycophenolate mofetil has replaced the use of azathioprine. Molecular target of rapamycin inhibitors or proliferation signal inhibitors (sirolimus and everolimus) may decrease the progression of
allograft vasculopathy and cancer as well as provide resistance to rejection [46-48]. Poor wound healing is a serious side effect associated with sirolimus and everolimus and limits its use early post-transplant [48].

In patients with allograft vasculopathy, sirolimus may limit progression and lead to reversal of the process [47-50]. In patients with severe renal failure (RF), calcineurin-free regimens (combining sirolimus and mycophenolate mofetil) late after transplantation can improve renal function without increasing the risk of rejection [51,52]. Belatacept, a co stimulatory signal inhibitor could represent an alternative to CNIs [53]. In de-novo renal transplant recipients, there was no significant difference in acute rejection rates between belatacept and cyclosporine [53]. Belatacept resulted in significantly lower rates of tubular atrophy and interstitial fibrosis. If proven efficacious and safe in renal transplantation, Belatacept will undergo investigation in heart transplantation. Individualization of immunosuppression with better immune monitoring and pharmacogenomics will eventually play a greater role in optimization of therapy [54].

The Methods for managing acute rejection are evolving. The management of acute rejection depends on the histological type of rejection (cellular vs. AMR) as well as its severity (hemodynamic compromise and/or high histological grade) and history of prior immunosuppression and rejection episodes. A high-dose corticosteroid (3-day course of methylprednisolone 1 g daily) is used for significant cellular rejection (>2 R ISHLT classification) or any rejection-associated hemodynamic compromise. Lymphocyte-depleting agents such as antithymocyte globulin are also considered in patients with hemodynamically compromising or high-grade (3R) cellular rejection [55]. Studies assessing the best treatment strategy for AMR are currently in progress [33]. Severe AMR with hemodynamic compromise is usually treated with high-dose corticosteroids and Plasmapheresis followed by intravenous immunoglobulin or rituximab (B-cell depleting monoclonal anti-CD20 antibody). T cell depleting antibodies such as antithymocyte globulin are also considered in patients with hemodynamically compromising or low-grade (3R) cellular rejection [55]. Studies assessing the best treatment strategy for AMR are currently in progress [33].

Transplantation across blood groups

Transplantation of hearts from ABO-incompatible donors is contraindicated because of the risk of hyper acute rejection mediated by preformed antibodies in the recipient to blood-group antigens of the donor. This contraindication may not apply to newborn infants, who do not yet produce antibodies to T-cell–independent antigens, including the major blood-group antigens. In particular, stimulation by T-cell–independent polysaccharide antigens, such as the capsular components of bacteria (e.g., pneumococci), does not elicit a serum antibody response early in life [59]. Similarly, the production of antibodies to the carbohydrate blood-group antigens begins at the age of six to eight months, in infants of susceptible genotypes, as a cross-reactive immune response after the colonization of the gut with polysaccharide-bearing Escherichia coli [59].

When ABO incompatible transplantation is performed, serum is hemagglutinin titers are measured before and after the transplant. Plasmapheresis, immunoabsorption or administration of soluble carbohydrate antigen is used, as well as plasma exchange during cardiopulmonary bypass as the transplant operation is taking place. Standard immunosuppressive therapy is used and rejection is monitored by endomyocardial biopsy. There is usually no damage to the graft, despite the eventual development of antibodies to antigens of the donor's blood group in some infants. The absence of antibody production or its delay beyond the time expected because of early immunosuppression, may be evidence of partial B-cell tolerance induced by exposure to donor antigens during the maturation of the immune system [59,60]. It is also thought that accommodation occurs. This term originally describes endothelial cell resistance to antibody-mediated rejection after ABO-incompatible kidney or experimental xenograft transplant [33]. The use of ABO-incompatible donors has resulted in the mortality rate among infants on the waiting list declining from 58 percent to 7 percent.

Donor specific alloreactivity

Hyper acute and delayed antibody-mediated rejection has devastating effects and may result in graft loss. It is mandatory to avoid situations where antibody-mediated rejection may occur. Recipients are screened for antibodies that react with lymphocytes from a panel representative of the major HLA allootypes (PRAs). High PRA levels indicate sensitization to various alloantigens and the risk of donor specific alloreactivity. These patients require donor-specific T-cell cross-matches before transplantation to exclude the presence of lymphocytotoxic IgG antibodies against donor class I HLA's, which can cause early graft failure resulting from complement-mediated humoral rejection [61,62]. A positive donor-specific T-cell cross-match is a contraindication to transplantation. Sensitized candidates have longer waiting times and higher mortality rates while waiting [61,62]. The presence of preformed anti-HLA antibodies predicts an increased number of cellular rejection episodes, earlier coronary allograft vasculopathy (CAV) onset, and decreased long-term graft survival [61]. These complications are related to the presence of preformed antibodies against allogeneic HLA class II molecules. There may be an underlying state of CD4 T-cell allo-sensitisation to class II antigens in sensitized candidates [63-65].

The proportion of highly sensitized patients on cardiac transplant waiting lists has increased as a result of widespread use of left ventricular assist devices (LVADs) [66] and more patients undergoing retransplantation [67]. Whereas alloreactivity in retransplant candidates, blood product recipients, and multiparous women is a result of repeated B- and T-cell exposure to alloantigen, the high frequency of alloreactivity in LVAD recipients seems to result additionally from polyclonal B-cell activation [68,69]. LVAD recipients are usually treated with induction immunosuppression.
Interventions in sensitized recipients usually result in Ig depletion and B-cell suppression. Pooled human intravenous Ig is effective in reducing allo-sensitization [70,71]. This may be due to the presence, in intravenous Ig, of anti-idiotypic antibodies [72,73], antibodies against membrane-associated immunologic molecules such as CD4 or CD5 [74,75], or soluble forms of HLA molecules [76,77]. Serum reactivity to HLA class I molecules in LVAD recipients may be reduced with intravenous Ig or plasmapheresis [78-82]. Alternative modalities for alloreactive antibody reduction include immunoadsorption, rituximab and cyclophosphamide [83,84]. Intravenous pulse cyclophosphamide therapy, together with pre-transplantation intravenous Ig as part of a CyA/steroid-based regimen in sensitized cardiac allograft recipients, is extremely effective and safe for decreasing recipient serum and cellular alloreactivity, shortening transplant waiting time, and reducing allograft rejection.

Post-transplant monitoring

Immune monitoring of cardiac transplants currently relies on endomyocardial biopsy, drug level monitoring, and echocardiography. Many patients still present with rejection, infection, or drug toxicity despite having the desired level of immunosuppression. Endomyocardial biopsy is the gold standard for the diagnosis of rejection and has been so for many years. It is limited by significant sampling error and inter-observer variability. There is also variability in frequency and duration of surveillance endomyocardial biopsy, with most centres now limit routine endomyocardial biopsies to <5 years [85]. Cellular rejection may result in abnormal diastolic parameters of allograft function [86,87]. A 10% change in maximal systolic or diastolic tissue Doppler velocity of the posterior wall of the left ventricle is a sensitive and specific marker of cellular rejection (grade>2 in the previous classification). Elevation in BNP is associated with cellular rejection [88]. Therapeutic monitoring of drug is very useful in the post-transplant surveillance period with CNIs monitored closely at C0 and now at C2 intervals [89-91].

Gene expression profiling (GEP) is useful in identifying rejection [92-94]. Genes activated during acute cellular rejection include those involved in the pathways of T cell activation, natural killer-cell activation, stem cell mobilization, hematopoiesis, alloimmune recognition, and steroid responsiveness. In the Cardiac Allograft Rejection Gene Expression Observation study, an algorithm was developed and validated based on the expression of 20 genes [92,94]. The algorithm weighs the contribution of each gene and generates a score from 0 to 40. Scores below threshold indicate a very low likelihood of moderate-to-severe acute cellular rejection on endomyocardial biopsy (ISHLT grade>3A/2R). Further information is needed to assess the safety of routine GEP instead of biopsies before GEP is widely adopted clinically [94]. There are direct immune assays that monitor antibody production and T cell function to assist in the recognition of rejection [6,94-97].

Anti-HLA donor-specific antibodies are associated with an increased incidence of early and severe allograft rejection and with the late development of cardiac allograft vasculopathy and decreased survival [6,98,99]. The importance of non-HLA antibodies is also being increasingly recognized [6]. Comprehensive monitoring will rely, in future, on a combination of biopsy with histopathology, graft functional monitoring with imaging modalities and B-type natriuretic peptide (BNP), drug level monitoring, GEP, monitoring of donor-specific antibodies, and direct immune function assays.

Long term complications of heart transplantation

Transplant vasculopathy and malignancy are the 2 most important causes of death after 1 year [5]. Significant allograft vasculopathy is found in approximately 30% to 50% of patients at 5 years [5,7]. It is characterized by diffuse intimal hyperplasia affecting the epicardial vessels and the microcirculation in a longitudinal and concentric fashion and plaque rupture is rare [7,100-102]. Non-immune risk factors for allograft vasculopathy include hyperlipidemia, hypertension, diabetes mellitus, homocysteinemia, older donor age, and donor brain stem death [5,103,104]. Immune risk factors are HLA donor/recipient mismatches (especially HLA DR Mismatches), recurrent cellular rejection, AMR and cytomegalovirus [32,87,103-105].

Intravascular ultrasound is very useful in the diagnosis and follow-up of allograft vasculopathy [104,106]. Intimal thickness progression of more than 0.5 mm during the first year is a powerful predictor of mortality, myocardial infarction, and later coronary artery disease [106]. Management focuses on the aggressive management of risk factors, particularly hyperlipidemia and the use of proliferation signal inhibitors such as sirolimus [48,107]. Statin therapy has also been recently shown to have sustained survival benefits with a decrease in allograft vasculopathy [108,109]. Percutaneous revascularization of allograft vasculopathy may be done for focal lesions, but the benefits of the procedure are limited by the diffuse nature of the disease [110]. Re-transplantation is also considered in selected patients with severe allograft vasculopathy. Post transplant lymphoproliferative disorder (PTLD) and skin cancers are the common malignancies seen after transplantation. Risks for PTLD include aggressive immunosuppression, OKT3 use young age and Epstein-Barr virus seronegative recipients, especially with a seropositive donor [111,112]. Proliferation signal inhibitors have anti tumour properties and may even lead to the regression of some malignancies, and rituximab an effective treatment for PTLD [111,112].

Tolerance induction

The induction of specific tolerance to donor antigens remains the ultimate goal in transplantation medicine. Specific tolerance would also retain the remaining immune repertoire to deal with infection and malignancy. Effective donor tolerance may be produced experimentally by bone marrow transplantation into recipients conditioned with co stimulatory blockade (anti CTLA4-1g), resulting in chimerism. A clinical trial is underway to investigate this possible treatment (Bone Marrow Transplant to Induce Tolerance in Heart Transplant Recipients). Heart transplantation usually involves no HLA matching, so such induction of chimerism would require potentablation of the
recipient bone marrow, significant radiation exposure, and ongoing immunosuppression [113,114].

Conclusion

Heart transplantation is evolving and now has excellent long term outcomes. It is the ideal solution for intractable end stage heart failure in eligible patients. Improvements in our understanding of the alloimmune activation response and its pathways have led to the development of new immunosuppressive agents and better regimens. In the future, advances in immunosuppression and the use of more specific monitoring tools are likely to lead to significant improvements in outcomes. With ongoing research in the scientific and clinical communities, it is hoped that transplant physicians would have the tools to induce immune tolerance, greatly improving outcomes further.

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