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Immunosuppression after Cardiac Transplantation: What is the Best Approach?

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Abstract

Cardiac transplantation is a life-saving procedure for patients in end-stage heart failure. Since the first heart transplant in 1967, survival rates have steadily increased. This is largely on account of advancing immunosuppressive therapies, although immunosuppression protocol still varies greatly among transplant centers, with no ideal regimen to follow. A fine balance lies between under-immunosuppression leading to rejection, and over-immunosuppression causing complications, toxicity, and adverse effects. Some successful therapies include steroids, lymphocyte proliferation inhibitors, and calcineurin inhibitors. Much of the available evidence as to which regimens have been successful is from retrospective analyses, indicating the need for more studies to be conducted to determine the best practices and to improve mortality after cardiac transplant. This review is a critical analysis comparing different current immunosuppressive therapies and rejection treatments following heart transplantation.

Immunosuppression in Cardiac Transplantation

The immune system is the human body's highly efficient method of rejecting and eliminating foreign bodies, using its variety of specialized cells. Every individual expresses a unique self-antigen on their body cells, called human leukocyte antigen (HLA), which is coded by major-histocompatibility complex (MHC). Non-reactivity of the cells of the immune system to these autoantigens, and conversely, reaction to any non-self antigen, contributes to a functioning immune system. In the case of cardiac transplantation, the donor HLA itself can act as a non-self antigen initiating immune response and, consequently, rejection (Anbalakan et al., 2020).

Since the first heart transplant in 1967, survival rates have steadily increased (Stehlik, et al., 2012). The median survival for adult heart transplant recipients has risen from under 2 years to 11 years between 1982 and 2016 (Khush et al., 2018). Cardiac allograft rejection, inflammation in response to recognition of non-self antigen with pathologic changes in the allograft, is the leading cause of death in heart transplant recipients within the first year of transplantation (Naik & Shawar, 2023). Transplant success is largely due to the development of effective immunosuppression strategies to reduce this inflammation (Kobashigawa & Patel, 2006).

While mortality following heart transplantation has improved worldwide since 1982, this is largely due to increased survival within the first year of transplant, a result of advancements in pre-transplant factors, such as donor-recipient matching, and preliminary anti-rejection measures. Mortality beyond the first year has remained generally constant, indicating a need for better long-term treatment for cardiac transplant recipients. Finding the balance between under- and over-immunosuppression, preventing rejection while avoiding the medical complications that immunosuppression can induce, is a key factor in long-term survival for these patients (Soderlund & Radegran, 2015).

Protocol for immunosuppressive regimens varies highly between transplant centers (Anbalakan et al., 2020). Some current immunosuppression strategies for cardiac transplant recipients include calcineurin inhibitors, which reduce the frequency of acute allograft rejection. Proliferation-signal inhibitors have a similar effect, in addition to reducing the frequency of cardiac allograft vasculopathy (CAV), which limits lasting graft survival. The use of statins, with their immunomodulating effects, is another immunosuppression strategy (Kobashigawa & Patel, 2006). Induction therapy using cytolytic agents and interleukin-2-receptor antagonists is a more recent strategy upon which studies have remained inconclusive as to its benefits (Amin et al., 2019).

Methods

Research for this review was conducted using databases available through Touro College and University System, such as Science Direct, EBSCO, and ProQuest. Keywords used to collect data included "heart transplant immunosuppression," "induction therapy in heart transplantation," and "quality of life after cardiac transplant."

Immunological Mechanisms Leading to Graft Rejection

Acute allograft rejection is initiated by the recognition of donor antigen by the recipient's antigen presenting cells (APCs). This process is known as indirect allorecognition and is carried out by the innate immune system. The antigen is then coupled with human leukocyte antigens (HLA), activating B lymphocytes and cytotoxic T-cells to attack the cells on which it is expressed (Anbalakan et al., 2020).

Simultaneously, recipient T-cells can recognize donor APCs in a process known as direct allorecognition that is carried out by the adaptive immune system. The TCR-CD3 complex on the recipient's T-cells recognizes alloantigens being carried by recipient APCs, activating the T-cell through costimulatory signals. This activates calcineurin, which enters the nucleus of the T-cell and binds to a variety of cytokine promoters, including interleukin-2, which stimulate clonal expansion of T helper cells and the expansion of other cells of the immune system (Lindenfeld et al., 2004).

Rejection Risk Factors

Transplant recipients at higher risk of acute cardiac allograft rejection include: young patients, Black people, those with increased mismatching of HLA between donor and recipient, those noncompliant with immunosuppression therapy, and female donors and/or recipients. Females have a higher rejection risk due to pre-existing anti-HLA antibodies to protect a fetus in the case of pregnancy (Anbalakan et al., 2020).

Types of Rejection

Under-immunosuppression following heart transplant can result in graft rejection. Transplant rejection can be categorized as hyperacute, acute, or chronic.

Hyperacute Rejection

Hyperacute rejection is the immediate rejection of a donor heart due to preexisting anti-graft antibodies in the recipient. If the recipient was somehow exposed to donor HLA during their lifetime, then they have preformed antibodies against it, otherwise known as sensitization. This plays a major role in hyperacute rejection.

Thoroughly analyzing donor-recipient compatibility before transplant is vital in predicting the risk of rejection. The International Society for Heart and Lung Transplant (ISHLT) recommends conducting a screening panel for reactive antibodies in heart transplant candidates. Reaction of greater than 10% is indicative of risk of rejection. In most patients, a complement-dependent cytotoxicity (CDC) crossmatch is also performed, using sample donor lymphocytes mixed with recipient serum in the presence of complement. If this crossmatch detects preformed cytotoxic antibodies, then there is contraindication for transplant (Anbalakan et al., 2020).

Acute Rejection

Acute rejection generally occurs within a few months of transplantation and is generally diagnosed through endomyocardial biopsy. Between 2004 and 2010, 19% of all cardiac transplant recipients reported to ISHLT stated at least 1 episode of acute rejection requiring treatment. Acute rejection can be categorized into acute cellular rejection (ACR) and antibody mediated rejection (AMR) (Soderlund & Radegran, 2015).

In ACR, recipient T-cells attack the myocardium of the donor heart (Soderlund & Radegran, 2015). This can occur through the direct pathway, in which donor APCs travel from the graft to the lymph node, or through the indirect pathway, in which recipient APCs process and present donor HLA to naïve T-cells. Once activated, T-cells produce cytokines such as IL-2, resulting in T-cell proliferation and consequently graft cytolysis.

In AMR, recipient antibodies attack the vasculature of the donor heart (Soderlund & Radegran, 2015). These can be newly developed antibodies or preexisting ones, which bind to HLA receptors on the endothelial lining of the donor heart vessels, activating the complement cascade and thereby damaging the vessels.

A 2009 U.S. study showed that up to 24% of heart transplant rejection cases between 1985-2004 involved both ACR and AMR occurring simultaneously. (Kfoury et al., 2009)

Chronic Rejection

Chronic rejection is known as cardiac allograft vasculopathy (CAV), and generally occurs several years after transplantation (Soderlund & Radegran, 2015). CAV is the pathologic immune-mediated remodeling of vasculature in a transplanted heart which causes graft loss by impairing perfusion. It is an inflammatory fibroproliferative disease that can lead to epicardial and coronary artery narrowing. CAV is a major late complication and remains the leading long-term cause of death in cardiac transplant patients (Asleh et al., 2018; Pober et al., 2021).

Approximately 30% of heart transplant recipients develop CAV within 5 years of transplantation, and almost 50% develop it within 10 years. However, incidence of CAV is changing with new diagnostic techniques and therapies to detect and prevent early CAV and its progression before it becomes fatal. This trend is supported by recent ISHLT registry data showing improved survival in CAV patients (Khush et al., 2019).

Rejection Prevention

Immunosuppressive treatments after heart transplant can be categorized into induction therapies and maintenance therapies. Induction therapies are temporary post-operative treatments, while maintenance therapies are long-term (Soderlund & Radegran, 2015).

Induction Therapies

The risk of rejection is highest in the period immediately post-transplant. Ischemic injury, which occurs before blood flow is restored to the new heart, activates the innate immune system, which in turn activates the adaptive immune system, causing the body to progressively attack the donor heart tissue. Induction therapies suppress the immune system to prevent such reactions, making it possible to delay initiation of other potentially nephrotoxic immunosuppressives. (Anbalakan et al., 2020)

The use of induction therapy is inconsistent between transplant centers, and its effect on long-term outcomes

is not well established. A study of 24,700 heart transplant recipients between 2005 and 2017, 50% of which received induction therapy at the time of transplantation, showed no significant difference in 1 year survival between the two groups (Cooper et al., 2020).

Induction immunosuppressive strategies used after cardiac transplant include anti-thymocyte globulins, interleukin-2 receptor antagonists, and Alemtuzumab, all of which are generally coupled with methylprednisolone.

Interleukin-2 (IL-2) receptor antagonists are monoclonal antibodies which bind to IL-2 receptors—also called CD25 antigen—on T lymphocytes, preventing their activation and proliferation. The most commonly used IL-2 receptor antagonist is Basiliximab. 20 milligrams are given in the operating room before blood flow is restored to the heart, and an additional 20 milligrams are given on the fourth day post-operation.

Poly anti-thymocyte antibodies are obtained by immunizing either a rabbit or horse with human thymocytes and harvesting the anti-thymocyte immunoglobulin G that it produces. These antibodies deplete the number of available T-cells through activation of the complement system. The use of polyclonal antibodies presents a disadvantage to monoclonal antibodies, like Basiliximab, in their unpredictability. Additionally, their administration is relatively difficult, requiring several pre-medications. Some risks of anti-thymocyte antibodies include serum sickness and cytopenia. White blood cells and platelets must be closely monitored following their administration.

Alemtuzumab is a newer immunosuppressive agent, obtained from humanized rat monoclonal antibodies which target CD52 antigen, which is present on both T and B lymphocytes. Administration involves a single 30 milligram dose given during surgery. The use of Alemtuzumab prolongs immunosuppression with lower doses of maintenance agents. (Anbalakan et al., 2020) A 2018 U.S. study observed no difference in hematological or infectious complications with the use of Alemtuzumab compared with other standard induction therapy protocols (Gale et al., 2019).

In a retrospective cohort analysis comparing rabbit-anti-thymocyte globulin (r-ATG) versus IL-2 receptor antagonist in post-heart transplant patients from 2006-2015 who received the same maintenance immunosuppressives, neither therapy showed survival benefit over no induction therapy. In fact, there was higher mortality in the group that received r-ATG. The ambiguity regarding the advantages and effects of induction therapies illustrates the need for more studies to be conducted on this topic (Amin et al., 2019).

Maintenance Therapies

Maintenance therapies are chronic immunosuppressive therapies that reduce the risk of rejection throughout a recipient's life. The multi-drug approach—while avoiding overlapping functions and toxicities—as well as avoiding over-immunosuppression are two central principles regarding maintenance therapy. Some common maintenance strategies are calcineurin inhibitors or proliferation signal inhibitors, along with cell cycle inhibitors and steroids (Anbalakan et al., 2020)

Corticosteroids

Steroids are immunosuppressive and non-specific anti-inflammatory effectors that alter gene expression for immune and inflammatory response in the body. They have multiple mechanisms that affect both the innate and adaptive immune systems (Radegran & Soderlund, 2015). Steroids affect the functions of leukocytes through altering the expression of several vital leukocyte genes. They also affect endothelial cells by decreasing their chemoattractant factors, inhibiting neutrophil adhesion and macrophage differentiation.

Corticosteroids, or glucocorticoids, were one of the first, albeit still used immunosuppression strategies in induction, maintenance, and rejection treatments. Steroid therapy is a standard operative and post-operative treatment, starting with high doses followed by gradual weaning. Corticosteroids are the first treatment for moderate rejection not affecting blood flow, to which up to 85% of such cases respond (Lindenfeld et al., 2004).

Some adverse effects associated with long-term steroid therapy include hypertension, cataracts, and ulcers. Associated cosmetic effects include acne, weight gain, and easy bruising. Associated metabolic effects include hyperlipidemia, diabetes mellitus, and growth retardation (Lindenfeld et al., 2004). Because of their complications with long term use, steroid therapy is generally stopped within the first year of transplantation (Miller et al., 1992).

Cyclosporin

Cyclosporin (CSA) is a fundamental therapy of cardiac allograft maintenance. This lipid-soluble compound blocks calcium-activated calcineurin, a protein phosphatase responsible for the transcription of multiple cytokines (Rusnak & Mertz, 2000; Lindenfeld et al., 2004) CSA binds to cyclophilin, a protein involved in key biochemical processes, forming a complex which binds to calcineurin, causing inhibition of cytokine transcription and thereby IL-2 mediated T-cell activation and proliferation. (Harikishore & Yoon, 2015).

CSA is used in anti-rejection regimens in cardiac, hepatic,

and renal transplant recipients. The introduction of CSA to immunosuppressive therapies in 1982 caused a 30% rise in 3-year survival rate in cardiac transplantation (Hosenpud et al., 1995).

Adverse effects of CSA include nephrotoxicity with arteriolar sclerosis and tubule-interstitial fibrosis, as well as hypertension, hyperlipidemia, and diabetes mellitus. Neurological side effects include tremors, seizures, and visual disturbance. Hypertrichosis is an observed side effect in over 50% of patients using CSA (Lindenfeld et al., 2004).

Tacrolimus

Tacrolimus (TAC) is an antibiotic derived from the fungus Streptomyces tsukubaensis, which inhibits calcineurin in a similar manner to CSA. TAC is used in place of CSA in many maintenance regimens, conversion from CSA to TAC can be used to treat recurrent rejection. TAC has now largely replaced CSA (Radegran & Soderlund, 2015; Lindenfeld et al., 2004).

A randomized trial of 85 patients in the United States found no difference in the 1-year survival or cases of significant rejection in cardiac transplantation when treated with TAC versus CSA, although hyperlipidemia and hypertension were more common in the CSA patients (Taylor et al., 1999).

Side effects of TAC are similar to those of CSA, but a comparison of the two shows a decrease in hypertension and hyperlipidemia and an increase in hyperglycemia and neurotoxicity. In contrast to CSA, alopecia may be a side effect of TAC (Lindenfeld et al., 2004).

Azathioprine

Azathioprine (AZA) is a prodrug, meaning it is biologically inactive until it is metabolized within the human body. Through its specific metabolic pathway, AZA is eventually converted to a purine analog, an antimetabolite which mimics physiological compounds found in DNA. It is thereby incorporated into newly synthesized DNA (Davies et al., 2006). From there, it inhibits the proliferation of both T and B lymphocytes (Lindenfeld et al., 2004). AZA is generally used in maintenance immunosuppression along with steroid therapy and a calcineurin inhibitor. Before it was used in combination with cyclosporin, it was widely used with prednisone alone, with a 5-year survival rate of under 40% (Lu et al., 1993). Triple therapy is now more commonly used, with favorable outcomes, including a decrease in renal failure and infections.

A major side effect of AZA is myelosuppression, leading to leukopenia, anemia, and thrombocytopenia. These generally resolve within 2 weeks of dose reduction. Some rare side effects of AZA include pancreatitis, hepatitis, and hepatic veno-occlusive disease (Lindenfeld et al., 2004).

Mycophenolate Mofetil

Like AZA, mycophenolate mofetil (MMF) is an antimetabolite. It inhibits lymphocyte proliferation, and is used in rejection prevention in kidney, liver, and heart transplant recipients. Proliferating lymphocytes depend on guanine nucleotide synthesis, a process in which inosine monophosphate dehydrogenase is a key enzyme. MMF functions as a selective inhibitor of this enzyme, thus inhibiting lymphocyte proliferation without inhibiting the growth of other cell lines, rendering it less myelosuppressive than AZA (Lindenfeld et al., 2004).

A trial comparing MMF versus AZA confirmed improved survival late after transplant in patients treated with MMF. In this trial, either MMF or AZA was given in combination with cyclosporin and steroids to treat patients who had survived initial cardiac transplant hospitalization. The MMF patients displayed decreased mortality after 1 year, with 6.2% in MMF patients and 11.4% in AZA patients. Additionally, the 3 year survival rate for MMF patients was 91% versus 86% for the AZA patients (Kobashigawa et al., 1998).

A drawback of MMF in comparison with AZA is its price. Its side effects include nausea, diarrhea, and vomiting, which have been found to resolve with a decrease in dose (Lindenfeld et al., 2004).

Target of Rapamycin Inhibitors

Sirolimus (SRL), also called Rapamycin, and its derivative Everolimus (EVR), are proliferation signal inhibitors (Anbalakan et al., 2020). SRL is a natural product of the bacteria Streptomyces hygroscopicus. Its structure is similar to that of TAC, and it binds to the same protein as TAC. However, while TAC blocks calcineurin-dependent T-cell activation, SRL inhibits the kinase mammalian target of rapamycin (mTOR) (Gaczynska & Osmulski, 2018).

Signals for growth factor are carried by mTOR for proliferation of T and B lymphocytes, as well as for smooth muscle and endothelial cells. The latter effect makes SRL effective in preventing graft atherosclerosis (Lindenfeld et al., 2004).

Cardiac allograft vasculopathy (CAV), as described above, is a major late complication and leading cause of death in cardiac transplant patients. Studies have reported that SRL is superior to calcineurin inhibitors in reducing CAV after heart transplant, especially with early conversion to SRL (Asleh et al., 2018). A large U.S. multicenter trial showed that a dose of at least 3 milligrams per day of EVR was associated with increased mortality compared to the use of MMF, and less episodes of reported

discontinuation due to adverse effects (Eisen et al., 2013).

Patients are not initially treated with SRL until at least 3 months post-operation, as it may delay wound healing after major surgery. For this reason, calcineurin inhibitors are preferred in most transplant centers. Additionally, SRL cannot be used together with a calcineurin inhibitor for increased risk of nephrotoxicity.

A study of 402 cardiac transplant patients showed a decrease in plaque volume and plaque index with the use of SRL instead of a calcineurin inhibitor, and long-term follow up showed lower mortality and less frequencies of CAV. However, increased plasma cholesterol and triglyceride levels were reported in association with SRL use (Asleh et al., 2018). Pneumonitis and lymphedema are possible complications caused by mTOR inhibitors, both of which are commonly mistaken for fluid overload and are inappropriately treated as such (Anbalakan et al., 2020).

Over-immunosuppression

Infection, malignancy, and chronic kidney disease contribute to mortality after cardiac transplant and can all be linked to immunosuppressive drug use. Infection is a significant cause of early death following heart transplant, causing 32% of deaths in cardiac transplant recipients 30 days-1 year post-transplant, according to data from 1994-2012.

Different infections are common at different stages following cardiac transplant. Post-operative infections occur shortly after transplantation, while opportunistic infections generally develop 1-6 months afterward, largely due to immunosuppressant use. After 6 months, community-acquired respiratory and urinary tract infections are most common.

Chronic kidney disease is generally a cause of late death in heart transplant recipients, to which calcineurin inhibitors, CSA, and TAC all contribute with their nephrotoxic effects. In a 2013 report from ISHLT, 8% of all mortalities 10-15 years post-heart transplant were due to renal failure, with 4% eventually requiring kidney transplant (Soderlund & Radegran, 2015).

Rejection Surveillance

Early detection of rejection in cardiac allograft is vital to its successful treatment. Early symptoms of rejection include fatigue, nausea, and shortness of breath, all of which can easily be overlooked in an early cardiac transplant recipient. For this reason, transplant centers have strict biopsy protocol during the first year after transplantation (Anbalakan et al., 2020).

The use of less invasive, modern molecular technologies to detect rejection has expanded over the last decade, including gene expression profiling and donor-derived cell-free DNA (dd-cfDNA) testing. Dd-cfDNA are fragments of DNA released from cells which can detect allograft injury in real time. However, not all injurious processes lead to elevated dd-cfDNA values (Huang et al., 2023). A U.S. study of 72 adult heart transplant recipients who underwent non-invasive biomarker-based surveillance suggested that variability in dd-cfDNA values may also help identify patients at increased mortality risk (Kamath et al., 2022). Multiple trials have shown that these and other similar new, non-invasive biomarker-based surveillance strategies are non-inferior to the traditional endomyocardial biopsy, and may have predictive uses as well (Anbalakan et al., 2020).

Acute Rejection Treatment

Being that ACR is T-cell mediated, its treatment involves T-cell depletion and the interruption of their function. In cases of ACR, steroids are administered intravenously in high doses to inhibit cytokine production. Responsive patients are weaned off the steroids, while those who do not respond are additionally given polyclonal anti-thymocyte antibodies for 5-14 days (Costanzo et al., 2010).

In contrast to ACR, AMR is B-cell mediated, and its treatment is more complex than ACR. Steroids are similarly administered to decrease cytokine response (Gelfand, 2001). Additionally, measures are taken to inhibit antibody function and to clear circulating antibodies. There are several strategies to accomplish this, including intravenous immunoglobulin administration; plasmapheresis, or plasma exchange; rituximab, a monoclonal antibody against CD20 antigen on B-cells; bortezomib, a proteasome inhibitor which consequently inhibits plasma cells; and polyclonal anti-thymocyte antibodies (Singh et al., 2009; Colvin et al., 2015).

Health-related Quality of Life

Health-related quality of life (HRQoL) is the impact of disease or chronic conditions on a patient's quality of life. Key aspects of HRQoL include physical status and function, as well as psychological status and well-being (Trackmann & Dettmer, 2020).

A study conducted in Spain comparing two patient samples, one 6 months post-heart transplant and the other 120 months post-transplant, showed that HRQoL improved significantly over time. (Delgaldo et al., 2015). A British study showed worse HRQoL than the general population at 1, 3, and 5 years post-heart transplant in all aspects except for mental health (Saeed et al., 2008). Additionally, HRQoL was generally lower in patients 20+ years post-transplant than those 1-11 years

post-transplant (Galeone et al., 2014).

Another study showed a significant increase in physical and psychosocial HRQoL from pre-heart transplant to 60 months post-transplant (Kugler et al., 2010). Similarly, HRQoL at 3, 6, and 12 months and physical function at 12 months post-transplant were significantly better compared to patients with a left ventricular assist device (LVAD) (Jakovljevic et al., 2014). While patients 6 months post-transplant reported better scores in bodily pain than the general population, those at 4.5 years post-transplant were significantly worse (Holtzman et al., 2010). Patients with severe pain, gastrointestinal symptoms, and sexual dysfunction reported lower HRQoL in all domains (Jokinen et al., 2010). Older patients generally reported greater satisfaction in HRQoL than younger ones, and depressed patients scored significantly lower in all domains (Shamaskin et al., 2012; Kugler et al., 2014). Satisfaction with emotional, tangible, and social support was associated with increased HRQoL, and social and economic satisfaction were significant predictors of survival at 5-10 years post-transplant (White-Williams et al., 2013; Farmer et al., 2013).

Conclusion

Preventing rejection after cardiac transplantation is critical to transplant success and to the health of the recipient. Numerous strategies to prevent rejection have been explored, including the various maintenance immunosuppressive drugs discussed above, as well as induction therapies and combination therapy. As recent research has not shown great success in induction therapy, maintenance immunosuppression therapies remain the standard of care. More research is needed to establish successful induction therapy regimens, which would reduce the need for long-term immunosuppression with its toxic side effects and common complications.

Further research would also work toward reducing cases of cardiac allograft rejection, including the investigation of new immunosuppressive drugs with less toxic side effects, research into new therapeutic targets, and developing more non-invasive methods for monitoring rejection, like the biomarker-based surveillance discussed above.

It is important to note that the optimal method for preventing allograft rejection may vary depending on the patient's individual characteristics, risk factors, and medical history. Thus, a personalized approach to preventing rejection may be the most effective strategy. While preventing rejection after heart transplantation is a complex and ongoing challenge, continued research and a personalized approach can improve the long-term success of this life-saving treatment option.

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