

Review Article



Heart Transplant Immunosuppression Strategies at Cedars-Sinai Medical Center

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ABSTRACT

Heart transplant is the optimal treatment for selected patients with end-stage heart failure. Immunosuppression after heart transplantation has significantly reduced the incidence of rejection and improved patient outcomes with the routine use of calcineurin inhibitors. Antimetabolites and proliferation signal inhibitors add to the improvement in patient outcomes as well. The goal of induction therapy is to provide intense immunosuppression when the risk of allograft rejection is highest. Most maintenance immunosuppressive protocols employ a 3-drug regimen consisting of a calcineurin inhibitor, an antimetabolite agent and glucocorticoids. The management of rejection proceeds in a stepwise fashion based on the severity of rejection detected on biopsy and the patient's clinical presentation. This review will cover induction, maintenance, rejection therapy and some special considerations including sensitization, renal sparing protocol, and corticosteroid weaning. It will end in consideration of potential future directions in immunosuppressive strategies to promote patient and graft survival.

Keywords: Heart transplantation; Immunosuppression; Desensitization, immunologic; Maintenance; Graft rejection

INTRODUCTION

Heart transplant is the optimal treatment for selected patients with end-stage heart failure.¹⁾ Current immunosuppression strategies in heart transplantation follow several general principles.²⁻⁴⁾ The first is that immune reactions leading to graft rejection are the highest early after graft implantation and gradually decrease thereafter. Thus, most regimens use the highest levels of immunosuppression immediately after surgery and decrease those levels over the first year, eventually settling on the lowest maintenance levels of immune suppression that are compatible with preventing graft rejection and minimizing drug toxicities. The second general principle is to use low doses of several drugs without overlapping toxicities over the use of higher doses of fewer drugs whenever feasible. The third principle is that excessive immunosuppression is undesirable because it leads to a myriad of undesirable effects, such as susceptibility to infection and malignancy. Finding the right balance between over- and under-immunosuppression in an individual patient is

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Conflict of Interest

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Author Contributions

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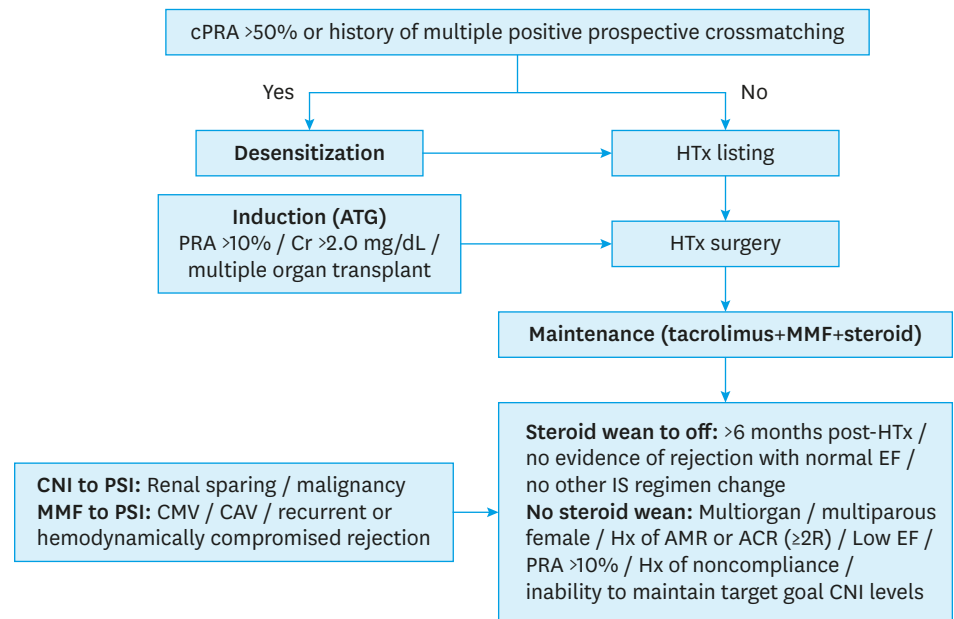


Figure 1. Summary flow diagram of immunosuppression strategies at Cedars-Sinai.

2R = moderate rejection; ACR = acute cellular rejection; AMR = antibody mediated rejection; ATG = anti-thymocyte globulin; CAV = cardiac allograft vasculopathy; CMV = cytomegalovirus; CNI = calcineurin inhibitor; cPRA = calculated panel reactive antibody; Cr = creatinine; EF = ejection fraction; HTx = heart transplant; PRA = panel reactive antibody; PSI = proliferation signal inhibitor; MMF = mycophenolate mofetil; IS = immunosuppressive; PSI = proliferation signal inhibitor.

truly an art that uses science.²⁾ Immunosuppressive regimens can be classified as induction, maintenance and rejection therapy. Induction regimens provide intense early postoperative immune suppression while maintenance regimens are used throughout the patient's life to prevent rejection.²⁾ Summary flow diagram of immunosuppression strategies at Cedars-Sinai is shown in **Figure 1**.

INDUCTION THERAPY

Induction therapy is used in approximately 50% of patients who undergo heart transplant.^{2,5)} The most common indication for induction therapy is antibody sensitization given the recipient's risk of hyperacute rejection in the immediate post-transplant period (**Figure 1**). Additional indications for induction therapy include multi-organ transplantation and in a renal-sparing strategy to allow for delay of calcineurin inhibitor (CNI) therapy. The 2 most common agents used for induction therapy are anti-thymocyte globulin (ATG) and basiliximab. Though there may be reduced risk of infection with use of basiliximab,⁶⁾ we favor use of the polyclonal rabbit formulation of ATG (rATG) given its improved efficacy⁷⁾ and reduced association with antibody production.⁸⁾ We consider rATG induction therapy if panel reactive antibody (PRA) is >10%. With use of the virtual crossmatch and rATG induction therapy, it is feasible to cross 2 low mean fluorescence intensity (MFI) (<5,000) donor specific antibody (DSA) (or one moderate MFI DSA [between 5,000 and 10,000 MFI]) with acceptable post-transplant outcomes.⁹⁾ For highly sensitized patients, rATG is given with premedication including acetaminophen, diphenhydramine, and methylprednisolone. We use a 1.5 mg/kg daily dose of rATG for 5 days post heart transplant, starting on post-operative day (POD) zero. For patients with known DSA at the time of transplant, rATG is followed by intravenous

pooled immunoglobulin (IVIG) for 2 days dosed at 1 g/kg/day (to a total maximum dosage of 140 g). Crossing these DSA would be ideal in the context of a prospective negative complement-dependent cytotoxicity (CDC) crossmatch and negative crossmatch by flow cytometry. Though not routinely utilized, when patients encounter moderate to severe left ventricular primary graft dysfunction post-transplant, patients are treated with a plasmapheresis session prior to each dose of rATG as the procedure of plasmapheresis will remove rATG from the serum. Sensitized patients are given high dose corticosteroids and started on tacrolimus (TAC) and mycophenolate mofetil (MMF) starting POD zero after heart transplant.

Many referral patients remain highly sensitized despite desensitization therapy. Transplantation across a positive (retrospective) CDC crossmatch in a group of pediatric heart transplant recipients was associated with increased early risk of rejection, including rejection with hemodynamic compromise despite use of perioperative plasmapheresis and rATG induction therapy.¹⁰⁾ In this study, approximately 90% of patients transplanted across a positive CDC crossmatch had rejection within 2 months post-transplant with nearly 40% of patients experiencing hemodynamically compromised acute rejection. Survival was 85% at 1 year and 73% at 3 years despite rejection episodes.

Based on prior experience in the renal transplant literature,^{11,13)} for very highly sensitized patients, we completed a twenty patient single arm trial with the use of the terminal complement inhibitor eculizumab for the prevention of antibody-mediated rejection after heart transplant in highly sensitized patients (<http://clinicaltrials.gov/ct2/show/NCT02013037>) (**Figure 2**). In this study, patients at very high immunologic risk (both MCS or non-MCS patients) were enrolled if their PRA was >70%.¹⁴⁾ Preliminary results from this trial show promise for this approach. For the initial 9 patients enrolled in the trial, the mean cPRA at time of transplant was 92%±5%. Mean retrospective flow crossmatch (8 patients) was 104±140 median channel shifts for T cells (positive >50) and 199±87 median channel shifts for B cells (positive >100). No patients had CDC a positive crossmatch. Terminal complement inhibition was added alongside conventional therapy highly sensitized patients (ATG, IVIG, TAC, MMF, and corticosteroids). At 12 months, freedom from any treated rejection was 75%. Survival at 12 months was 88.9% with one intraoperative death due to driveline-mediated mediastinitis. There were no other significant infections. Graft function was preserved in all the surviving patients.¹⁴⁾

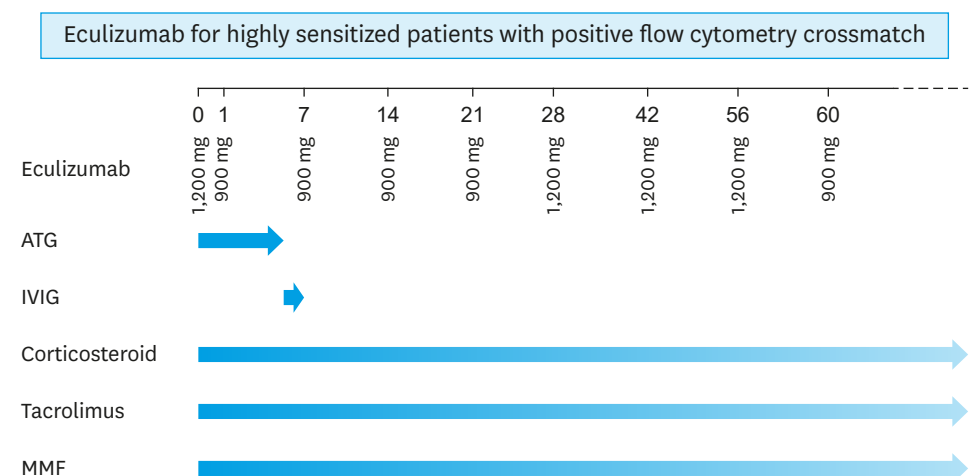


Figure 2. Induction therapy with eculizumab.

ATG = anti-thymocyte globulin; IVIG = intravenous pooled immunoglobulin; MMF = mycophenolate mofetil.

Complement inhibition in select patients with pre-formed DSA prior to heart transplant and positive flow cytometry crossmatch may prevent hyperacute rejection in these immunologically high-risk patients. These patients will need to be followed longitudinally in time for their survival, risk of antibody-mediated and cellular rejection, as well as for development of cardiac allograft vasculopathy. These early encouraging results may lead to additional attempts with complement inhibition either in an induction strategy at the time of transplant or for treatment of hemodynamically compromised acute rejection.

MAINTENANCE THERAPY

Maintenance immunosuppression is generally a combination of 2 of 3 classes of medications: CNI plus, anti-metabolites, or proliferation signal inhibitors (PSI). CNI include TAC and cyclosporine (CSA). Anti-metabolite medications include mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS) and azathioprine (AZA). Proliferation signal inhibitors include sirolimus (SIR) and everolimus (EVL).

After the Federal Drug Administration approval of CSA for use in heart transplantation in the early 1980s, adequate maintenance immunosuppression, with CSA based regimens, allowed for an expeditious rise in heart transplantation. CNI still form the foundation of maintenance immunosuppression regimens after heart transplantation. Based on prior clinical trials,¹⁵⁾¹⁶⁾ our group starts with a triple drug maintenance regimen of TAC, MMF and corticosteroid therapy (intravenous methylprednisolone followed by oral prednisone). In the first month post-transplant, the TAC trough level is maintained between 10–15 ng/mL. The TAC trough level is reduced to 8–12 ng/mL in the second- and third month post-transplant. At the end of third month, the routine TAC trough level is maintained within 5–10 ng/mL. We do not routinely check MMF trough levels, but rather treat with the maximally tolerated dose (of 1,500 mg twice daily). Common dose limiting side effects include gastrointestinal tolerance and the concomitant toxicity of cytopenia. We generally avoid PSI in the first 6 months post-transplant due to wound dehiscence, poor wound healing and the enhanced nephrotoxicity of the CNI. Patients with an active history of fungal infection or deep vein thrombosis/pulmonary embolism are usually not candidates for PSI therapy, unless long-term concomitant therapy is adequately addressed. Most suitably, patients who are treated for rejection, form de novo DSA post-transplant, are a cytomegalovirus (CMV) mismatch (or acquire CMV infection), are diagnosed with a malignancy, or have cardiac allograft vasculopathy are optimal candidates for MMF to PSI conversion. Baseline check for proteinuria, lipid disorders, and glucose control are completed prior to initiation of PSI and followed during therapy. For certain malignancies, such as post-transplant lymphoproliferative disorder (PTLD), PSI with MMF can be used in a CNI free regimen with low dose maintenance immunosuppression. For patients who develop asymptomatic complement binding DSA, we often utilize our outpatient desensitization protocol with IVIG/rituximab.

In the first year after transplant, infection prophylaxis is used to reduce infectious risk of immunosuppressant therapy. For 3 months post-transplant, clotrimazole troche is taken to prevent oral thrush. For patients at high risk for CMV disease (CMV donor positive/recipient negative), renal dosed valganciclovir is taken for 1 year. Patients at lower risk of CMV (CMV donor positive plus recipient positive or CMV donor negative plus recipient positive) take valganciclovir for a period of 6 months. Sulfamethoxazole/trimethoprim is taken for 1 year to prevent pneumocystis jiroveci pneumonia (PJP), toxoplasmosis, and nocardia infections.

REJECTION SURVEILLANCE AND THERAPY

Protocol-based endomyocardial biopsy is performed in the first year after heart transplant for rejection surveillance in our program. Endomyocardial biopsy with right heart catheterization is completed weekly for 4 weeks the first month post-transplant, biweekly for month 2, then monthly for month 3 through 6 post-transplant, then every other month to 12 months (months 6–12) post heart transplant. Patients with antibody sensitization who are at higher risk for antibody mediated rejection (AMR) have surveillance testing with standard endomyocardial biopsy. Each endomyocardial biopsy is assessed for acute cellular rejection (ACR) and AMR according to ISHLT criteria. Echocardiogram is routinely done after endomyocardial biopsy to ensure no damage is done to the graft; in particular, pericardial effusion and tricuspid regurgitation are assessed as well as left and right ventricular systolic function and wall thickness. For low risk patients, non-invasive testing with blood gene expression profile (Allomap®) is possible to minimize need for invasive endomyocardial biopsy. A low score is associated with a high negative predictive value for ACR only.¹⁷⁴⁹⁾ Post-transplant, we routinely send human leukocyte antigen (HLA) for DSA and assess for DSA at months 1, 3, and 6 post-transplant and every 6 months thereafter. If patients develop de novo DSA that require treatment, repeat HLA for DSA are sent 2 weeks after completion of therapy.

Rejection after heart transplant correlates with increased morbidity and mortality. De novo DSA may develop after an episode of rejection.²⁰⁾ Each center will determine appropriate trough immunosuppressant levels, but generally, target trough immunosuppression levels are highest immediately post-transplant and slowly reduced in time (**Table 1**). Maintenance of CNI target trough level is critical. Changes to CNI dosing should be followed with lab work in one week to insure CNI target goals are met. Due to variations of renal function and other factors, blood work is required frequently in the first 2 months after transplant. We recommend blood work twice weekly to include CNI trough level in the first month post-transplant and weekly blood work to include CNI trough level in the second month post-transplant. Inadequate maintenance immunosuppression with subtherapeutic immunosuppressant trough levels can be due to patient noncompliance with medications, nonadherence to medications due to side effects or cost, malabsorption of medications, changes in the patient's cytochrome P450 metabolic capacity, drug-drug and or drug-food interactions, infection, cytopenia, or intolerance that leads to dose reduction of immunosuppressant medications. Patients can have asymptomatic rejection that requires treatment, highlighting the need for protocols to assess for rejection.²¹⁾ Echocardiographic findings can be a later finding in rejection, but new left ventricular hypertrophy may reflect myocardial edema. New onset systolic dysfunction usually represents rejection when seen early post heart transplant. Electrocardiogram (ECG) may show low voltage due to myocardial edema. Blood work may be remarkable for elevated brain natriuretic peptide or troponin.

Symptomatic patients with rejection require more intense augmentation of immunosuppression.²²⁾ Common symptoms that suggest heart transplant rejection include shortness of breath, orthopnea and paroxysmal nocturnal dyspnea. Symptoms that preceded transplant can reoccur with post heart transplant rejection. Supraventricular tachycardia, most commonly atrial fibrillation or atrial flutter are suggestive of heart transplant rejection in the appropriate clinical context. Caution should be taken with adenosine use for supraventricular tachycardia as the atrioventricular node is sensitive to adenosine post heart transplantation. Telemetry or continuous ECG monitoring and 50% dose reduction to 3 mg of adenosine should be tried initially to minimize the occurrence of prolonged heart block.

Table 1. Pharmacology and side effects of immunosuppressive agents for heart transplantation recipients

Drug	Dosing	Target levels	Major toxicities
CNIs: inhibits T cell activation and proliferation via blocking action of calcineurin			
Cyclosporine	4–8 mg/day in 2 divided doses, titrated to keep target 12-hour trough levels	0–1 months: 250–350 ng/mL 2–3 months: 200–250 ng/mL >3 months: 100–200 ng/mL	Renal insufficiency Hypertension Dyslipidemia Hyperkalemia Hypomagnesemia Hyperuricemia Neurotoxicity (encephalopathy, seizures, tremors, headaches, neuropathy) Gingival hyperplasia Hirsutism
Tacrolimus	0.05–0.1 mg/kg/day in 2 divided doses, titrated to keep target 12-hour trough levels	0–1 months: 10–15 ng/mL 2–3 months: 8–12 ng/mL >3 months: 5–10 ng/mL	Renal insufficiency Hypertension Hyperglycemia and diabetes mellitus Dyslipidemia Hyperkalemia Hypomagnesemia Neurotoxicity (encephalopathy, seizures, tremors, headaches, neuropathy)
Cell cycle agents: inhibits proliferation of T and B lymphocytes via blocking nucleoside synthesis			
Azathioprine	1.5–3.0 mg/kg/day, titrated to keep WBC up to 3K	None	Bone marrow suppression Hepatitis (rare) Pancreatitis
Mycophenolate mofetil	2,000–3,000 mg/day in 2 divided doses	Mycophenolic acid: 2–5 mcg/mL	Gastrointestinal disturbances (nausea, gastritis, and diarrhea) Leukopenia
Mycophenolate sodium	1,440–2,160 mg/day in 2 divided doses	None	Fewer gastrointestinal disturbances compared with mycophenolate mofetil (nausea, gastritis, and diarrhea) Leukopenia
Proliferation signal inhibitors: inhibits T cell activation and proliferation by blocking the action of the mTOR C1 complex			
Sirolimus	1–3 mg/day, titrated to keep therapeutic 24-hour trough levels	4–8 ng/mL	Oral ulcerations Hypercholesterolemia and hypertriglyceridemia Poor wound healing Lower extremity edema Pulmonary toxicities (pneumonitis, alveolar hemorrhage) Leukopenia, anemia, and thrombocytopenia Potentiation of CNI nephrotoxicity
Everolimus	1.5 mg/day in 2 divided doses	3–8 ng/mL	Similar to sirolimus (but in general better tolerated than sirolimus)
Corticosteroids: binds to glucocorticoid receptor leading to changes in gene transcription			
Prednisone	1 mg/kg/day in 2 divided doses, tapered to 0.05 mg/kg/day by 6–12 months	None	Appetite stimulation Hypertension Hyperlipidemia Osteopenia and osteoporosis Hyperglycemia Poor wound healing Salt and water retention Proximal myopathy Peptic ulcer disease/GI ulceration Growth retardation

WBC = white blood cell; CNI = calcineurin inhibitor.

IV beta blockers should be cautiously used early post-transplant given the upregulation of beta receptors. Careful use of amiodarone is acceptable for treatment of supraventricular arrhythmias. If there is suspicion for rejection, when possible, endomyocardial biopsy should be performed to assess for ACR and AMR. However, in the event that endomyocardial biopsy is unremarkable, due to sampling error with the biopsy amongst other confounders, biopsy negative rejection (BNR) should be considered if there is graft systolic dysfunction and clinical signs and symptoms of heart failure. In the context of biopsy-negative rejection, we consider the use of cardiac magnetic resonance or molecular microscope (MMDx®)

testing.²³⁾ Myopericarditis, myocardial edema, or late gadolinium enhancement may be suggestive of rejection.

Treatment for ACR, AMR, and BNR involves a number of modalities for acute immunosuppression.²²⁾ For symptomatic patients, high dose corticosteroids, with intravenous methylprednisolone, can be used as a pan-immunosuppressant in conjunction with rATG for cytolytic T and B cell activity. After methylprednisolone 500 mg is given daily for 3 days, the corticosteroid dose is reduced and used as a pre-medication for rATG. Depending on the clinical context, 3 to 7 days can be considered for rATG therapy (albeit, 5 days is the usual course). HLA should be repeated at the time of suspected or confirmed rejection. Assessment of non-HLA antibodies is considered at the time of rejection particularly if no HLA antibodies are detected. When DSA are present, IVIG can be used at 1 g/kg daily for 2 days to a maximum total dosage of 140 g. For patients in cardiogenic shock, pulmonary artery Swan Ganz catheter hemodynamic monitoring is established to optimize cardiac filling pressures and guide inotropic therapies to target cardiac index >2.0 L/min/ m^2 . When a patient has rejection, inotropes use may be limited due to tachycardia and rhythm issues and mechanical circulatory support with IABP may be required. For patients decompensating on inotropic support in conjunction with IABP, use of VA ECMO as a bridge to recovery should be strongly considered. Timing of VA ECMO use is critical to promote acceptable patient outcome.²⁴⁾ Patients in cardiogenic shock who have VA ECMO placed after cardiac arrest have poor outcomes.

Persistent and recurrent rejections reflect an overactive immune system and present significant challenges to the care of post heart transplant patients. Photopheresis may be considered for recurrent rejection.²⁵⁾ Given the risk of hyperacute rejection, redo heart transplant is generally contra-indicated within 6 months of an episode of treated rejection.

SPECIAL CONSIDERATION

Sensitization

Stimulation of the humoral arm of the adaptive immune system can lead to antibody sensitization. A number of clinical events, including prior surgery (particularly surgery that incorporates biologic graft materials), infection, blood and blood product transfusion, pregnancy and multiparous state, placement of durable mechanical circulatory support, repaired congenital heart disease with a homograft and prior organ transplant can lead to alloantibody formation.²⁶⁻²⁸⁾

When B cells are stimulated in secondary lymphoid tissue, they can convert to plasmablasts secreting low affinity antibodies or form germinal centers by interaction with CD4 T cells and dendritic cells. In secondary lymphoid tissue germinal centers, B cells can mature into plasma cells or memory B-cells, capable of producing high affinity antibodies.²⁹⁾ Upon repeat antigen stimulation, memory B cells can return from secondary lymphoid tissue and rapidly be mobilized to produce and secrete antibodies against previously identified foreign antigens.³⁰⁾ In heart transplant recipients with antibody sensitization, this memory B cell response can manifest as an amnestic response, which can occur 5 to 7 days after heart transplantation. The amnestic response can manifest clinically in many different ways, such as recurrent heart failure symptoms, reduced left or right ventricular dysfunction on echocardiogram, poor hemodynamics at the time of endomyocardial biopsy with right

heart catheterization, heart rhythm abnormalities, and, in its most severe manifestation, as cardiac arrest. Though relatively rare, it is critical to recognize the amnestic response post heart transplant. In cases where heart transplant recipients are at elevated risk of amnestic response, one can repeat human leukocyte single antigen testing in the first week post heart transplant to assess for de novo DSA or acute rise in antibody burden.

The issue of antibody sensitization in patients being considered for heart transplant led to a consensus conference in April 2008.³¹⁾ In this consensus conference, 71 experts from 51 heart transplant centers from Asia, Australia, Europe, and the United States participated. As reported from the consensus conference, at that time, approximately 8% of patients referred for heart transplant were treated for antibody sensitization. The prevalence of antibody sensitization has been on the rise for over the past decade. In the 2014 registry update from the ISHLT,³²⁾ the rates of sensitized patients with PRA over 10% were noted to have increased. From 1992–2000, 7.4% of patients had PRA over 10%. From 2006–2013, the rate of patients with PRA >10% was increased to 12%. By 2014 approximately 14% of transplant candidates had a panel reactive antibody of >10%.³³⁾ Data from the Scientific Registry of Transplant Recipients (SRTR) reported a rise in PRA >20% from 2005 to 2015 with rates of antibody sensitization by 2015 to over 17% in adults and over 28% in pediatric heart transplant recipients.³⁴⁾ Furthermore, the American Heart Association, in March 2019, published a scientific statement on emerging knowledge regarding sensitization in heart transplantation.²⁶⁾ This scientific statement built on the foundation laid by the April 2008 consensus conference. Due to utilization of novel desensitization strategies in heart transplant recipients, Cedars-Sinai has become a national and international referral source for patients with antibody sensitization. Amongst other factors, antibody sensitization has led to Cedars-Sinai to become the highest volume center for heart transplantation in the United States from 2014–2019 (**Table 2**) with excellent clinical outcomes by SRTR data.

Desensitization protocols

Based on data obtained from the United Network of Organ Sharing (UNOS) database, patients with antibody sensitization have longer wait times prior to heart transplant, higher risk of being removed from the transplant list, and increased risk of death awaiting transplantation.³⁵⁾ Patients at highest risk for adverse outcome prior to transplant had cPRA >80%. Moreover, UNOS data showed that compared to patients who are not sensitized, patients with antibody sensitization have reduced survival and increased risk of AMR after initial heart transplant.³⁶⁾ The greatest risk post heart transplant was seen in patients who maintained a PRA >25%.

Desensitization protocols for heart transplant patients have largely stemmed from the experience of patients who have undergone desensitization prior to renal transplant. Studies of desensitization in renal, heart, and lung transplant candidates are relatively small

Table 2. Numbers of adult heart transplant cases in United States

Institute	2014	2015	2016	2017	2018	2019
Cedars-Sinai	120	131	122	102	122	118
Vanderbilt	32	53	77	83	100	96
Duke	60	44	62	72	72	84
Stanford	50	67	56	70	68	63
NYP-Columbia	47	38	52	55	56	61
Cleveland Clinic	56	39	46	49	49	50
All centers	2,251	2,347	2,747	2,813	2,940	3,045

<https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/>.

studies, with between 18–211 patients.³³⁾ The major categories of desensitization treatments include circulating antibody removal (with therapeutic plasma exchange, plasmapheresis, or immunoadsorption), neutralizing antibody treatment with IVIG, therapy to target B cells (rituximab), therapy to target plasma cells (bortezomib), and removal of secondary lymphoid organ with splenectomy. In addition to antibody neutralization, IVIG can inhibit B cell maturation, induce B cell apoptosis, and reduce the activity of antigen presenting cells due to the role of the Fc gamma receptor. IVIG is one of few desensitization therapies which may not increase risk of infection.³⁷⁾ Many of these therapies are used in combination. The main risk of desensitization therapies is potential infection. Several desensitization trials paired desensitization therapy with induction strategies at the time of transplant, such as therapy to inhibit the complement pathway (terminal complement inhibition with eculizumab).

At Cedars-Sinai, we consider desensitization therapy for patients with cPRA >50% (**Figure 3**).³⁸⁾ For listed patients, we typically repeat HLA testing by Luminex SAB testing, list avoid antigens, and repeat cPRA 2 weeks after a sensitizing event such as blood transfusion or infection. For non-sensitized outpatients on the heart transplant waitlist, HLA, avoid antigens listed and cPRA are reassessed every 6–12 months. If patients merit desensitization, repeat HLA and cPRA are assessed approximately 2 weeks after completion of therapy.

For outpatients who are expected to respond to therapy, we utilize IVIG in conjunction with rituximab patterned after data from prior renal transplant desensitization strategies.³⁹⁾ Patients with active infection, chronic hepatitis B, or a history of progressive multifocal leukoencephalopathy are not considered for IVIG and rituximab therapy. Patients treated

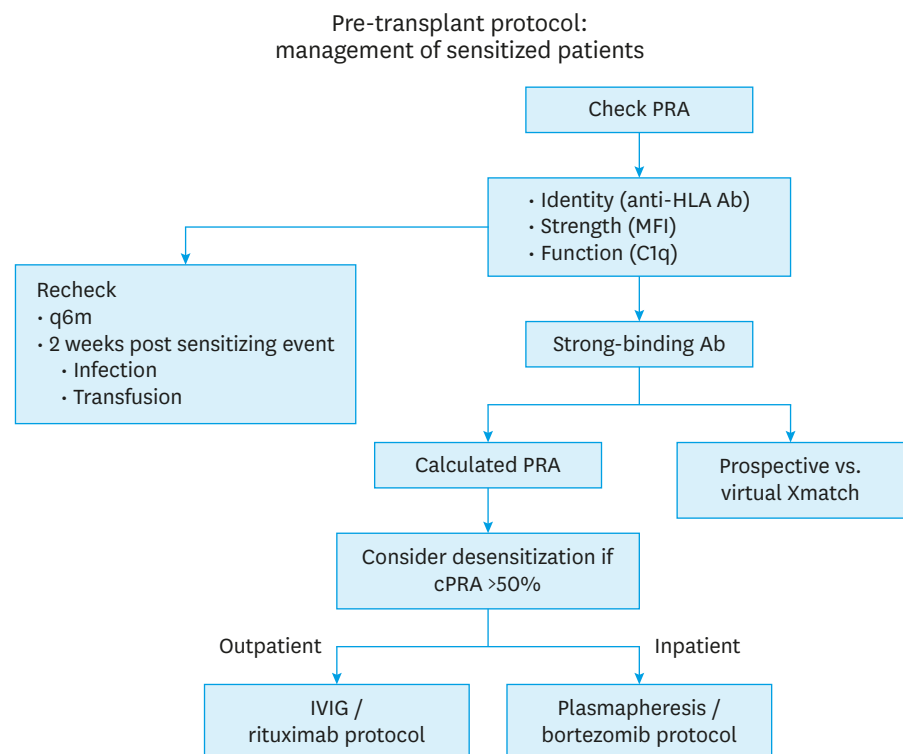


Figure 3. Management of sensitized patients.

cPRA = calculated panel reactive antibody; HLA = human leukocyte antigen; IVIG = intravenous pooled immunoglobulin; MFI = mean fluorescence intensity; PRA = panel reactive antibody.

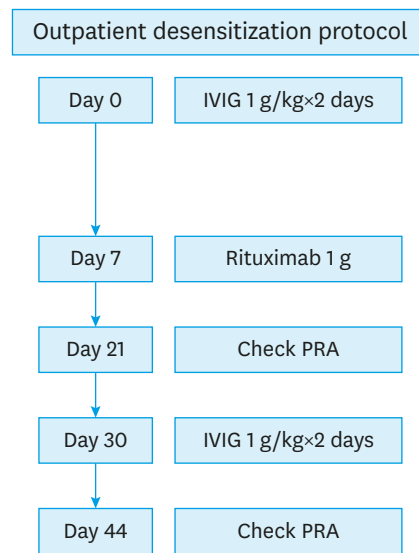


Figure 4. Outpatient desensitization protocol.
PRA = panel reactive antibody.

within 4 weeks with cyclophosphamide, anakinra, or etanercept or patients treated within 8 weeks with infliximab, adalimumab or abatacept are generally not enrolled for IVIG and rituximab therapy. In this protocol, we use IVIG 1 g/kg daily for 2 days (to a total maximal dosage of 140 g). Pre-treatments for IVIG therapy include acetaminophen, diphenhydramine, and low dose methylprednisolone. On day 7, the patient receives rituximab 1 g (or 375 mg/m² if weight is <55 kg) after treatment with acetaminophen, diphenhydramine, and methylprednisolone. On day 30, the patient has repeat IVIG 1 g/kg daily (with medication pre-treatment) for 2 additional days to a total maximal dosage of 140 g (**Figure 4**).⁴⁰⁾

For patients who are broadly and highly sensitized, particularly patients with Class I HLA sensitization, or if patients have not had a sufficient response from outpatient IVIG/rituximab desensitization, inpatient desensitization with plasmapheresis with bortezomib may be utilized. This desensitization process is a 2-week process and requires placement of a central venous catheter for plasmapheresis. Our protocol (**Figure 5**) is a modification of a protocol used for treatment of DSA after renal transplant.⁴¹⁾⁴²⁾ Once venous access for plasmapheresis is obtained, the patient receive plasmapheresis on both a Monday and Tuesday with 1.3 mg/m² bortezomib given after plasmapheresis session on Tuesday. Side effects from the subcutaneous administration is generally better tolerated (including less peripheral neuropathy) than IV administration. After one day rest, plasmapheresis is resumed on Thursday and Friday, followed again by bortezomib (1.3 mg/m²) subcutaneous administration. This same time course is repeated on the second week of bortezomib desensitization. Prior studies have shown greater reduction of HLA Class I antibodies and a variable reduction of HLA Class II antibodies.⁴³⁻⁴⁵⁾

Patients treated with IVIG and rituximab or plasmapheresis and bortezomib are at risk for infection after treatment. There is likely a higher risk of infection after the latter therapy. Due to antibody removal and reduction of B cells and plasma cells, a patient's immune system may respond in time with additional antibody production (rebound effect).⁴⁶⁾ The clinical implications of this rebound effect are not fully understood.

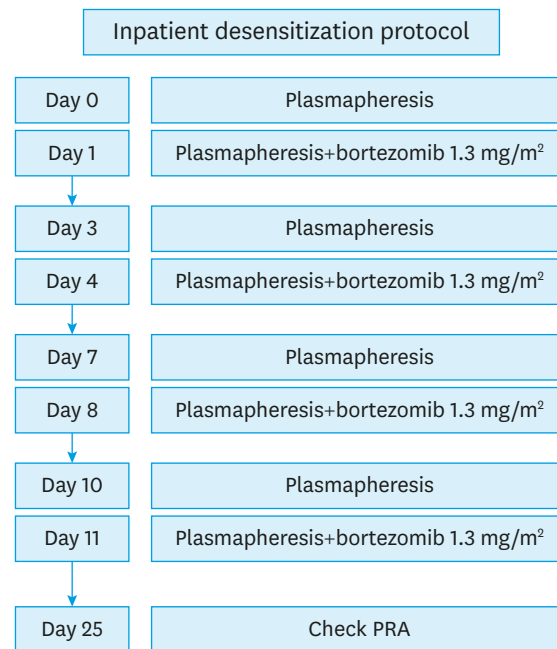


Figure 5. Inpatient desensitization protocol.
PRA = panel reactive antibody.

Renal sparing protocol

A renal sparing protocol can be approached as either CNI minimization or CNI withdrawal depending on the degree of renal insufficiency and CNI withdrawal possibility. When renal insufficiency is mild (serum creatinine 1.8–2.2 mg/dL), CNI minimization method is preferred. CNI withdrawal protocol may be used when renal insufficiency is moderate (serum creatinine >2.0–2.5 mg/dL) and is performed after 6 months post-transplant. For this protocol, patients should not currently be weaning off steroids, be without a history of PSI intolerance, left ventricular dysfunction or humoral rejection or cellular rejection >2R. In converting to a CNI free regimen, we maintain MMF and reduce CNI dose by 50% while initiating a PSI. Low dose CNI is maintained until target trough levels of PSI are achieved. For SIR and EVL, we target trough levels of 4–8 ng/mL and 3–8 ng/mL respectively, depending on the clinical context for their use. Approximately 20% of patients do not tolerate PSI.⁴⁷⁾ Fatigue and fluid retention are the most common side effects of PSI. Less common or long-term side effects include: eased risk of fungal infection, pneumonitis, venous thromboembolism, hypertriglyceridemia, oral ulcers, cytopenia, and acute kidney injury.²²⁾ In the context of change to PSI, given the possibility of intolerance, follow up within 4 weeks should be arranged. PSI use should be made on an individual basis.²²⁾

Corticosteroid weaning

Due to the long-term side effects of corticosteroid therapy, for lower risk heart transplant recipients, we try to wean prednisone off by twelve months post-transplant. By 3 months post-transplant, patients wean to prednisone 10 mg daily and by 6 months post-transplant, patients have weaned to prednisone 5 mg daily. Patients with normal left ventricular systolic function, no history of treated heart transplant rejection, no evidence of DSA, and medication adherence with acceptable doses of immunosuppressive medications are considered for prednisone wean from 5 mg daily to off prednisone (**Figure 1**). Due to side

effects of prednisone weaning, at 6 months we wean prednisone by 1 mg per month to off. Each month with prednisone wean to off, endomyocardial biopsy is performed to assess for asymptomatic rejection in higher risk patients. Allomap[®] can be used in this prednisone wean to off protocol in low risk patients.¹⁸⁾¹⁹⁾ Echocardiogram is obtained monthly to confirm intact graft function. Prednisone wean to off protocol should be instituted with caution if there is change to class of maintenance immunosuppressive medications. Myalgia, arthralgia and fatigue may be seen with prednisone weaning. Rarely, patients will manifest rejection requiring treatment during a prednisone wean to off protocol. Prednisone wean is terminated and after treatment, patients are maintained on prednisone 5 mg daily, but have successfully weaned select patients. We generally maintain prednisone at 5 mg daily for multi-organ transplant recipients. Moreover, patients with certain etiologies for cardiomyopathy requiring heart transplant, including sarcoidosis and giant cell myocarditis, are maintained on prednisone 5 mg daily without attempts at prednisone wean to off.

FUTURE DIRECTIONS

Based on early clinical work in renal transplant patients,⁴⁸⁾⁴⁹⁾ we are interested in the effect of either obinutuzumab or tocilizumab for desensitization prior to heart transplant and for highly sensitized patients post-transplant. Obinutuzumab is a type II anti CD20 antibody that is more effective (greater direct cell death with less complement dependent cytotoxicity) in depletion of B cells than rituximab. With our current protocol of IVIG and rituximab, we have moved to use of IVIG plus obinutuzumab in similar fashion with obinutuzumab replacing rituximab in select patients. This protocol is completed in approximately one month. Tocilizumab is an antibody to the interleukin 6 receptor. IL6 is involved in many aspects of immune system activation. Tocilizumab desensitization is done with monthly tocilizumab infusions that cover a 6-month period. After patients are treated with plasmapheresis and IVIG, patients then have monthly tocilizumab treatments.⁵⁰⁾

Currently, we are enrolling patients in the twenty center trial of tocilizumab therapy along with triple drug therapy in immunologically low risk patients. This trial, Targeting Inflammation and Alloimmunity in Heart Transplant Recipients with Tocilizumab (ALL IN) is funded by the NIAID/NIH in the United States. Target enrolment is 200 patients over 3 years and patients will be followed for a minimum of 12 months post enrollment (National Clinical Trial Number: NCT0364467).

Induction therapy is common at the time of heart transplant, but there is little randomized data regarding the use of rATG in lower risk patients as an induction strategy at the time of heart transplant. In a single center study, we are examining use of rATG in a prospective, randomized trial for approximately 60 patients with PRA <25%. One hypothesis is that there will be less treated rejection or DSA in the rATG arm of the study, but increased risk of infection in patients treated with rATG.

There are many potential avenues of research for the near and long term with respect to the clinical conundrum of antibody sensitization. Current desensitization strategies focus on the removal of circulating antibodies, which is needed at the time of transplant. Imlifidase is an IgG endopeptidase derived from *Streptococcus pyogenes* that cleaves IgG into Fc and F(ab)'2 fragments. It has been used in kidney transplant,⁵¹⁾ but not yet in heart transplant patients to our knowledge. Removal of pathologic IgG at time of transplant is promising,

but antibody rebound may lead to severe rejection one to 2 weeks post heart transplant. Focus on modulation or depletion of immune effector cells, like memory B cells, in secondary lymphoid tissue may better prime the immune system to accept a transplanted organ. Obinutuzumab is a promising agent in this regard in that there is some evidence of penetration into secondary lymphoid tissue. Agents that target non-T cell and non-B cell targets of the immune system hold promise. Terminal complement inhibition holds promise for induction strategies and in the treatment of AMR. Agents that act more proximally in the complement pathway, like C1 esterase inhibitors may favourably assist patients and induce accommodation to the transplanted graft. Clazakizumab, like tocilizumab, interferes with IL-6 signalling and, as obinutuzumab is to rituximab, may be more potent in immune modulation. The use of MMDx[®] with endomyocardial biopsy specimen uses machine learning to predict probability of ACR and AMR. Key components of the MMDx[®], as they relate to heart transplant rejection, hold potential promise to guide future therapeutics that target natural killer cells, macrophages, endothelial cell targets, and cytokines involved in rejection in addition to T cell targets. Significant advances in immunotherapies have been made in the treatment of malignancy.⁵²⁾⁵³⁾ As malignancy remains the major limitation to long term longevity after solid organ transplant,⁵⁴⁾ if immunotherapy used for treatment of malignancy can cross over and be used in maintenance immunosuppression post-transplant, there is hope that limited lifespan due to malignancy will be addressed.

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