Survival after heart transplantation has improved considerably over the past 20 years. Half of all patients now live >9 years, and ≈25% live ≥17 years. Currently, ≈20 000 heart transplant recipients live in the United States. Improved longevity means prolonged immunosuppression and the concomitant use of drugs to prevent or treat the long-term complications of immunosuppressive agents, such as infection, obesity, hypertension, hyperlipidemia, renal insufficiency, diabetes, osteoporosis, gout, and malignancies. In 1989, heart transplant recipients surviving 1 year were reported to be taking 16±6 drug doses per day (prescription and nonprescription). In 2001, heart transplant recipients surviving an average of 76 months were taking 7 prescription drugs (range, 2 to 14), along with a number of nonprescription drugs. Thus, despite prolonged survival, heart transplant recipients continue to take multiple medications. With the large number of heart transplant recipients in the community and the increasing number of immunosuppressive and nonimmunosuppressive drugs used by these patients, it is important that the general cardiologist understand these drugs, their side effects, and the very real potential for drug–drug interactions. These interactions may result in adverse events caused by supratherapeutic and subtherapeutic drug concentrations. In this series, we review mechanisms and types of rejection, immunosuppressive drugs commonly used in the heart transplant recipient, common medical problems after transplantation, and clinically significant drug–drug interactions.

Rejection

A brief review of known immunologic mechanisms leading to graft rejection highlights the action of individual immunosuppressive drugs, as well as the rationale for combination therapy5–8 (Figure). The rejection of a transplanted organ is primarily a T-lymphocyte (T-cell)–mediated event, although other T helper cells, cytotoxic T cells, B cells, and natural killer cells. Engagement of the IL-2R, like many other cytokines. Secreted IL-2 activates the cell-surface IL-2 receptor (IL-2R), stimulating clonal expansion of T cells. IL-2 (along with other cytokines) produced by these T helper cells stimulates expansion of other cells of the immune system, including other T helper cells, cytotoxic T cells, B cells, and natural killer cells. Engagement of the IL-2R, like many other
Immunologic mechanisms leading to graft rejection and sites of action of immunosuppressive drugs. Immunologic mechanisms are shown in blue; immunosuppressive drugs and their site of action are shown in red. Acute rejection begins with recognition of donor antigens that differ from those of recipient by recipient APCs (indirect allorecognition). Donor APCs (carried passively in graft) may also be recognized by recipient T cells (direct allorecognition). Alloantigens carried by APCs are recognized by TCR-CD3 complex on surface of T cell. When accompanied by costimulatory signals between APC and T cells such as B7-CD28, T-cell activation occurs, resulting in activation of calcineurin. Calcineurin dephosphorylates transcription factor NF-AT, allowing it to enter nucleus and bind to promoters of IL-2 and other cytokines. IL-2 activates cell surface receptors (IL-2R), stimulating clonal expansion of T cells (T helper cells). IL-2, along with other cytokines produced by T helper cells, stimulates expansion of other cells of immune system. Activation of IL-2R stimulates TOR, which regulates translation of mRNAs to proteins that regulate cell cycle. Sites of action of individual drugs (highlighted in red) demonstrate multiple sites of action of these drugs, underscoring rationale for combination therapy. AZA indicates azathio- prine; MMF, mycophenolate mofetil; GR, glucocorticoid receptor; DAC, daclizumab; and BAS, basiliximab.

**Types of Rejection, Timing, and Consequences**

Rejection of the transplanted heart is a major cause of morbidity and mortality in the first year after heart transplantation. Rejection is classified as hyperacute, acute cellular, acute humoral (vascular), or chronic. Hyperacute rejection occurs within minutes to hours of the blood flow being reestablished and is caused by preformed antibodies to ABO blood group antigens, HLA, or endothelial antigens. With ABO matching of recipients to donors and prospective cross-matching of patients who have been previously sensi-
tized to HLA, hyperacute rejection is rare. When it does occur, it is catastrophic because preformed antibodies bind to endothelial antigens on the transplanted heart, resulting in activation of complement. An acute inflammatory infiltrate results in fibrinoid necrosis of the vessels of the grafted organ.

Acute cellular rejection may occur at any time after transplantation but is most common in the first 3 to 6 months. It is a T-cell–mediated response with infiltration of lymphocytes and macrophages and resultant myocytolysis. The diagnosis is made by endomyocardial biopsy with a standardized grading scheme ranging from mild to moderate to severe acute rejection. Moderate rejection by endomyocardial biopsy is associated with mononuclear cell infiltrates and myocytolysis. A diagnosis of moderate rejection generally prompts antirejection therapy that varies according to historical severity (grade of rejection) and hemodynamic function. Patients with acute cellular rejection may have no signs or symptoms but often notice mild symptoms of fatigue or shortness of breath. Signs of right ventricular dysfunction are often noted with elevated jugular venous pressure. More severe rejection may be associated with signs of left heart failure and left ventricular dysfunction. Therapy may include intravenous or oral steroids, monoclonal or polyclonal antilymphocyte agents, or an increase or change in oral therapy. The type of therapy generally depends on timing after transplantation, the severity (particularly the severity of hemodynamic compromise), and the protocols of individual centers. In the early 1980s, 70% to 85% of heart transplant recipients experienced acute cellular rejection in the first 6 months after transplantation. More recently, the reported incidence of acute cellular rejection during the first 6 postoperative months is 40% to 70%. Acute cellular rejection does occur after the first 6 months, most often in patients who have had substantial rejection early after transplantation, a recent reduction in immunosuppression, an intercurrent infection, or noncompliance with medication.

Acute humoral (also called vascular) rejection occurs days to weeks after heart transplantation and is initiated by antibodies rather than T cells. The alloantibodies are directed against donor HLA or endothelial cell antigens. Patients at greatest risk of acute humoral rejection include women, patients with a high panel reactive antibody screen and/or a positive cross-match, cytomegalovirus-seropositive recipients, and recipients with sensitization to OKT3. Acute humoral rejection is much less common than acute cellular rejection, occurring in ~7% of patients. Its importance stems from its common association with severe ventricular dysfunction, presumably caused by diffuse ischemia secondary to a lack of coronary vasodilatory reserve. The diagnosis is made by demonstrating immunoglobulin and complement in the vessels of the transplanted heart in an endomyocardial biopsy specimen or by the presence of swollen endothelial cells on hematoxylin and eosin staining. Humoral rejection is treated with intensification of the immunosuppressive regimen but also with therapy directed specifically at either modulating antibody production or removing antibody such as cyclophosphamide immunoglobulin and plasmapheresis. Given the endothelial injury and dysfunction associated with
chronic rejection, it is not surprising that vascular rejection is associated with an increased risk of chronic rejection.14

Chronic rejection occurs months to years after transplantation.15,16 The mechanism is incompletely understood but results from the humoral and cellular consequences of allore cognition. In heart transplant recipients, chronic rejection is also referred to as coronary allograft vasculopathy (CAV) and manifests as diffuse atherosclerosis with myointimal proliferation in the coronary arteries. The diffuse involvement of the coronary arteries results in ischemia and infarction. Angioplasty and coronary bypass surgery are not effective in many patients because of the diffuse nature of the disease.15 However, angioplasty is frequently performed when focal ischemia is demonstrable. Although the procedure is generally technically successful, the underlying diffuse atherosclerotic process usually progresses rapidly. As many as 50% of heart transplant recipients have angiographically confirmed CAV by 5 years after transplantation, and severe CAV is a major cause of death in patients surviving the first posttransplantation year.1,15,16 It remains uncertain whether more intense immunosuppression would ameliorate CAV or whether newer regimens incorporating sirolimus, which may inhibit myointimal proliferation, will prove beneficial.

**Immunosuppression**

**Immunosuppression Regimens**

Immunosuppression regimens are generally defined as induction, maintenance, and rejection regimens. Induction therapy is intense perioperative immunosuppressive therapy. Although originally designed to induce tolerance to the graft, this goal has not been realized.7 Nonetheless, the concept of induction is useful because it highlights the fact that antidonor responses are typically more vigorous shortly after the transplantation when stimuli such as donor brain death, ischemia/reperfusion, and surgical trauma increase donor antigen expression, thus augmenting the recipient’s immune response. The benefits of induction therapy are a marked reduction in rejection in the early postoperative period when graft dysfunction and renal dysfunction are problematic. However, there is increased late rejection after induction therapy is completed. Induction therapy also allows later introduction of calcineurin inhibitors, thus avoiding exacerbation of renal dysfunction. Disadvantages of induction therapy are the increased risk of infection, malignancy, or both and increased cost. Lympholytic agents (ATGAM, Thymoglobulin), generally given for 7 to 14 days postoperatively, have been standard induction drugs. More recently, IL-2R antagonists have been used for induction therapy. In renal and heart transplant recipients, IL-2R antibodies appear to decrease the risk of rejection in the early postoperative period without increasing infection. With the introduction of more potent drugs for maintenance immunosuppression, induction therapy, especially with lympholytic agents, is often reserved for patients at highest risk of rejection or renal failure.

Maintenance therapy generally consists of combination therapy with an antimetabolite, a calcineurin inhibitor, and steroids (Table 1). Maintenance regimens are evolving with efforts to diminish the nephrotoxicity of calcineurin inhibitors and metabolic toxicity of steroids. Thus, some regimens may add TOR inhibitors to lower doses of calcineurin inhibitors or to eliminate calcineurin inhibitors or steroids. Combination therapy targets several steps in T-cell activation, allowing lower doses of each individual drug (Figure). Specific maintenance regimens vary at individual transplantation centers and are based on age, presensitization, race, and previous rejection because each of these factors determines a patient’s risk for rejection. Early maintenance therapy generally consists of a steroid, a calcineurin inhibitor with either cyclosporine or tacrolimus, and an antiproliferative agent (mycophenolate mofetil or azathioprine). Prednisone is started in high doses early after transplantation and gradually is tapered to 0 to 5 mg QD by 6 months. Doses of the calcineurin inhibitor also are gradually decreased over time. Newer regimens have substituted a TOR inhibitor for either a calcineurin inhibitor or an antiproliferative agent.

**TABLE 1. Common Maintenance Immunosuppressive Regimens**

<table>
<thead>
<tr>
<th>Calcineurin Inhibitor</th>
<th>Antiproliferative Agent</th>
<th>Steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporin or tacrolimus</td>
<td>Mycophenolate mofetil or azathioprine</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Sirolimus or everolimus</td>
<td>Sirolimus or everolimus</td>
<td></td>
</tr>
</tbody>
</table>

Maintenance immunosuppressive regimens generally consist of a regimen of a calcineurin inhibitor (cyclosporin or tacrolimus) and an antiproliferative agent (mycophenolate mofetil or azathioprine). Prednisone is started in high doses early after transplantation and gradually is tapered to 0 to 5 mg QD by 6 months. Doses of the calcineurin inhibitor also are gradually decreased over time. Newer regimens have substituted a TOR inhibitor for either a calcineurin inhibitor or an antiproliferative agent.

Chronic rejection occurs months to years after transplantation. The mechanism is incompletely understood but results from the humoral and cellular consequences of allore cognition.
Rejection (or rescue) therapy refers to immunosuppressive therapy given to reverse an episode of rejection. The intensity and type of rejection therapy depend on the severity and hemodynamic consequences of the rejection, whether it is thought to be T-cell mediated or humoral, as well as centerspecific protocols. Rejection may be treated with an increase in oral therapy, oral or intravenous pulse steroids, a change in oral therapy, or monoclonal or polyclonal anti-lymphocyte agents. Protocols for induction, maintenance, and rejection therapy vary among transplantation centers and often draw on renal transplantation experience, in large part because of the scarcity of randomized, controlled trials in heart transplant recipients.

**Immunosuppressive Therapy: General Comments**

Immunosuppressive drugs result in 3 categories of outcomes: the desired immunosuppressive effects, the adverse effects of immunodeficiency such as infection and malignancy, and the nonimmune toxicities such as diabetes, hypertension, and renal insufficiency.⁸ Infectious complications, frequent after cardiac transplantation, are a common cause of death in the first year after transplantation and continue to be a significant problem even after the first year.¹ All immunosuppressive drugs contribute to increased risk of infection, with the probable exception of IL-2R antagonists. Malignancy is another significant problem after cardiac transplantation. Risk factors for malignancy are multifactorial and include impaired immunoregulation, a synergistic effect with other carcinogens such as nicotine or ultraviolet light exposure, and oncogenic viruses such as the Ebstein-Barr virus and the papilloma virus.²¹ Lymphoproliferative diseases, skin and lip cancers, and Kaposi’s sarcoma have a particularly high incidence relative to the general population. A relatively common cause of death after the first year after transplantation, malignancies account for 24% of deaths after 5 years.¹

All immunosuppressive drugs contribute to the risk of malignancy, with the possible exception of steroids. Data in animals suggest that the antigrowth properties of a new immunosuppressive drug, sirolimus, may result in fewer malignancies.²² The cumulative amount of immunosuppression, especially with OKT3 and polyclonal anti-lymphocyte preparations, is positively correlated with the risk of malignancy.²³ The following discussions of each drug focus on the immunosuppressive drug, sirolimus, may result in fewer malignancies.²² The cumulative amount of immunosuppression, especially with OKT3 and polyclonal anti-lymphocyte preparations, is positively correlated with the risk of malignancy.²³ The following discussions of each drug focus on the

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**TABLE 2. Commonly Used Intravenous-Only Immunosuppressive Drugs**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Trade Name</th>
<th>Pharmacology</th>
<th>Adjustment for Renal/Hepatic Dysfunction</th>
<th>Dosing</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-thymocyte globulin*</td>
<td>ATGAM</td>
<td>Elimination by protein degradation and antibody formation to equine (ATGAM) or rabbit (Thymoglobulin) proteins</td>
<td>No</td>
<td>10–15 mg·kg⁻¹·d⁻¹ IV over 6–8 h for 3–14 d</td>
<td>• ATGAM requires skin test before first dose.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Premedication† is required.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Monitoring is done following CD3 counts.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Various targets include⁴⁻⁴,⁸,¹⁰ CD3 at 5%–10% baseline. (&lt;50 CD3 + cells/mL, 50–100 CD3 + cells/mL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Repeating daily dose when CD3 + cells increase may decrease number of daily doses, especially with Thymoglobulin.¹⁷</td>
</tr>
<tr>
<td>Polyclonal anti-lymphocyte preparations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-thymocyte globulin</td>
<td>Thymoglobulin</td>
<td>Elimination by protein degradation and binding to target cells with opsonization and phagocytosis</td>
<td>No</td>
<td>1.5 mg·kg⁻¹·d⁻¹ IV over 6–8 h for 3–14 d</td>
<td>• CD3 counts do not change.</td>
</tr>
<tr>
<td>Muromonab CD3</td>
<td>Orthoclone, OKT3</td>
<td>Elimination by protein degradation and binding to target cells with opsonization and phagocytosis</td>
<td>No</td>
<td>5 mg/d for 7–14 d</td>
<td>• IL-2R + lymphocytes may be measured but are not generally followed clinically.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Rare cases of hypersensitivity to basiliximab have been reported.⁴⁴</td>
</tr>
<tr>
<td>Anti-cytokine receptor antibodies</td>
<td></td>
<td>Elimination via protein degradation similar to IgG³⁹</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dacizumab</td>
<td>Zenapax</td>
<td></td>
<td></td>
<td>1 mg·kg⁻¹·d⁻¹ within 24 h of transplantation and q 14 d for 4 additional doses. Other dose schedules have been reported.⁴⁵</td>
<td></td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Simulect</td>
<td></td>
<td></td>
<td>20 mg within 2 h of surgery and 4 d postoperatively</td>
<td></td>
</tr>
</tbody>
</table>

HAMA indicates anti-human mouse antibodies.

*Generally administered through central line, although Thymoglobulin has been administered through a peripheral line.⁹
†Premedication for cytokine release syndrome includes antipyretics, intravenous steroids, antihistamines, and H₂ blockers.

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The following discussions of each drug focus on the nonimmune adverse effects.
Polyclonal Anti-Lymphocyte Antibodies

There are 2 general types of anti-lymphocyte antibodies, polyclonal and monoclonal.

**Mechanism of Action.** Polyclonal antibodies (Figure) result in substantial lymphocyte depletion. These preparations contain antibodies to many surface T- and B-cell molecules, including HLA. Antibodies to CD45, a protein that plays a role in T-cell activation, may be particularly important in reversing rejection and inducing tolerance.

Treatment results in complement-dependent opsonization and eventual cell lysis and may contribute to apoptosis of these cells. There may be binding to granulocytes and platelets and a reduction of these cells in peripheral blood. The xenogeneic origin of these polyclonal antibodies can induce a host antibody response that results in acute hypersensitivity response or serum sickness on subsequent exposure. Because batches of polyclonal antibodies vary in potency, monitoring of T cells with flow cytometry is helpful in assessing effectiveness and adjusting dosing.

**Uses and Clinical Trials.** Polyclonal antibodies are used for induction and for the treatment of steroid-resistant rejection in heart transplant recipients. Both ATGAM and Thymoglobulin have Food and Drug Administration (FDA) approval for the management of acute rejection in renal transplant recipients. The few comparisons between ATGAM and Thymoglobulin appear predominantly in the renal transplantation literature. From the limited data available, Thymoglobulin appears to be moderately more efficacious than ATGAM when used for induction therapy or for treating steroid-resistant rejection. ATGAM is also used in the early perioperative management of patients with worsening renal insufficiency when treatment with calcineurin inhibitors is delayed to prevent the development of acute renal failure.

**Adverse Effects.** Because both of these agents are foreign proteins, there is a risk of allergic reactions. Urticaria is more common with ATGAM, and fever, chills, and rash may occur with both compounds, especially after the first dose. The cytokine release syndrome, more common with OKT3, can occur with the polyclonal antibodies. Hypertension, diarrhea, and headache are common. Serum sickness can occur, especially with the equine-derived ATGAM. Leukopenia and thrombocytopenia may require either a reduction in dose or termination of therapy. There is an increased incidence of either primary or reactivation cytomegalovirus infections with the use of both monoclonal and polyclonal antibodies, and prophylactic doses of ganciclovir are given during and for up to 3 months after the course of intravenous anti-lymphocyte therapy.

Monoclonal Anti-Lymphocyte Antibodies

- **Muromonab CD3.** Muromonab-CD3 (OKT3) is a murine antibody that recognizes the epsilon chain of the CD3 molecule on T cells.

- **Mechanism of Action.** CD3 is required for the TCR to generate the intracellular signals that activate T cells.

- **Uses and Clinical Trials.** OKT3 has FDA approval for the treatment of acute allograft rejection in renal transplant patients and for the treatment of steroid-resistant acute allograft rejection in cardiac and hepatic transplant patients. In heart transplant recipients, OKT3 has been used primarily for treatment of steroid-refractory rejection.
pecially when it is associated with hemodynamic compromise, and for induction therapy in recipients at greater risk of rejection.33 OKT3 has a 90% rate of complete or partial reversal of biopsy-proven steroid-resistant rejection in heart transplant recipients.34 The experience with induction therapy with OKT3 has not been as promising as the original studies indicated. Although the incidence of early cellular rejection is lower than with conventional triple-drug therapy, there is an increased incidence of late rejection, a higher rate of humoral (vascular) rejection, and no overall benefit at 1 year after cardiac transplantation.35

• Adverse Effects. Major adverse reactions with OKT3 are due to either cytokine release or development of antibodies to the mouse immunoglobulin. The cytokine release syndrome is the most dramatic and potentially life-threatening adverse response to this antibody.36 The syndrome usually occurs with the first and second doses of drug, and the incidence greatly diminishes with subsequent doses. Symptoms include fever, chills, rigors, dyspnea, wheezing, chest pain or tightness, headache, nausea, vomiting, and diarrhea. Cardiogenic and noncardiogenic pulmonary edema can occur, and both aseptic meningitis and encephalopathy have been reported. Pulmonary edema is uncommon if fluid overload has been corrected before administration. To prevent major manifestations of this syndrome, antipyretics, intravenous steroids, antihistamines, and occasionally H2 blockers are routinely prescribed 1 hour before administration of OKT3. As with polyclonal antibodies, routine prophylactic treatment with ganciclovir is recommended.38 Development of anti-mouse antibodies by the recipient prevents a therapeutic benefit and has been associated with an increased incidence of humoral rejection.14

Anti-Cytokine Receptor Antibodies

Anti-cytokine receptor antibodies used in transplantation are daclizumab and basiliximab. Daclizumab is a humanized anti–IL-2R (CD25) monoclonal antibody that has the murine antigen-binding sequences molecularly engrafted onto a human antibody. Basiliximab is a chimeric (mouse/human) anti–IL-2R monoclonal antibody with mouse variable regions fused to the constant regions of a human IgG.

Mechanism of Action

Both basiliximab and daclizumab bind the α subunit of IL-2R expressed on antigen-activated T cells. This prevents binding of IL-2 to the IL-2R, inhibiting proliferation of T cells.40,41 However, this action alone is not sufficient to prevent rejection, and there appear to be other important, although incompletely understood, actions of these antibodies.36,42

Uses and Clinical Trials

Basiliximab and daclizumab are used as induction therapy in many heart transplantation centers. Some centers reserve these agents only for high-risk recipients. Both are FDA approved for the prophylaxis of acute organ rejection in patients receiving renal transplants in a regimen that includes cyclosporine and corticosteroids. One small trial randomized 55 heart transplant recipients receiving prednisone, mycophenolate mofetil, and cyclosporine to daclizumab or no additional therapy.40 During the induction period (3 months), acute rejection, defined as an endomyocardial biopsy grade of ≥2, was decreased from 63% to 18% (P = 0.04). Mortality was not different. The need for anti-lymphocyte therapy and the frequency of development of anti-HLA antibodies were significantly reduced. Duration of hospitalization, readmission, infections, and malignancy were not different, although there was a trend for the duration of hospitalization to be shorter in the daclizumab group. Several randomized studies in renal transplant recipients have shown similar results, demonstrating a 28% to 37% reduction in biopsy-proven rejection at 6 to 12 months in recipients of a first renal transplant.31,43,44 However, a recent, as-yet-unpublished, double-blind, randomized, controlled trial comparing daclizumab with placebo in 434 heart transplant recipients demonstrated an increase in mortality in the daclizumab group.45

Adverse Effects

Few serious common adverse events have been reported. Cytokine release syndrome does not occur after administration of these drugs, and there has been no reported increased risk of infection or malignancy.40,41,43,44 Hypersensitivity has been reported with initial exposure and reexposure to both basiliximab and daclizumab. The second dose should be withheld if complications such as hypersensitivity occur.46–48

Table 3 describes the costs of intravenous drugs commonly used for indication or antirejection immunosuppression. Methyl prednisolone is included in Table 2 but is described in Part II with other corticosteroids.29–31,37,39,49,50

Acknowledgment

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Drug Therapy in the Heart Transplant Recipient: Part I: Cardiac Rejection and Immunosuppressive Drugs
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