19 Monoclonal Antibodies in Solid Organ Transplantation

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INTRODUCTION

Administration of targeted immunosuppression, in the form of genetically engineered antibodies, is commonplace in solid organ transplantation. Polyclonal antibodies, such as rabbit antithymocyte globulin, offer global immunosuppression by targeting several cell surface antigens on B and T lymphocytes. However, secondary to their broad therapeutic targets, they are associated with infection, infusion-related reactions, inter-batch variability, and posttransplant malignancies. Nevertheless, polyclonal antibodies are still commonly administered for induction and treatment of allograft rejection and offer an important role in current solid organ transplantation, which is beyond the scope of this chapter.

In an attempt to target solid organ transplant immunosuppression, monoclonal antibodies directed against key steps in specific immunologic pathways were introduced. The first agent, muromonab-CD3 (OKT3), was initially introduced in the early 1980s for the treatment of allograft rejection (Morris 2004). The use of monoclonal antibodies has evolved and expanded over the past two decades and today monoclonal antibodies are routinely included as part of the overall immunosuppression regimen. Both the innate and adaptive immune systems have multiple components and signal transduction pathways aimed at protecting the host from a foreign body, such as transplanted tissue. The ultimate goal of posttransplant immunosuppression is tolerance, a state in which the host immune system recognizes the foreign tissue but does not react to it. This goal has yet to be achieved under modern immunosuppression secondary to immune system redundancy as well as the toxicity of currently available agents. Therefore, monoclonal antibodies are used to provide targeted, immediate immunomodulation aimed at attenuating the overall immune response. Specifically, monoclonal antibodies have been used to (1) decrease the inherent immunoreactivity of the potential transplant recipient prior to engraftment, (2) induce global immunosuppression at the time of transplantation allowing for modified introduction of other immunosuppressive agents (calcineurin inhibitors or corticosteroids), (3) spare exposure to maintenance immunosuppressive agents, and (4) treat acute allograft rejection. Monoclonal antibody selection, as well as dose, is based on patient-specific factors, such as indication for transplantation, type of organ being transplanted, and the long-term immunosuppression objective. To understand the approach that the transplant clinician uses to determine which agent to administer and when, it is necessary to briefly describe how immunoreactivity can be predicted and review the immunological basis for the use and development of monoclonal antibodies in solid organ transplantation.

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IMMUNOLOGIC TARGETS: RATIONAL DEVELOPMENT/ USE OF MONOCLONAL ANTIBODIES IN ORGAN TRANSPLANT

The rational use of monoclonal antibodies in transplantation is focused on the prevention of host immune recognition of donor tissue. There are two ways in which allograft tissue can be immediately impaired secondary to the host immune response: complement-dependent antibody-mediated cell lysis (antibody-mediated rejection) and T-cell-mediated parenchymal

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Monoclonal antibody	Molecular weight	Animal epitope	Molecular target	Target cells	Use
Alemtuzumab (Campath-1H®)	150 kDa	Murine/ human	CD52	Peripheral blood lymphocytes, natural killer cells, monocytes, macrophages, thymocytes	Induction Antibody-mediated rejection
Daclizumab (Zenapax®)	14.4 kDa	Murine/ human	CD25 alpha subunit	IL2-dependent T-lymphocyte activation	Induction
Basiliximab (Simulect®)	14.4 kDa	Murine/ human	CD25 alpha subunit	IL2-dependent T-lymphocyte activation	Induction
Muromonab-OKT3 (Orthoclone-OKT3®)	75 kDa	Murine	CD3	T lymphocytes (CD2, CD4, CD8)	Treatment of polyclonal antibody-resistant cellular-mediated rejection
Rituximab (Rituxan®)	145 kDa	Murine/ human	CD20	B lymphocytes	Desensitization Antibody-mediated rejection Focal segmental glomerulosclerosis
Belatacept (Nulojix®)	90 kDa	Humanized	CD80 and CD86	T lymphocytes	Maintenance immunosuppression
Eculizumab (Soliris®)	148 kDa	Murine/ human	C5	Block formation of membrane attack complex	Desensitization Antibody-mediated rejection Hemolytic uremic syndrome

Table 19.1 ■ Use of monoclonal antibodies in solid organ transplantation.

destruction leading to localized allograft inflammation and arteritis (cellular-mediated rejection) (Halloran 2004). Pre-transplant screening for antibodies against donor tissues has significantly reduced the incidence and severity of antibody-mediated rejection. However, as will be discussed, preferential destruction of cells that produce these antibodies using monoclonal technology, such as rituximab, prior to transplant has become an option for recipients with preformed alloantibodies. Prevention and treatment of cellular-mediated rejection, therefore, is the main focus of maintenance immunosuppression and the rationale for use of monoclonal antibodies in the posttransplant period. Cellular-mediated rejection is characterized by initial recognition of donor tissue by T cells. This leads to a complex signal transduction pathway traditionally described as three signals (Halloran 2004):

- Signal 1: Donor antigens are presented to T cells leading to activation, characterized by T-cell proliferation.
- Signal 2: CD80 and CD86 complex with CD28 on the T-cell surface activating signal transduction pathways (calcineurin, mitogen-activated protein kinase, protein kinase C, nuclear factor kappa B) which leads to further T-cell activation, cytokine release, and expression of the interleukin-2 (IL2) receptor (CD25).
- Signal 3: IL-2 and other growth factors cause the activation of the cell cycle and T-cell proliferation (Halloran 2004).

Monoclonal antibodies have been developed against various targets within this pathway to prevent propagation and lymphocyte proliferation providing profound immunosuppression (Table 19.1). Monoclonal antibodies that were originally developed for treatment of various malignancies have also been employed as immunosuppressant agents in solid organ recipients. Use of these agents must be balanced with maintenance immunosuppression to minimize the patient's risk of infection or malignancy from over-immunosuppression. Table 19.2 describes common adverse effects associated with maintenance immunosuppressant medications. Table 19.3 summarizes recent trends regarding the use of monoclonal antibodies for induction immunosuppression in solid organ transplantation.

■ Monoclonal Antibodies Administered Pre-transplant

Immunologic barriers to solid organ transplantation are common. Improved management of end-stage organ disease has increased the number of potential organ recipients and produced a significant shortage of organs available for transplant in comparison to the growing demand. Therefore, clinicians have sought to transplant across previously contraindicated immunologic barriers. In addition, more patients are surviving through their first transplant and are now waiting for a subsequent transplant. Monoclonal antibodies are now

	Hypertension	Hyperlipidemia	Hyperglycemia	Hematologic	Renal dysfunction	Dermatologic
Corticosteroids	+	++	++	–	–	++
Cyclosporine	+++	+++	++	+	+++	++
Tacrolimus	+++	+++	+++	+++	+++	++
Mycophenolate mofetil[a]	–	–	–	+++		–
Sirolimus	++	+++	–	+++	+	+++
Everolimus	++	+++	–	+++	+	+++
Belatacept	–	–	–	–	–	–

Incidence based on manufacturer package insert clinical trial approval reports, +<1 %, ++ 1–10 %, +++>10 %
[a]Adverse effects reported for mycophenolate mofetil (CellCept®) are based on clinical trials using this agent in combination with cyclosporine or tacrolimus and corticosteroids, values modified to account for concurrent agents

Table 19.2 ■ Complications of current maintenance immunosuppressants.

Organ	Who receive induction (%)	Alemtuzumab (%)	Basiliximab (%)	Daclizumab (%)	Muromonab (%)
Kidney	72	7	20	10	0
Pancreas	80	43	15	5	0
Heart	47	0	10	15	4
Lung	50	3	23	15	0
Liver	11	2	6	5	0
Intestine	50	19	0	9	0

Based on reported immunosuppression trends from 1994 to 2004, with data Adapted from Meier-Kriesche et al. (2006)

Table 19.3 ■ Current trends of monoclonal antibody induction use in solid organ transplantation.

being employed prior to transplant to desensitize the recipient's immune system. Desensitization is a strategy where immunosuppression is administered prior to transplant to prevent hyperacute or early rejection in patients who are known to have circulating antibodies against other human antigens. This strategy is generally reserved for patients who are "highly sensitized" during their evaluation for transplant. As the long-term significance of these sensitizing events is better understood, varying degrees of "desensitization" therapy are initiated based upon varying levels of sensitization. The long-term impact of this empirical therapy is yet to be defined. Specifically, as a patient develops end-stage organ disease, their medical and immunologic profiles are characterized. Blood samples from these potential recipients are screened for the presence of antibodies against the major histocompatibility complexes (MHC) on the surface of other human cells, specifically human leukocyte antigens (HLA). Potential recipients who have received blood products, previous organ transplants, or have a history of pregnancy are at higher risk for the development of antibodies against HLA. In addition, all humans have preformed IgG and IgM antibodies against the major blood group antigens (A, B, AB, and A1) (Reid and Olsson 2005). These antibodies will recognize donor tissue and quickly destroy (hyperacute rejection) the implanted organ if the tissue contains previously recognized HLA within minutes to hours following transplant. Therefore, it is necessary to evaluate the presence of preformed circulating antibodies against HLA in the potential organ recipients. Some centers will implement desensitization, which incorporates monoclonal antibodies prior to transplant to diminish the production of antibodies against a new organ, allowing for transplant across this immunologic barrier.

■ Monoclonal Antibodies Administered at the Time of Transplant

Current maintenance immunosuppression is aimed at various targets within the immune system to halt its signal transduction pathway. Available agents, although effective, are associated with significant patient and allograft adverse effects, which are correlated with long-term exposure (Table 19.2). The leading cause of death in noncardiac transplant recipients is a

cardiovascular event. These cardiovascular events have been linked to long-term corticosteroid exposure. In addition, chronic administration of calcineurin inhibitors (cyclosporine and tacrolimus) is also associated with acute and chronic kidney dysfunction leading to hemodialysis or need for a kidney transplant. Monoclonal antibodies given at the time of transplant (induction) have been used to decrease the need for corticosteroids and allow for the delay or a reduction in the amount of calcineurin inhibitor used. Determination of the solid organ transplant recipient's immunologic risk at the time of transplant is necessary to determine which monoclonal antibody to use in order to minimize the risk of early acute rejection and graft loss. Recipients are stratified based on several donor, allograft, and recipient variables to determine their immunologic risk. Patients at high risk for acute rejection or those in which maintenance immunosuppression is going to be minimized should receive a polyclonal or monoclonal antibody that provides cellular apoptosis, for example, alemtuzumab or rabbit antithymocyte globulin. Recipients at low risk for acute rejection may receive a monoclonal antibody which provides immunomodulation without lymphocyte depletion, such as basiliximab.

Several important pharmacokinetic parameters must be considered when these agents are administered to the various organ transplant recipients. The volume of distribution, biological half-life, and total-body clearance can differ significantly from a kidney transplant recipient to a heart transplant recipient. Clinicians must consider when to administer monoclonal antibodies in different transplant populations to maximize efficacy and minimize toxicity. For example, heart and liver transplant recipients tend to lose large volumes of blood around the time of transplant; therefore, intraoperative administration may not be the optimal time to administer a monoclonal antibody since a large portion may be lost during surgery. Monoclonal antibodies are also removed by plasma exchange procedures, such as plasmapheresis, which may be performed during the perioperative period in solid organ transplant recipients (Nojima et al. 2005).

■ Monoclonal Antibodies Administered Following Transplant

Monoclonal antibodies given following transplantation are used to treat allograft rejection and more recently as maintenance immunosuppressants. Administration of these agents is mainly reserved for severe allograft rejection in which the immunologic insult must be controlled quickly. Under normal homeostatic conditions the humoral immune system provides immediate control of infectious pathogens through secretion of antibodies. Cell-mediated immunity, in addition to fighting infections, provides surveillance against the production of mutant cells capable of oncogenesis. Interruption of either of these immune systems through the use of monoclonal antibodies places these patients at significant risk for infection and malignancy. Careful post-administration assessment of infection and posttransplant malignancy is commonplace. While those monoclonal antibodies employed as maintenance immunosuppressants have been developed to decrease the toxicity of long-term exposure to traditional agents such as calcineurin inhibitors, which can lead to chronic kidney damage in all organ transplant recipients, the use of these monoclonal antibodies is not without their own risks.

SPECIFIC AGENTS USED IN SOLID ORGAN TRANSPLANT

■ Muromonab

Muromonab was the first monoclonal antibody used in solid organ transplantation. Muromonab is a murine monoclonal antibody directed against human CD3 receptor, which is situated on the T-cell antigen receptor of mature T cells, inducing apoptosis of the target cell (Wilde and Goa 1996). Cells which display the CD3 receptor include CD2-, CD4-, and CD8-positive lymphocytes (Ortho Biotech 2004). Other investigators suggest that muromonab may also induce CD3 complex shedding, lymphocyte adhesion molecule expression causing peripheral endothelial adhesion, and cell-mediated cytolysis (Wilde and Goa 1996; Ortho Biotech 2004; Buysmann et al. 1996; Magnussen et al. 1994; Wong et al. 1990). Muromonab is approved for the treatment of kidney allograft rejection and steroid-resistant rejection in heart transplant recipients (Ortho biotech 2004). Muromonab was initially employed as an induction agent for kidney transplant recipients, in conjunction with cyclosporine, azathioprine, and corticosteroids. When compared to patients who received no muromonab induction, the rate of acute rejection was lower and the time to first acute rejection was substantially greater (Wilde and Goa 1996). Liver recipients with renal dysfunction at the time of transplant who received muromonab induction were also able to run their posttransplant cyclosporine levels lower without an increased incidence of acute rejection (Wilde and Goa 1996). Therefore, administration of OKT3 enabled preservation of renal function in the setting of reduced calcineurin inhibitor exposure when compared to those who did not receive muromonab (Wilde and Goa 1996). The use of OKT3 as an induction agent is nearly extinct with the introduction of newer agents that have more favorable side effect profiles.

Today, muromonab is of historical value as it is no longer being manufactured. Although prior to its

withdrawal from the market, it was reserved for treatment of refractory rejection. Muromonab is extremely effective at halting most corticosteroid as well as polyclonal antibody-resistant rejections. These rejections are treated with 5 mg of muromonab given daily for 7–14 days (Ortho Biotech 2004). The dose and duration of therapy is often dependent on clinical or biopsy resolution of rejection or may be correlated with circulating CD3 cell concentrations in the serum.

Most patients who are exposed to OKT3 will develop human anti-mouse antibodies (HAMA) following initial exposure. These IgG antibodies may lead to decreased efficacy of subsequent treatment courses, but premedication with corticosteroids or antiproliferative agents during initial therapy may reduce their development (Wilde and Goa 1996). Following administration, in vitro data indicates that a serum concentration of 1000 μg/L is required to inhibit cytotoxic T-cell function (Wilde and Goa 1996). In vivo concentrations near the in vivo threshold immediately (1 h) following administration but diminish significantly by 24 h (Wilde and Goa 1996). Steady-state concentrations of 900 ng/mL can be achieved after three doses, with a plasma elimination half-life of 18 h when used for treatment of rejection and 36 h when used for induction (Wilde and Goa 1996; Ortho Biotech 2004).

Muromonab administration is associated with significant acute and chronic adverse effects. Immediately following administration, patients will experience a characteristic OKT3 cytokine release syndrome. The etiology of this syndrome is characterized by the pharmacodynamic interaction the OKT3 molecule has at the CD3 receptor. Muromonab will stimulate the target cell following its interaction with the CD3 receptor prior to inducing cell death. Consequently, CD3 cell stimulation leads to cytokine production and release, which is compounded by acute cellular apoptosis leading to cell lysis and release of the intracellular contents. The cytokine release syndrome associated with muromonab manifests as high fever, chills, rigors, diarrhea, capillary leak, and in some cases aseptic meningitis (Wilde and Goa 1996). Capillary leak has been correlated with increased tumor necrosis factor release leading to an initial increase in cardiac output secondary to decreased peripheral vascular resistance, followed by a reduction in right heart filling pressures which leads to a decrease in stroke volume (Wilde and Goa 1996). Sequelae of this cytokine release syndrome can occur immediately, within 30–60 min, and last up to 48 h following administration (Wilde and Goa 1996; Ortho Biotech 2004). This syndrome appears to be the most severe following the initial dose when the highest inoculum of cells is present in the patient's serum or when preformed antibodies against the mouse epitope exist. Subsequent doses appear to be better tolerated, though cytokine release syndrome has been reported after five doses, typically when the dose has been increased or the CD3-positive cell population has rebounded from previous dose baseline (Wilde and Goa 1996). Pretreatment against the effects of this cytokine release is necessary to minimize the host response. Specifically, corticosteroids to prevent cellular response to cytokines, nonsteroidal anti-inflammatory agents to prevent sequelae of the arachidonic acid cascade, acetaminophen to halt the effects of centrally acting prostaglandins, and diphenhydramine to attenuate the recipient's response to histamine.

In addition to immediate adverse effects, the potency of muromonab has been associated with a high incidence of posttransplant lymphoproliferative disease and viral infections. For all patients, the 10-year cumulative incidence of posttransplant lymphoproliferative disease is 1.6 % (Opelz and Dohler 2004). Review of large transplant databases revealed that deceased donor kidney transplant recipients who received muromonab for induction or treatment had a cumulative incidence of posttransplant lymphoproliferative disease that was three times higher than those who did not received muromonab or other T-cell depleting induction (Opelz and Dohler 2004). This observation may be multifactorial. It is well known that posttransplant lymphoproliferative disease may be induced secondary to Epstein-Barr viral B-cell malignant transformation. Muromonab's potent inhibition of T lymphocytes over a sustained period of time diminishes the immune system's normal surveillance and destruction of malignant cell lines, consequently leading to unopposed transformed B-cell proliferation and subsequent posttransplant lymphoma (Opelz and Dohler 2004).

Early use and development of muromonab in solid organ transplantation was beneficial for the novel development and use of newer monoclonal agents. The immunodepleting potency of muromonab, combined with the significant risk for malignancy, has made its use obsolete in the setting of modern transplantation. However, this agent still serves as a template for treatment of severe allograft rejection and the use of monoclonal antibodies posttransplant.

■ Interleukin-2 Receptor Antagonists

Interleukin-2 antagonists were the next monoclonal antibodies to be used and were specifically developed for use in solid organ transplantation. As previously mentioned, monoclonal antibody use and development in solid organ transplantation is rational. The IL-2 receptor was targeted for several reasons. Interleukin-2, the ligand for the IL-2 receptor, is a highly conserved protein, with only a single gene locus on chromosome 4 (Church 2003). Animal IL-2 knockout models have

decreased lymphocyte function at 2–4 weeks of age and early mortality at 6–9 weeks of age (Chen et al. 2002). These models also display significantly diminished myelopoiesis leading to severe anemia and global bone marrow failure (Chen et al. 2002). This observation confirms the significant role that IL-2 and the IL-2 receptor complex play in immunity. The function and biological effect of IL-2 binding to the IL-2 receptor was first reported by Robb and colleagues in 1981 (Robb et al. 1981). This in vitro study evaluated murine lymphocytes and found that the IL-2 receptor is only present on activated cells (CD4+ and CD8+) (Church 2003). Uchiyama and colleagues (1981) reported one of the first monoclonal antibodies developed against activated human T cells. This compound displayed in vitro preferential activity against activated T cells, including terminally mature T cells, but did not exhibit activity against B cells or monocytes (Uchiyama et al. 1981). Later it was determined that this antibody actually bound to the alpha subunit of the activated T-cell receptor, CD25 (Church 2003). The actual T-cell receptor is made up of three subunits, alpha, beta, and gamma. When the beta and gamma subunits combine, they can only be stimulated by high concentrations of IL-2; however, in conjunction with the alpha subunit, the receptor shows high affinity for IL-2 and can be stimulated at very low concentrations. The expression of IL-2 and the IL-2 receptor alpha region is highly regulated at the DNA transcription level and is induced following T-cell activation (Shibuya et al. 1990). The alpha subunit is continuously expressed during allograft rejection, T-cell-mediated autoimmune diseases, and malignancies (Church 2003). The beta and gamma subunits, however, have constitutive expression, resulting in low levels of expression in resting T lymphocytes (Vincenti et al. 1997, 1998). There is no constitutive expression of IL-2 or the alpha receptor subunit (Shibuya et al. 1990; Noguchi et al. 1993). Both, the beta and gamma subunits, have similar molecular structures and are members of the cytokine receptor superfamily, but are structurally dissimilar to the alpha subunit (Noguchi et al. 1993). Therefore, the alpha subunit (CD25) became a rational target for monoclonal development since it is only expressed on activated T cells. Blockade of the CD25 receptor was to halt the activity of IL-2, thereby decreasing proliferation and clonal expansion of T cells when activated by foreign donor antigens.

DACLIZUMAB

In 1997, daclizumab became the first anti-CD25 monoclonal antibody approved for use in the prevention of allograft rejection in kidney transplant recipients, when combined with cyclosporine and corticosteroids. Daclizumab was the first "humanized" monoclonal antibody approved in the United States for human administration (Tsurushita et al. 2005). The daclizumab molecule is a humanized IgG1 adapted from a mouse antibody against the alpha portion of the IL-2 receptor (Uchiyama et al. 1981). Daclizumab was developed as an alternative to the initial mouse antibody developed against the IL-2 receptor. The mouse antibody led to the development of human anti-mouse antibodies (HAMA) and inability to administer subsequent doses. Although daclizumab bound with one-third the affinity for the T-cell receptor site when compared to the original mouse molecule, it was still able to exhibit a high-binding capacity ($Ka = 3 \times 10^9\ M^{-1}$) (Tsurushita et al. 2005; Queen et al. 1988). A daclizumab serum concentration of 1 μg/mL is required for 50 % inhibition of antigen-induced T-cell proliferation (Junghans et al. 1990). Early, phase I clinical trials in kidney transplant recipients, who received corticosteroids in combination with cyclosporine and azathioprine, used five doses of daclizumab (Vincenti et al. 1997). Pharmacokinetic studies revealed a mean serum half-life of 11.4 days, a steady-state volume of distribution of 5 l, and displayed weight-dependent elimination. There was no change in the number of circulating CD3-positive cells following administration. Five doses of 1 mg per kg body weight given every other week were required to produce the serum concentrations needed to achieve 90 % inhibition of T-cell proliferation for 12 weeks. One patient did develop neutralizing antibodies against the daclizumab molecule after receiving weekly doses for 2 weeks. Saturation of the IL-2 receptor did not change. Intravenous doses were well tolerated with no infusion-related reactions. No infection or malignancies were reported up to 1 year following daclizumab administration. The authors concluded that daclizumab stayed within the intravascular space and doses should be based on patient weight at the time of transplant (Vincenti et al. 1997). Subsequent premarketing clinical trials confirmed these results and dosing schematic and were able to show that daclizumab administration reduced the incidence of acute rejection by 13 % in low-risk kidney transplant recipients (Vincenti et al. 1998). Following daclizumab's approval, several trials have been conducted using various dosing regimens and immunosuppression combinations within various solid organ recipients. Secondary to low utilization in solid organ transplant, however, its manufacturing has recently been halted.

BASILIXIMAB

Basiliximab was developed as a more potent anti-IL-2 receptor antagonist when compared to daclizumab and may have several logistical advantages.

Basiliximab, in combination with cyclosporine and corticosteroids, was approved for the prevention of acute allograft rejection in renal transplant recipients in May of 1998. Basiliximab is a murine/human (chimeric) monoclonal antibody directed against the alpha subunit of the IL-2 receptor on the surface of activated T lymphocytes. The antibody is produced from genetically engineered mouse myeloma cells. The variable region of the purified monoclonal antibody is comprised of murine hypervariable region, RFT5, which selectively binds to the IL-2 receptor alpha region. The constant region is made up of human IgG1 and kappa light chains (Novartis Pharmaceuticals 2005). Since the variable region is the only portion with a nonhuman epitope, there appears to be low antigenicity and increased circulating half-life associated with its administration (Amlot et al. 1995). Following administration, basiliximab rapidly binds to the alpha region of the IL-2 receptor and serves as a competitive antagonist against IL-2. The estimated receptor binding affinity (Ka) is 1×10^{10} M^{-1}, which is three times more potent than daclizumab (Novartis Pharmaceuticals 2005). Complete inhibition of the CD25 receptor occurs after the serum concentration of basiliximab exceeds 0.2 μg/mL and inhibition correlated with increasing dose (Novartis Pharmaceuticals 2005; Kovarik et al. 1996). Initial dose finding studies of basiliximab were similar to daclizumab. Basiliximab, combined with cyclosporine and corticosteroids, was administered to adult kidney transplant recipients for the prevention of acute cellular rejection.

Kovarik and colleagues (1997) performed a multicenter, open-label pharmacodynamic analysis evaluating basiliximab dose escalation in adult patients undergoing primary renal transplantation. Patients received a total of 40 or 60 mg of basiliximab in combination with cyclosporine, corticosteroids, and azathioprine. Thirty-two patients were evaluated and were primarily young (34 ± 12 years), Caucasian (29/32) males (23/32). Basiliximab infusions were well tolerated without changes in blood pressure, temperature, or hypersensitivity reactions. Thirty patients underwent pharmacokinetic evaluation. Basiliximab blood concentrations showed biphasic elimination with an average terminal half-life of 6.5 days. Significant intra- and interpatient variability in observed volume of distribution and drug clearance was observed. This could not be corrected through body weight adjustment. Gender did not appear to influence the pharmacokinetic parameters of basiliximab; however, this cohort contained only a small number of female recipients that may have limited the detection of a difference.

Results also indicated that the use of basiliximab with a combination of cyclosporine, corticosteroids, and azathioprine may be an inadequate immunosuppression regimen to prevent acute rejection, especially if cyclosporine initiation is delayed posttransplant. A total of 22 patients had an acute rejection episode, 16 patients in the 40 mg groups and 6 in the 60 mg group. These rejections appeared within the first 2 weeks following transplantation with a mean time to rejection of 11 days. The study was designed for cyclosporine to begin on day 10 posttransplant. Also, three patients experienced graft loss, two of which were immunologically mediated. There was no difference in the basiliximab serum concentration in the patients who experienced rejection versus those who did not. The authors concluded that increased cyclosporine concentrations, which would inhibit IL-2 production, within the first few days posttransplant may increase the efficacy of basiliximab when used for induction (Kovarik et al. 1996).

The clinical efficacy of basiliximab has been confirmed in several prospective post-marketing trials. Currently, the recommended basiliximab dosing regimen is a total dose of 40 mg, with 20 mg administered 2 h prior to transplanted organ reperfusion and a subsequent 20 mg dose on postoperative day 4.

IL-2 receptor antagonists are currently used in all solid organ transplant populations for induction (Table 19.3), but are only approved for use in kidney transplant recipients. Administration does not reduce the total number of circulating lymphocytes or the number of T lymphocytes expressing other markers of activations, such as CD26, CD38, CD54, CD69, or HLA-DR (Chapman and Keating 2003). Consequently, it is necessary that additional immunosuppressive agents, such a calcineurin inhibitors and antiproliferative agents, be administered as soon as possible to decrease the risk of early acute rejection.

The advantage of IL-2 receptor antagonists is that they confer a decreased risk of infusion-related reactions, posttransplant infection, and malignancy when compared to immunodepleting agents. The use of these agents has increased since the introduction of more potent maintenance immunosuppressant agents, and they are now the agents of choice in kidney, lung, liver, and pancreas transplant recipients. Although these agents have been evaluated in organ recipients who are at high risk for acute rejection, they are mainly reserved for patients who are at low to moderate risk. Also, these agents are still being evaluated for use in immunosuppression protocols which withdraw or avoid corticosteroids or calcineurin inhibitors.

There may be an increased risk of anti-idiotypic IgE anaphylactic reaction in patients who receive repeat courses of IL-2 receptor antagonists. Two published case reports describe patients who had been previously exposed to an IL-2 receptor antagonist and upon subsequent exposure developed dyspnea, chest

tightness, rash, and angioedema. However, in one case where basiliximab was the offending agent, daclizumab was successfully administered following a negative skin test. Therefore, caution may be warranted in patients who receive a dose of an IL-2 antagonist without concomitant corticosteroids following previous exposure in the past 6 months when circulating antibodies are expected to be present.

■ Alemtuzumab

Alemtuzumab is a recombinant DNA-derived, humanized, rat IgG1κ monoclonal antibody targeting the 21–28 kDa cell surface protein glycoprotein CD52, which is produced in a Chinese hamster ovary cell suspension (Genzyme Corporation 2009; Kneuchtle et al. 2004). Initially, the first anti-CD52 antibodies were developed from rat hybrid antibodies that were produced to lyse lymphocytes in the presence of complement (Morris and Russell 2006). Campath-1 M was the first agent developed. This molecule was a rat IgM antibody which produced little biological effect. In contrast, the rat IgG (Campath-1G) produced profound lymphopenia (Morris and Russell 2006). In order to prevent the formation of antibodies against the rat IgG, the molecule was humanized and called alemtuzumab or Campath-1H (Morris and Russell 2006). The biologic effects of alemtuzumab are the same as Campath-1G and include complement-mediated cell lysis, antibody-mediated cytotoxicity, and target cell apoptosis (Magliocca and Knechtle 2006). The CD52 receptors account for 5 % of lymphocyte surface antigens (Morris and Russell 2006). Cells which express the CD52 antigen include T and B lymphocytes, natural killer cells, monocytes, macrophages, and dendritic cells (Genzyme Corporation 2009; Bloom et al. 2006). However, plasma cells and memory type cells appear to be unaffected by alemtuzumab (Magliocca and Knechtle 2006). Following administration, a marked decrease in circulating lymphocytes is observed. Use in the hematology population indicates that this effect is dose dependent (see Chap. 17). However, single doses of 30 mg or two doses of 20 mg are currently used in the solid organ transplant population.

The plasma elimination half-life after single doses is reported to be around 12 days, and the molecule may be removed by posttransplant plasmapheresis (for more details, please see Chap. 17) (Magliocca and Knechtle 2006). The biological activity of alemtuzumab, however, may last up to several months. One in vivo study of kidney transplant recipients aimed to observe the recovery and function of lymphocytes following administration of 40 mg of alemtuzumab (Bloom et al. 2006). Authors reported a 2-log reduction in peripheral lymphocytes following administration. Absolute lymphocyte counts at 12 months remained markedly depleted, falling below 50 % of their original baseline. Monocytes and B lymphocytes were the first cell lines to recover at 3–12 months post-administration. T lymphocytes returned to 50 % of their baseline value by 36 months.

Currently, alemtuzumab is only FDA approved for the treatment of B-cell chronic lymphocytic leukemia. The first report of alemtuzumab use in solid organ transplantation appeared in 1991. Friend and colleagues (1991) published a case series on the use of alemtuzumab to reverse acute rejection in renal transplant recipients. Shortly thereafter, Calne and colleagues (1999) issued the first report of alemtuzumab use as an induction agent. The authors reported the results of 31 consecutive renal transplant recipients. Patients received two 20 mg doses of alemtuzumab; the first dose was given in the operating room and the second dose was given on postoperative day 1. Patients were initiated on low-dose cyclosporine monotherapy 72 h after transplant, with a target trough range of 75–125 ng/mL. Six patients experienced corticosteroid responsive rejection (20 %). Three of these were maintained on corticosteroids and azathioprine following rejection, while the other three remained on cyclosporine monotherapy. Allografts remained functional in 94 % (29/31) of patients at 15–28 months posttransplant (Calne et al. 1999).

The largest multicenter randomized controlled trial assessing alemtuzumab induction in low- and high-risk renal transplant recipients showed that biopsy-confirmed acute rejection was reduced in low-risk patients receiving alemtuzumab when compared to basiliximab after 3 years of follow-up. In high-risk renal transplant patients, alemtuzumab and Thymoglobulin® appeared to have similar efficacy. However, patients who received alemtuzumab had increased rates of late rejections (between 12 and 36 months) when compared to conventional therapies (8 % versus 3 %, $p = 0.03$). All patients were withdrawn from steroids by postoperative day 5. Adverse effects were similar with more leukopenia observed in the alemtuzumab group (54 %) compared to basiliximab (29 %), and more serious adverse effects related to malignancy were seen with alemtuzumab (5 %) when compared to a composite of all basiliximab- and Thymoglobulin®-treated patients (1 %). However, overall adverse events related to malignancy were similar between treatment groups (Hanaway et al. 2011).

Currently, the most data on the use of alemtuzumab in solid organ transplantation are with kidney transplant recipients. However, alemtuzumab is currently being used for induction and for treatment of rejection in other organs as well (Morris and Russell 2006). In the most recent review of immunosuppression trends in the United States, alemtuzumab use

markedly increased from 2001 to 2004, with use primarily limited to induction of immunosuppression (see Table 19.3).

In 2004, alemtuzumab was the predominant agent used for induction in both pancreas and intestinal transplant recipients (Meier-Kriesche et al. 2006). Use in liver transplant has been limited but has appeared in a couple of published trials. Specific findings from these trials indicate that patients without hepatitis C were able to tolerate lower levels of calcineurin inhibitors which corresponded to lower serum creatinine levels at 1-year posttransplant (Tzakis et al. 2004). In contrast, administration of alemtuzumab positively correlated with early recurrence of hepatitis C viral replication (Marcos et al. 2004).

Alemtuzumab in heart transplantation has been rarely reported in the literature with only 2 % of heart transplant patients receiving alemtuzumab for induction in 2004 (Meier-Kriesche et al. 2006). Teuteberg and colleagues recently published a retrospective study on 1-year outcomes on the use of alemtuzumab for induction in cardiac transplantation at a single center. Freedom from rejection was higher in the alemtuzumab group (versus no induction); however, survival at 1 year was similar between groups with more adverse effects in the alemtuzumab group (Teuteberg et al. 2010). Despite this recent publication, there remains a paucity of data in the cardiac transplant population regarding alemtuzumab for induction immunosuppression, which has resulted in limited use in this population.

A retrospective review of 5-year outcomes on the use of alemtuzumab induction in lung transplant recipients at a single center showed an improvement in patient and graft survival with alemtuzumab compared to no induction or daclizumab induction and higher rates of freedom from cellular rejection than no induction or Thymoglobulin® or daclizumab induction (Shyu et al. 2011). The results of the previous study are consistent with another retrospective study that showed decreased rejection rates with alemtuzumab induction in comparison to Thymoglobulin® and daclizumab in lung transplant patients (McCurry et al. 2005). In 2004, 3 % of lung transplant recipients received alemtuzumab for induction (Meier-Kriesche et al. 2006); however, this number may be increasing as more data emerges regarding alemtuzumab use in the lung transplant population.

Alemtuzumab induction has allowed for early withdrawal of corticosteroids in several clinical trials, thereby decreasing long-term steroid exposure. This may lead to improved clinical outcomes since the use of steroids has been correlated with an increased incidence of cardiovascular disease, endocrine, and metabolic side effects. However, the long-term benefit of steroid withdrawal after alemtuzumab induction requires further study. Several trials have also shown success with using low-dose calcineurin inhibitors with alemtuzumab induction. However, early trials in which calcineurin inhibitor avoidance was initiated, the rate of early acute antibody-mediated rejection was 17 % compared to 10 % under traditional immunosuppression which included calcineurin inhibitors (Magliocca and Knechtle 2006).

The infusion of alemtuzumab is well tolerated. In general, induction doses are administered immediately preceding reperfusion of the transplanted allograft. Pretreatment with corticosteroids, diphenhydramine, and acetaminophen is generally advised to prevent sequelae from cellular apoptosis. However, cytokine release associated with alemtuzumab is insignificant in comparison to other agents (Morris and Russell 2006).

Until recently, there were few published experiences detailing long-term outcomes in patients who received alemtuzumab induction (Magliocca and Knechtle 2006). Initially clinicians were concerned that the profound lymphodepletion that was observed following administration would lead to a significant increase in the number of severe infections. Therefore, lymphocyte response to donor antigens following alemtuzumab administration was also evaluated in vitro (Bloom et al. 2006). Lymphocytes from patients treated with alemtuzumab were able to respond to donor antigens and cytokines. However, a small subset of patients were hyporesponsive, which is similar to the control patients observed in this study (Bloom et al. 2006). In addition, several reports detailing the use of alemtuzumab thus far suggest that both infection and malignancy rates are minimal when compared to other agents used for the same indication (Morris and Russell 2006; Magliocca and Knechtle 2006). These findings are confirmed with the prospective 3-year data published by Hanaway et al. in kidney transplant recipients as well as the retrospective 5-year data published by Shyu et al. in lung transplant recipients (Hanaway et al. 2011; Shyu et al. 2011).

At present, a concern associated with alemtuzumab administration is an increased incidence of autoimmune diseases. The exact incidence and etiology of autoimmune diseases following alemtuzumab administration in solid organ transplant is currently unknown, although the most well-designed trial with 3-year follow-up to date did not report autoimmune diseases developing in kidney transplant recipients receiving alemtuzumab for induction (Hanaway et al. 2011). Initial reports of autoimmune diseases associated with alemtuzumab administration came from the multiple sclerosis population. A single center observed the development of Grave's disease in 9 out of 27 patients who received alemtuzumab (Coles et al. 1999).

Thyroid function in all patients was normal prior to alemtuzumab and the mean time to development of autoimmune hyperthyroidism was 19 months (range 9–31 months) (Coles et al. 1999). Autoimmune hyperthyroidism was first reported in a kidney transplant recipient who received alemtuzumab induction 4 years earlier (Kirk et al. 2006). Watson and colleagues (2005) published a 5-year experience with alemtuzumab induction, in which they reported a 6 % (2/33) incidence of autoimmune disease development following administration. One patient developed hyperthyroidism in the early posttransplant period, and one patient developed hemolytic anemia, which was refractory to corticosteroids. With the increased use of alemtuzumab in solid organ transplantation, it is important to continually assess the risk of autoimmune disease development in this population.

■ Rituximab

Rituximab is a chimeric murine/human IgG1 monoclonal antibody directed at the CD20 cell surface protein (Tobinai 2003). Rituximab is currently FDA approved for the CD20-positive forms of non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL) and Wegener granulomatosis, microscopic polyangiitis, and refractory rheumatoid arthritis (see Chaps. 17 and 20) (Genentech 2011). The CD20 antigen is a 35-kDa phosphoprotein expressed on B cells, from pre-B cells to mature B cells. This protein is not expressed on hematopoietic stem cells, plasma cells, T lymphocytes, or other tissues (Tobinai 2003). The CD20 protein is a calcium channel and is responsible for B-cell proliferation and differentiation (Tobinai 2003). Early monoclonal antibodies developed against CD20 revealed that antibody binding did not result in modulation of activity or shedding of the surface protein, making the development of a humanized anti-CD20 antibody rational (Tobinai 2003). Rituximab was originally developed to treat B-cell lymphomas, as the vast majority of malignant B cells express the CD20 receptor. Following continuously infused, high doses of engineered anti-CD20 monoclonal antibodies clearance of CD20-positive cells occurred within 4 h of administration (Press et al. 1987). Circulating B-cell clearance was immediate; however, lymph node and bone marrow B-cell clearance were dose dependent.

Rituximab was initially used in solid organ transplant recipients to treat posttransplant lymphoproliferative disorder (PTLD). PTLD is a malignancy that develops following exposure to high levels of T-cell depleting immunosuppression (see section "Immunologic Targets: Rational Development/Use of Monoclonal Antibodies in Organ Transplant"). Under normal physiologic conditions, both the humoral and cellular immune systems work in concert to fight infection. In addition, cytotoxic T lymphocytes survey the body for malignant cells. Current immunosuppression and induction therapy are focused on decreasing communication and proliferation of T lymphocytes, which may lead to unopposed B-cell proliferation. The most significant risk factors for the development of PTLD are the use of potent T-cell depleting therapies as well as an Epstein-Barr virus (EBV) negative recipient serostatus. Approximately 60–70 % of PTLD cases are associated with EBV. Certain B cells that are infected with EBV or other viruses may go into unopposed cellular differentiation leading to PTLD (Evens et al. 2010).

This disorder was first reported in five living donor renal transplant recipients in 1969 with four of the five patients dying from their disease. The fifth patient survived following radiation and reduction in immunosuppression (Penn et al. 1969). The incidence of posttransplant malignancy, specifically PTLD, increased as the number of solid organ transplants increased. Specific agents linked to the development of PTLD included OKT3 and rabbit antithymocyte globulin (Swinnen et al. 1990; Evens et al. 2010). The initial treatment for PTLD is a reduction in maintenance immunosuppression, to allow T-cell surveillance to resume and aid in the destruction of malignancy causing cells. However, pharmacotherapeutic agents have been used successfully in patients who fail to respond to decreased immunosuppression. Rituximab is the most studied medication for the treatment of PTLD and can be considered in patients with CD20-positive tumors. Rituximab was initially used in the 1990s to target B-cell-specific forms of PTLD that did not involve the central nervous system (Faye et al. 1998; Cook et al. 1999; Davis and Moss 2004). The molecular size of rituximab generally precludes its use for central nervous system tumors with <5 % of rituximab penetrating the blood brain barrier, although some recent reports have shown success with rituximab for the treatment of CNS PTLD (Patrick et al. 2011; Kordelas et al. 2008; Jagadeesh et al. 2012). Administration of rituximab in patients with peripheral lymphomas resulted in clearance of malignant B cells for up to 12 months (Davis and Moss 2004). Currently, rituximab is reserved for patients with CD20-positive PTLD who fail to respond to reduction in maintenance immunosuppression. Rituximab can be used alone or in combination with chemotherapy in patients with severe or refractory PTLD.

Rituximab has also been employed as a desensitizing agent (see section "Monoclonal Antibodies Administered Pre-transplant") prior to solid organ transplant. Doses of 375 mg per m^2 administered prior to transplant enabled transplantation across ABO incompatible blood types and transplantation of highly

sensitized patients. Often rituximab is given in combination with other immunosuppressants to halt the production of new B lymphocytes and prevent the formation of new plasma cells. Desensitization protocols involve administration of pooled immunoglobulin followed by plasmapheresis to remove donor-specific antibody complexes. Rituximab is administered following the course of plasmapheresis for two reasons: (1) rituximab is removed by plasmapheresis and (2) rituximab only targets B lymphocytes, not the plasma cells currently secreting antibody. Therefore, timing of administration is crucial to the success of the desensitization protocol (Pescovitz 2006).

Following transplant, rituximab is also used for the treatment of acute, refractory antibody-mediated rejection. Antibody-mediated rejection is characterized by host recognition of donor antigens followed by T-cell proliferation and antigen presentation to B cells. B cells then undergo clonal expansion and differentiation into mature plasma cells, which secrete anti-donor antibody. This immune process may occur before or after transplantation. Often the presence of antibodies against donor tissue is discovered prior to transplant, during final crossmatch, thus preventing hyperacute rejection. In some cases, low levels of antibody or memory B cells exist which can facilitate antibody-mediated rejection within the first several weeks following transplant. Rituximab, therefore, is used to induce apoptosis of the B cells producing or capable of producing antibodies against the allograft. Unfortunately, the CD20 receptor is absent on mature plasma cells; therefore, rituximab can only stop new B cells from forming. Plasmapheresis is necessary to remove antibodies produced by secreting plasma cells. It is important to remember that rituximab may be removed by plasmapheresis and timing of administration is necessary to ensure optimal drug exposure. The optimal number of doses and length of therapy necessary to suppress antibody-mediated rejection is unknown (Pescovitz 2006; Stegall and Gloor 2010).

In 2005 and 2006, rituximab was shown to improve the clinical course of renal transplant patients with recurrent focal segmental glomerulosclerosis (FSGS) in patients who were receiving rituximab for the treatment of PTLD (Nozu et al. 2005; Pescovitz et al. 2006). A subsequent study described 7 pediatric patients who had a relapse of proteinuria after transplantation and who failed to respond to initial plasmapheresis. After failure of plasmapheresis, patients received rituximab for treatment of refractory FSGS. Three patients had complete resolution of proteinuria; urine protein decreased by 70 % in one patient and by 50 % in one patient. One patient failed to respond to therapy and one patient was unable to tolerate the rituximab infusion. This study confirmed that rituximab is a possible treatment option for recurrent FSGS (Strologo et al. 2009). Additional studies are needed to further delineate the role of rituximab in the treatment of recurrent FSGS.

■ Eculizumab

Eculizumab is a recombinant-humanized IgG2/4 monoclonal antibody with murine complementarity-determining regions grafted onto the framework of the human antibody on the light- and heavy-chain variable regions. Eculizumab binds with specificity and with high affinity to C5, a complement protein. By binding to C5, eculizumab prevents cleavage of C5 to C5a and C5b, which prevents the formation of the membrane attack complex. Currently, eculizumab is approved for use in the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (Alexion Pharmaceuticals 2011; McKeage 2011).

Because antibody-mediated rejection (AMR) is associated with complement activation evidenced by $C4d^{+}$ staining on biopsy, the use of eculizumab for the prevention and treatment of AMR holds promise (Stegall and Gloor 2010). The first case describing the use of eculizumab for the treatment of severe AMR was published in 2009. The patient was a highly sensitized kidney transplant recipient who received desensitization therapy before and after transplant. However, he became anuric with a biopsy that was positive for AMR approximately 8 days after transplant. After clinical failure of plasmapheresis and intravenous immunoglobulin, eculizumab was initiated. Intravenous immunoglobulin was also given in order to decrease donor-specific antibodies, and rituximab was given in order to prevent B-cell proliferation. Donor-specific antibodies did not decrease initially; however, C5d-9 staining was reduced on biopsy, and AMR was completely resolved on follow-up biopsies (Locke et al. 2009).

The use of eculizumab for the prevention of AMR has also been reported. In one study, patients with a positive crossmatch to their living kidney donor received plasmapheresis and eculizumab preoperatively and were compared to a historical control who received only plasmapheresis pre- and postoperatively. The treatment group also received eculizumab post-transplant for at least 4 weeks. Treatment continued in patients who did not have a decrease in donor-specific antibody. The incidence of AMR at 3 months was 7 % in the eculizumab group compared to 41 % in the historical control group (Stegall and Gloor 2010).

Recent evidence has proven that complement activation is involved in the development of hemolytic uremic syndrome. There have been a few case reports that show that eculizumab can improve the outcomes of patients who develop hemolytic uremic syndrome

after renal transplant (Van den Hoogen and Hilbrands 2011).

There is limited data on the use of eculizumab in solid organ transplantation at this time. However, it is likely that its role in the prevention and treatment of AMR, hemolytic uremic syndrome after transplantation, and other possible indications will be more clearly defined by the next decade.

■ Belatacept

In an effort to achieve the "immunotolerant" state posttransplant, research has been focused in the area of costimulation blockade. Simplistically, when a T cell is exposed to an antigen particle expressed on an antigen presenting cell through the T-cell receptor, additional co-stimulation is required for full activation of the T cell (Wekerle and Grinyo 2012). If co-stimulation is blocked, then the T cell becomes unresponsive and in essence tolerant. CD28 is expressed on human T cells and is upregulated on activated T cells, while its ligands, on the surface of the antigen presenting cell, are CD80 and CD86 (Wekerle and Grinyo 2012). Cytotoxic T-lymphocyte antigen-4 (CTLA-4) was identified as a compound that would bind the same ligands as CD28 but to a much higher affinity (Wekerle and Grinyo 2012). A modification of CTLA-4, giving it higher binding affinity for CD80/86, was fused with a mutated (no longer able to fix complement) human IgG1, yielding belatacept (Wekerle and Grinyo 2012). Therefore, belatacept binds to CD80 and CD86 with high affinity, blocking their interaction with CD28 on T cells. An artifact of belatacept is that it also blocks intrinsic CTLA-4, which normally acts as an inhibitory ligand on the surface of activated T cells, responsible for limiting the proliferation of the immune response (Wekerle and Grinyo 2012). Blockade of CTLA-4 could prevent tolerance from being achieved when administered posttransplant; however, phase II trials indicate that the synthesis of CD4+ CD25+ regulatory T cells is not interrupted following belatacept exposure (Gupta and Womer 2010). Belatacept is an intravenous infusion, dosed based on actual body weight, and is unaffected by renal or hepatic function, which is administered frequently during the first 1–3 months posttransplant then monthly thereafter (Martin et al. 2011).

Belatacept has been mainly studied and demonstrated efficacy in kidney transplant recipients in combination with basiliximab induction and mycophenolate mofetil/prednisone maintenance immunosuppression. Belatacept has been touted as calcineurin inhibitor sparing and therefore more renal protective posttransplant. Recently the 3-year results of the BENEFIT study were published detailing the safety and efficacy of belatacept versus cyclosporine in combination with mycophenolate mofetil and prednisone (Vincenti et al. 2012). The BENEFIT trial evaluated 663 kidney transplant recipients who received low intensity (0–3 months; 10 mg/kg on days 1 and 5, 10 mg/kg on weeks 2, 4, 8, 12, 3–36 months 5 mg/kg every 4 weeks; $n=226$), moderate intensity (0–6 months) 10 mg/kg on days 1 and 5, 10 mg/kg on weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24; 7–36 months 5 mg/kg ($n=219$) belatacept or cyclosporine ($n=221$) in combination with mycophenolate mofetil and prednisone. Graft survival at 3 years was 92 % in the low- and moderate-intensity groups and 89 % in the cyclosporine group. A total of 6 patients died, 2 in each group, and 9 patients lost their graft (4 in the low intensity, 3 in the moderate intensity, and 2 in the cyclosporine group). Calculated glomerular filtration rate was 66 ± 27 mL/min/1.73 m^2 in the low intensity, 65 ± 26 mL/min/1.73 m^2 in the moderate intensity, and 44 ± 24 mL/min/1.73 m^2 in the cyclosporine group, $p<0.0001$. Acute rejection mainly occurred in the first-year posttransplant with a cumulative rate of 17 % in the low intensity and 24 % in the moderate intensity versus 10 % in the cyclosporine group. PTLD occurred in five patients who received belatacept versus one patient in the cyclosporine group (Vincenti et al. 2012). Similar results were found at 3 years in extended criteria kidney transplant recipients (Pestana et al. 2012). When more intensive belatacept dosing was used in combination with mycophenolate mofetil ($n=33$) or sirolimus ($n=26$) versus tacrolimus with mycophenolate mofetil ($n=30$) following rabbit antithymocyte globulin and early corticosteroid withdrawal (4 days), acute rejection rates were low (12 % belatacept-mycophenolate, 4 % belatacept-sirolimus, and 3 % in the tacrolimus-mycophenolate). Graft survival was 100 % at 1 year in the tacrolimus group versus 91 % in the belatacept-mycophenolate group and 92 % in the belatacept-sirolimus group; however, graft function was roughly 8 mL/min/1.73 m^2 higher in the belatacept groups. However, less than 80 % of patients in the belatacept groups remained steroid-free at 12 months versus 93 % in the tacrolimus group (Ferguson et al. 2011). Patients 6–36 months post-kidney transplant were also enrolled in a conversion trial in which they were randomized to continue their current immunosuppression or be converted to belatacept to evaluate if an improvement in renal function could be obtained following discontinuation of a calcineurin inhibitor (Rostaing et al. 2011). An average improvement in glomerular filtration rate was noted in the belatacept group (7 mL/min versus 2.1 mL/min, $p=0.0058$) at 12 months following conversion. Six patients did develop acute rejection following their conversion to belatacept, but these rejections did not result in graft loss (Rostaing et al. 2011).

Monoclonal antibody	Dose[a]	US cost per course (AWP)[b]
Alemtuzumab	30 mg × 1	$6,354
Basiliximab	20 mg × 2	$5,605
Rituximab	375 mg/m^2 weekly × 4 doses	$20,682
Belatacept	10 mg/kg days 1 and 5 10 mg/kg after 2 and 4 weeks 10 mg/kg after 8 and 12 weeks 5 mg/kg after 16 weeks and every 4 weeks thereafter	$42,090 for the first year $28,798 subsequent years
Eculizumab	1,200 mg × 1[c] 600 mg × 1 then 600 mg weekly × 3	$74,880

[a]Based on 70 kg dosing weight, rounded to nearest vial size
[b]Actual wholesale price (AWP) Adapted from Red Book; Thomson Reuters (2012)
[c]Dosing is based on Stegall et al. (2011) study. Adequate dose for transplantation has not yet been established

Table 19.4 ■ Per dose cost comparison between monoclonal antibodies currently used in solid organ transplantation.

Evidence for the use of belatacept is currently lacking in nonrenal transplant recipients and high immunologic risk and non-Caucasian organ recipients. Additionally, patients who are EBV positive are at high risk of developing posttransplant lymphoproliferative disease in the central nervous system. This observation warranted a black box warning to be issued in the belatacept package insert detailing that the use of belatacept is contraindicated in patients who are EBV negative (Bristol Myers Squibb Company 2011).

CONCLUSION

Currently, there are several challenges remaining in solid organ transplantation. These challenges may be grouped as follows. One challenge is optimizing patient-specific immunosuppression based on risk factors for acute rejection. Monoclonal antibodies provide targeted immunosuppression that when used in conjunction with specific maintenance immunosuppressants may allow more specific therapy. Another challenge is preventing over-immunosuppression, which may lead to infection and malignancy. Although monoclonal antibodies provide targeted therapy, the toxicity and potency must be balanced with over-immunosuppression. Consideration of the mechanism of action of both the monoclonal antibody and maintenance immunosuppression must be evaluated to ensure that appropriate antimicrobial prophylaxis and malignancy screening tools are utilized to minimize the patient's risk. Finally, increasing patient and graft survival through reducing the incidence of adverse effects associated with long-term exposure to maintenance immunosuppression, such as cardiovascular events or kidney dysfunction, is necessary. Monoclonal, along with polyclonal antibodies, may allow for withdrawal or minimization of specific maintenance immunosuppressants that lead to the increased incidence of these long-term adverse effects. Oftentimes the use of specific monoclonal antibodies in institutional protocols is driven by cost (Table 19.4) with careful consideration of the goals of therapy.

SELF-ASSESSMENT QUESTIONS

■ Questions

1. Monoclonal antibodies are used for several reasons in solid organ transplantation. What benefit do they provide over polyclonal antibodies?
2. The rational development and use of monoclonal antibodies in solid organ transplantation is focused on the prevention of host recognition of donor tissue (rejection). What are the two ways in which the host immune system recognizes donor tissue and may cause tissue damage?
3. What are the molecular targets for monoclonal antibodies currently used in solid organ transplantation?
4. Monoclonal antibodies are used at various times in solid organ transplantation. Describe the reasons why a monoclonal antibody would be administered before transplant, at the time of transplant, or following transplant?
5. There are several important pharmacokinetic parameters that must be considered when administering monoclonal antibodies to solid organ transplant recipients. What are these pharmacokinetic parameters?
6. Muromonab has a characteristic infusion-related reaction. Why does this reaction occur and how can it be attenuated?

7. Daclizumab and basiliximab are two monoclonal antibodies directed against the alpha subunit of the interleukin-2 receptor. What is the difference between these two antibodies?
8. There are several benefits, as well as several risks associated with the use of monoclonal antibodies in solid organ transplantation. What are these benefits and risks?

■ Answers

1. Monoclonal antibodies provide targeted immunosuppression. The advantage monoclonal antibodies offer over polyclonal antibodies is that the receptor target is known. Polyclonal antibody development involves the introduction of human lymphocytes into an animal host immune system. The animal will then develop polyclonal antibodies directed against human lymphocyte cell surface targets. As a consequence, each inter-batch variability and potency may vary. Although significant outcome data exists with the use of polyclonal antibodies, monoclonal antibodies have a known target allowing for in vivo and in vitro pharmacokinetic and pharmacodynamic data to aid incorporation into novel immunosuppression regimens.
2. The two ways in which the host immune system recognizes donor tissue. Complement-dependent antibody-mediated rejection occurs when the host (recipient) develops or has preformed antibodies against the donor tissue. Preformed antibodies will aggregate to the implanted tissue and initiate the complement cascade, which facilitates cell lysis. The majority o these antibodies are usually directed against the major histocompatibility complexes (MHC) located on the surface of the donor tissue. An absolute contraindication to transplantation is the presence of preformed antibodies against MHC complex I, which is located on the surface of all nucleated cells. The second way in which the host immune system attacks donor tissue is through T-cell-mediated rejection. This occurs when the donor tissue is recognized as foreign by host antigen presenting cells. Antigen presenting cells present donor tissue antigens to the T cells which stimulates T-cell proliferation and graft infiltration leading to inflammation and arteritis.
3. Alemtuzumab (Campath-1H®) targets the CD52 receptor, located on peripheral blood lymphocytes, natural killer cells, monocytes, macrophages, and thymocytes.

   Daclizumab (Zenapax®) targets the CD25 alpha subunit of the IL-2 receptor, located on activated T lymphocytes.

   Basiliximab (Simulect®) targets the CD25 alpha subunit of the IL-2 receptor, located on activated T lymphocytes.

   Muromonab-OKT3 (Orthoclone-OKT3®) targets the CD3 receptor located on CD2-, CD4-, and CD8-positive lymphocytes.

   Rituximab (Rituxan®) targets the CD20 receptor located on B lymphocytes.

   Eculizumab (Soliris®) targets C5 in the complement pathway.
4. The administration of monoclonal antibodies prior to transplant is called desensitization. This strategy is reserved for "highly sensitized" patients, meaning they have high titers of circulating antibodies against donor-specific antigens. Monoclonal antibodies that target cells which produce these antibodies are employed, in conjunction with plasmapheresis and pooled human immune globulins. Removal of these antibodies may facilitate successful transplantation across this immunologic barrier.

   Monoclonal antibodies administered at the time of transplant are called induction. Induction is provided at the time of transplant to decrease the ability of the host immune system to respond to implantation of foreign tissue. In addition, monoclonal antibodies which provide profound T-cell depletion given at the time of transplant may facilitate the need for certain maintenance immunosuppressants.

   Following transplantation, monoclonal antibodies may be used to treat cell-mediated or antibody-mediated rejection. Cell and antibody infiltrates found in biopsy specimens in correlation with the clinical status of the patient will dictate the type, dose, and duration of the monoclonal antibody chosen.
5. The volume of distribution, biological half-life, and total-body clearance can differ significantly between solid organ transplant recipients. Careful consideration of these pharmacokinetic parameters must be employed to maximize the efficacy and minimize the toxicity associated with administration of these agents. For example, weight-based dosing in obese patients must be carefully considered, and biological markers of efficacy should be evaluated to determine the appropriate dose and dosing schedule. In addition, monoclonal antibodies are also removed by plasma exchange procedures, such as plasmapheresis, which may be performed during the perioperative period. Therefore, it would be prudent to administer the monoclonal antibody following the plasma exchange prescription to avoid removal of the drug and avoid a possible decrease in efficacy.
6. Muromonab's infusion-related reaction occurs because when the molecule binds to the CD3 receptor. It actually activates the cell prior to inducing apoptosis. T-cell activation leads to increased production of inflammatory cytokines and when the

cell undergoes apoptosis these cytokines are released causing a "cytokine release syndrome." This cytokine release syndrome is characterized by fever, chills, rigors, diarrhea, and potentially capillary leak leading to pulmonary edema. Often times this reaction is the worst when the largest number of cells are present, namely, the first dose. However, this reaction can occur after several days of dosing. This reaction can be attenuated by administration of corticosteroids, histamine blockers, and cyclooxygenase antagonists. Pharmacotherapy aimed at reducing the production or the interaction of cytokines with their receptors may decrease the severity of the cytokine release syndrome.

7. *Structure activity relationship*: Daclizumab has a binding capacity of 3×10^9 M^{-1} versus basiliximab which has a binding capacity of 1×10^{10} M^{-1}. Therefore, basiliximab is three times more potent than daclizumab.
8. *Dosing*: Daclizumab is dosed based on weight, while basiliximab is given as a 20 mg dose. The dosing schedule varies based on the type of solid organ transplanted as well as concomitant immunosuppression given. These agents, however, are only approved for prevention of acute rejection in kidney transplant recipients.
9. Benefits include targeted immunosuppression, no batch variability, and low antigenicity in humanized products. The risks associated with any type of immunosuppression include an increased risk for infection, as well as malignancy. Patients who receive monoclonal antibodies which specifically target a cell line, such as muromonab, are associated with a significantly increased risk of posttransplant lymphoproliferative disease. Appropriate antimicrobial prophylaxis and vigilant screening for posttransplant malignancy may allow for safe and effective use of these monoclonal antibodies in solid organ transplantation.

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