

NEPHROLOGY

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Immunosuppressive Strategies in Human Renal Transplantation – Induction Therapy

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Renal transplantation is the treatment of choice for patients with chronic kidney disease (CKD). The short-term outcomes of renal transplantation have dramatically improved over the past several decades; in a large part, this success is due to improvements in immunosuppression and posttransplantation medical care. The goal of immunosuppressive strategies in transplantation is to deliver immunosuppression that results in long-term allograft and patient survival, while minimizing the complications of this immunosuppression (eg, infectious complications, malignancy). Generally, clinical immunosuppression is divided into 3 major stages: induction therapy, maintenance therapy, and treatment of an established acute rejection episode. This issue of *Nephrology Rounds* is focused on the use of biologic agents in managing the first stage, induction therapy.

Induction therapy in renal transplantation

The introduction of highly potent and selective agents for the initiation of immunosuppression has reduced the frequency of acute rejection rates.¹ However, acute rejection remains a concern in organ transplantation and is an important antigen-dependent risk factor for the development of chronic rejection. Recently, much attention has been given to subclinical acute rejection that could be an important determinant of outcome in renal transplant recipients (RTRs).² The goal of induction therapy is to provide a high level of immunosuppression at the time of transplant when the risk of acute rejection is the highest.^{1,3-6} Induction therapy is often initiated intraoperatively or immediately postoperatively, and is generally concluded within the first 3-14 days after transplantation. Although it is not a mandatory stage of recipient immunosuppression, it is often considered critical for optimizing outcomes, particularly in high-risk individuals.^{1,3-6} Over the past decade, instituting induction therapy has increased as standard therapy in many centers,⁷ and there are several rationales underlying the use of induction therapy.

- A number of trials have demonstrated significant reductions in the incidence of acute rejection and improved 1-year graft survival in RTRs with induction therapy using the currently available potent immunosuppressive strategies.^{1,3,4,6,8-14}
- Given their potent effects in controlling enhanced alloimmune responses, these agents are often considered vital in patients at high risk for poor short-term outcomes, such as patients with preformed antibodies, with a history of previous organ transplants, with multiple human leukocyte antigen (HLA) mismatches, or in transplantation of organs after prolonged cold-ischemic time or from expanded-criteria donors.
- Induction therapy in RTRs also plays a vital role in preventing calcineurin inhibitor-induced nephrotoxicity in the immediate posttransplant period.¹ With induction therapy, the initiation of a calcineurin inhibitor can often be delayed until the graft regains some degree of function.
- Importantly, induction therapies may also help to reduce the risk of nephrotoxicity from either cyclosporine or tacrolimus.^{1,15,16} However, the improved short-term outcomes inferred from induction therapies are associated with an increase in the risk of infectious complications and malignancy.^{1,16}

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Currently available induction therapies

Immunosuppressants for induction therapy include the monoclonal antibodies (muromonab-CD3, basiliximab, daclizumab, alemtuzumab), and the polyclonal antibodies (antithymocyte globulin [ATG] equine and ATG rabbit). These agents are further classified as either nondepleting proteins (basiliximab and daclizumab) or depleting proteins (alemtuzumab, antithymocyte globulins, and muromonab), depending on their ability to deplete T-cells. The following sections review the pharmacology, adverse event profiles, and pertinent literature related to the clinical efficacy of each group of agents.

Depleting agents

A major fraction of induction therapies exert their function through the depletion of lymphocytes.^{1,3,16} In general, these agents cause T-cell lysis and/or clearance with a resultant depletion in circulating lymphocytes. Administration of depleting agents is often accompanied by an extensive release of cytokines due to cell destruction that may cause significant adverse events. Reconstitution of the immune system can take several months, possibly up to a year, and full recovery is questionable, especially in the elderly population.³ Due to the nature of immunosuppression induction, the adverse events generally associated with the use of depleting proteins are an increased risk of infectious complications and malignancy, above and beyond standard immunosuppression. The following sections review some of the primary depleting agents used in induction therapy.

Antithymocyte globulins

Pharmacology: There are two ATG formulations used for induction therapy in the United States and they are prepared by immunizing either horses (eATG), or rabbits, (ATG rabbit; thymoglobulin) with lymphoid tissue and then harvesting and stabilizing the resultant immune sera.¹⁷ Equine ATG leads to the depletion of thymus-produced lymphocytes through complement-dependent (CD) lysis after the antibody preparation binds to a variety of cell-surface markers, including CD2, CD3, CD4, CD8, CD11a, and CD18.¹⁷⁻¹⁹ Thymoglobulin is thought to induce T-cell depletion and modulation by a variety of methods, including fragment, crystallizable (Fc)-receptor-mediated complement-dependent lysis, opsonization and phagocytosis by macrophages, and immunomodulation leading to long-term depletion via apoptosis and antibody-dependent cell-mediated cytotoxicity.^{20,21} Regardless of the mechanism, immune reconstitution after the administration of thymoglobulin may take several months.²⁰⁻²² T-cell recovery after thymoglobulin-induced depletion may be associated with an expansion of cell subsets that are linked to suppressor functions.²³ This is an interesting mechanism that

promotes the function of immunoregulatory T cells resulting in long-term immunomodulation.

Dosing: As an induction agent, the dose of eATG ranges from 10-30 mg/kg intravenous (IV) for 4-14 days, and is typically infused over 4-6 hours per dose.^{1,17,19,20} Short-term courses are often preferred, due to high costs and the multiple barriers related to outpatient administration (eg, the need for a high-flow vein, long infusion times).¹⁸ To combat these barriers, many centers using eATG have adopted a 15 mg/kg/day dosing regimen with discontinuation once maintenance therapy is maximized.¹⁸ Although thymoglobulin is not Food and Drug Administration (FDA) approved for induction, many transplant centers use it as their induction agent of choice.^{7,17} When used for induction, dosing can range from 1-4 mg/kg/day for 3-10 days after transplantation, but doses of 1.5 mg/kg/day for 3-5 days are the most common dosing stratagems.^{17,20,21} Therapy should be initiated in the operating room to prevent ischemic reperfusion injury.

Adverse events: The short-term adverse events of ATG formulations are generally related to either cytokine release or myelosuppression. Cytokine-release side effects from thymoglobulin and eATG may include fever (63% and 63%), chills (57% and 43%), headache (40% and 35%), nausea (37% and 28%), diarrhea (37% and 32%), malaise (13% and 4%), dizziness (9% and 25%), and pain (46% and 43%), respectively.¹⁷ Premedication with antihistamines and acetaminophen is highly recommended to reduce the overall number and severity of these reactions. Leukopenia and thrombocytopenia may occur in up to 30% of patients treated with either preparation.¹⁷ Anaphylactic reactions secondary to the administration of one of these polyclonal antibodies are rare, but possible.¹⁷

Clinical efficacy: Brennan et al²⁴ conducted an analysis of thymoglobulin (1.5 mg/kg/day) versus eATG (15 mg/kg/day) as induction therapy for at least 7 days, with the initial dose occurring during transplantation. The study followed 72 patients (thymoglobulin, n=48; eATG, n=24) for 12 months while on maintenance therapy of a combination of cyclosporine, azathioprine, and prednisone, or cyclosporine, mycophenolate, and prednisone. After 1 year, biopsy-proven acute rejection (BPARG) occurred in only 4% of thymoglobulin-treated patients and 25% of eATG-treated patients ($P=0.014$). Graft survival at 12 months was 98% in the thymoglobulin group and 83% in the eATG group ($P=0.02$). Leukopenia was noted to occur at a much higher rate (56%) in the thymoglobulin group compared with the eATG group (4%; $P<0.0001$). Despite the higher incidence of leukopenia, thymoglobulin was associated with a lower rate of cytomegalovirus (CMV) disease (12.5% vs 33.3% for eATG; $P=0.025$).²⁴ Survival rates at 5-years and 10-years also indicated the superiority of thymoglobulin.^{25,26}

Muromonab-CD3 (OKT3)

The manufacturer of this medication is voluntarily withdrawing it from the United States market due to decreased utilization. Current OKT3 supplies are expected to be exhausted by mid-2010.

Pharmacology: OKT3 is a murine monoclonal antibody directed against the CD3 receptor. When OKT3 is bound to CD3, the T-cell receptor (TCR) undergoes endocytosis resulting in an inert T-cell. T cells are then removed via opsonization and ultimately, phagocytosis.^{19,21,27} A substantial T-cell loss could occur within the first few hours after an initial dose; furthermore, it is noted that as the T-cell counts begin to fall, several T-cell-derived cytokines (eg, tumor necrosis factor [TNF], interleukin-2 [IL-2], and interferon-gamma [IFN- γ]) are released into the circulation.

Dosing: OKT3 does not have an indication for induction, but it has been frequently used as an induction therapy agent. For induction therapy in RTRs, doses of 2-5 mg/day have been employed for a duration of therapy from 3-14 days.¹⁷

Adverse events: Many severe short-term adverse events have been associated with the use of OKT3 due to the massive cytokine release after T-cell depletion. This phenomenon and the resultant adverse events have been labeled "first-dose effect."^{19,21} The most common adverse events include fever (77%), chills (43%), diarrhea (37%), nausea (32%), tachycardia (26%), vomiting (25%), and dyspnea (16%).¹⁷ As with the polyclonal antibodies, use of antihistamines, acetaminophen, and corticosteroids is warranted prior to infusions to aid in reducing the number and severity of adverse events. One major complication of OKT3 is the development of severe pulmonary edema. The use of diuretics or hemodialysis may be justified prior to initiation of OKT3 therapy to achieve euvolemia, or minimize volume overload.^{16,19,22} Another problematic adverse reaction is the development of nephropathy²⁸ and, although the cause of nephropathy is not fully understood, it is thought to be induced by cytokine release; however, the changes in renal function are usually reversible.²⁸ The use of OKT3 is limited, especially after an initial course has been completed. Formation of neutralizing antibodies against the monoclonal murine antibody may reduce its efficacy, also known as an "anti-OKT3 response,"²⁹⁻³¹ and the response has been noted in ~50% of patients who have received a full course of OKT3 therapy. As a result, a second course may be much less effective or may involve increased risk due to a greater hypersensitivity, since the immune system can easily mount responses to a reintroduction.²⁹⁻³¹ For this reason, OKT3 should be used judiciously, if at all, in the treatment of rejection when chosen for induction.

Clinical efficacy: Analyses comparing OKT3 to ATG preparations as induction therapies clearly indicate that ATG is the preferred choice. Improved efficacy through a decrease of both the incidence of rejections and graft loss, as well as increased tolerability due to less hypersensitivity and the reduced risk of cytokine syndrome have demonstrated that ATG is superior.²⁹⁻³³

Alemtuzumab

Pharmacology: Alemtuzumab is an anti-CD52 humanized, monoclonal antibody that has an FDA indication for use in B-cell chronic lymphocytic leukemia.^{34,35}

CD52 is present on virtually all B- and T-cells as well as macrophages, natural killer (NK) cells, and some granulocytes. When the alemtuzumab antibody binds to CD52, it is thought to trigger an antibody-dependent lysis of the cell. The depletion of lymphocytes is so marked that it takes several months to a year postadministration for the immune system of a patient to be fully reconstituted.^{34,35}

Dosing: Currently, the dosages of alemtuzumab for induction therapy are not completely agreed upon. Doses of 20 mg-30 mg on the day of transplant and then again on postoperative day 1 or 4 have demonstrated effectiveness.³⁶⁻⁴⁰ The use of a single intraoperative dose of 30 mg is under evaluation, based on the hypothesis that it will have better efficacy and improved tolerance than previously studied regimens.^{34,35}

Adverse events: The mechanism of depletion with alemtuzumab is so profound that its side-effect profile occurs frequently and at a high level of severity. Adverse events associated with the use of alemtuzumab include neutropenia (70%), thrombocytopenia (52%), anemia (47%), nausea (54%), vomiting (41%), diarrhea (22%), headache (24%), dyesthesia (15%), dizziness (12%), and autoimmune hemolytic anemia (<5%).^{17,34,35} These side effects warrant the administration of acetaminophen and an antihistamine prior to infusion in an attempt to decrease both the number and severity of the events.

Clinical efficacy: The use of alemtuzumab as an induction agent has recently become increasingly popular due to its overwhelming effects as a depleting agent.^{36,37,41-44} Currently, few randomized controlled trials are available for safety and efficacy data. Vathsala et al⁴⁵ completed the first such trial in 30 patients (alemtuzumab, n = 20; control group, n = 10). The treatment arms were 20 mg of alemtuzumab on postoperative day zero and with maintenance immunosuppression consisting of low-dose cyclosporine (goal trough concentrations of 90 to 110 ng/mL) versus a high-dose cyclosporine arm (goal trough concentrations of 180 to 225 ng/mL) with azathioprine and steroids. At the end of 6 months, there were no obvious differences between graft and patient survival, BPAR, or treatment failures. Similar observations have been reported by others.^{46,47}

Nondepleting agents

Interleukin (IL)-2 receptor antagonist

Pharmacology: Currently, there are two nondepleting proteins used for induction therapy, daclizumab and basiliximab.^{8,17} Both of these monoclonal antibodies bind with high affinity to the alpha subunit of the IL-2 receptor, also known as CD25. The antagonistic effect on the IL-2 receptor prevents T-cell activation and subsequent proliferation without causing lysis or cell destruction.^{8,17} The chemical compositions of daclizumab and basiliximab differ only by the degree of murine protein present in the variable region of the antibody. In daclizumab, murine protein is found strictly in the hypervariable region of the antibody, rather than throughout the entire variable region, like basiliximab.^{17,27} Daclizumab is classified as a humanized antibody because it possesses 90% human sequences and 10% murine sequences, whereas basiliximab is considered a chimeric antibody because it consists of 70% and 30% human and murine proteins, respectively.^{8,17,27}

Dosing: Both IL-2 receptor antibodies are FDA approved for induction therapy in RTRs.¹⁷ The dose of basiliximab is 20 mg IV given two hours prior to the transplant, followed by a second 20 mg dose on postoperative day 4.^{9,22} Daclizumab's dosing schedule is 1 mg/kg within 24 hours of transplantation plus an additional four doses of 1 mg/kg at a schedule of every two weeks after surgery.^{8,17} Basiliximab causes a complete saturation of the CD25 receptor for 5-8 weeks, whereas the dosing scheme of daclizumab causes saturation that lasts up to 120 days.^{8,9} Recent trials have indicated that a reduced dosing schedule for daclizumab with an initial dose of 1 mg/kg on the day of transplant and postoperative day 4 is equally efficacious and safe compared with the 5-dose regimen.^{10,11}

Adverse events: Safety is one of the most evident benefits of induction therapy with the IL-2 receptor antibodies, especially the absence of any increased risk of cytomegalovirus (CMV) infection or malignancy. The most common adverse reaction with daclizumab is hyperglycemia; clinical studies find that approximately 32% of patients receiving daclizumab develop hyperglycemia.^{8,12,22} The majority of the high-glucose levels occur the day after transplant or in patients with pre-existing diabetes mellitus. All other adverse events in the daclizumab and basiliximab clinical trials have no statistically significant differences compared with placebo.^{8,9,22} Hypersensitivity reactions are considered the most serious side effects associated with the use of IL-2 receptor antagonists, but they are

extremely infrequent (<1%) for both basiliximab and daclizumab during initial and subsequent dosing.^{8,9,17} The most serious side effects for hypersensitivity reactions include hypotension, tachycardia, cardiac failure, bronchospasms, pulmonary edema, and respiratory failure.¹⁷ One other possible advantage with the IL-2 receptor antibodies may be their apparent low risk of malignancy when compared with the antilymphocyte antibodies.^{8,9,22}

Clinical efficacy: At this time, basiliximab and daclizumab, as induction therapies, have been studied sparingly in a head-to-head fashion. Nair et al¹³ assessed the use of both IL-2 receptor antagonists in an open-labelled, prospective trial that included 23 patients (basiliximab, n=10; daclizumab, n=13). Both medications were used at standard doses approved by the FDA for their respective indications. All patients received regimens of prednisone (tapered to 10 mg/day), cyclosporine (tapered to 1 or 2 mg/kg/day) and mycophenolate (1 g twice daily). Each group had one patient present with a severe rejection episode that was ultimately resolved with the administration of OKT3. Patient survival was determined to be similar between the two groups (basiliximab, 100%; daclizumab, 100%), as was the rate of infection (basiliximab, 100%; daclizumab, 90%), and the risk of developing diabetes (basiliximab, 0%; daclizumab, 0%).¹³

Lin et al¹⁴ performed a second trial comparing basiliximab, given 2 hours prior to surgery and on postoperative day 4, and daclizumab administered on a two-dose schedule similar to basiliximab, with the first dose given within 24 hours prior to transplant and the second on postoperative day 14. This was a randomized, prospective analysis involving 58 patients (basiliximab, n=30; daclizumab, n=28) who received a kidney transplant from a cadaveric donor and had no previous transplantations. All patients received prednisolone (tapered to 10 mg-15 mg/day), cyclosporine (tapered to 3 mg-4 mg/kg/day) and mycophenolate (tapered to 500 mg twice daily). At 6 months, the basiliximab group experienced no acute rejections, whereas the daclizumab group reported 7 episodes of BPAR. The incidence of both bacterial infections and the presence of CMV disease at the end of 1-year was similar for both groups.¹⁴

Comparative efficacy: nondepleting (basiliximab) versus depleting (thymoglobulin) proteins

Lebranchu et al⁴⁸ conducted the first comparisons of these two agents for the purposes of induction therapy in an open-label, randomized, multicenter study over 6 months. The 101 patients included in the trial (basiliximab, n=51; thymoglobulin, n=50),

Table 1: Immunosuppressive agents used for induction therapy			
Generic name (Brand name)	FDA approved for induction (yes/no)	Common dosage	Common adverse effects
Alemtuzumab (Campath®)	No	20 - 30 mg × 1 – 2 doses	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression
Anthithymocyte globulin equine (ATGAM®)	Yes	15 mg/kg IV × 3 – 14 days	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression
Anthithymocyte globulin rabbit (Thymoglobulin®)	No	1.5 mg/kg IV × 3 – 14 days	Flu-like symptoms, chills, rigors, fever, rash, myelosuppression
Muromonab-CD3 (OKT3) (Orthoclone OKT3®)	No	5 mg IV × 7 – 14 days	Headache, hypertension, pulmonary edema, tremor, fever, aseptic meningitis, cytokine release syndrome
Daclizumab (Zenapex®)	Yes	1 mg/kg IV × 2 – 5 doses	Hyperglycemia (only after infusion)
Basiliximab (Simulect®)	Yes	20 mg IV × 2 doses	None reported compared with placebo

were all patients undergoing kidney transplantation from a cadaveric donor with no previous transplantations. The initial dose of basiliximab was 20 mg administered within 2 hours of surgery, and a second dose given on the fourth day posttransplantation. Thymoglobulin was dosed for 6-10 days at 1.0–1.5 mg/kg/day, with the initial dose administered within 24-hours pretransplant. All patients received cyclosporine microemulsion, steroids, and mycophenolate for maintenance therapy. Efficacy endpoints, including patient survival, graft survival, episodes of BPAR, and treatment failure were found to be similar in the two groups. While basiliximab produced an increased incidence of central nervous system and urinary disorders, the thymoglobulin arm demonstrated a greater risk of active CMV infection.⁴⁸

Mourad et al⁴⁹ also completed an open-label, randomized, multicenter trial comparing a total of 105 patients (thymoglobulin, n = 53, basiliximab, n = 52). The results of this analysis were similar to the previously mentioned trial for both efficacy and toxicity.

Brennan et al⁵⁰ conducted a prospective, randomized trial to assess a composite endpoint of BPAR, delayed graft function, graft loss, or patient death at 12-months posttransplantation. The composite endpoint was not found to be statistically significant between the 2 groups, ie, 50.4% and 56.2% in the thymoglobulin and basiliximab group respectively ($P = 0.34$). However, BPAR alone was shown to be more frequent in the basiliximab group, 25.5% versus 15.6% for thymoglobulin ($P = 0.02$). Surprisingly, basiliximab was also associated with an increased rate of CMV infection, 17.5%, versus only 7.8% in the thymoglobulin group ($P = 0.02$) but aside from CMV, thymoglobulin was associated with

a higher rate of infection (85.8% vs 75.2%, $P = 0.03$). Also, leukopenia again demonstrated a significantly higher incidence with thymoglobulin use.⁵¹

Conclusion

Induction therapy with biological agents continued a 9-year trend of increasing utilization for 74% of kidney transplants in 2004-2005.⁷ Nevertheless, there is no universal consensus on the optimal agent for induction therapy following renal transplantation. The current agents used for induction therapy are summarized in Table 1. In 2005, thymoglobulin was the most frequently used induction agent in the United States. It was used in 39% of RTRs about whom information was available; in contrast, the IL-2 receptor antibodies were used in 28% (basiliximab = 16%; daclizumab = 12%), alemtuzumab in 9%, and eATG or OKT3 in <2% of all transplant recipients.^{7,20}

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