

Rabbit anti-thymocyte globulin induction in renal transplantation: review of the literature

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Abstract: Rabbit anti-thymocyte globulin (rATG) has proven benefit as induction therapy in renal transplant recipients, achieving reduced acute rejection rates and better short-term allograft function, with slightly higher rates of complications such as infections and malignancy. Compared with other agents, the most benefit from rATG induction has been observed in renal transplant recipients at high immunologic risk for rejection. However, in special populations, such as pediatrics, the elderly, and hepatitis C-positive and human immunodeficiency virus-positive renal transplant recipients, additional information is needed to delineate the absolute benefit of rATG induction compared with other induction agents. Selection of rATG as the choice of induction therapy in renal transplant recipients should be guided by a cost-effective approach in balancing efficacy, safety, and cost. This review summarizes the published literature on efficacy, safety, and cost of rATG induction in renal transplantation.

Keywords: anti-thymocyte globulin, renal transplantation, induction therapy

Introduction

Nearly all renal transplant recipients require immunosuppressive therapy to prevent rejection. Antibody induction therapy often augments maintenance immunosuppression during and shortly after kidney transplantation. The current literature supports its use, particularly in patients at high immunologic risk for acute graft rejection and loss. Several antibody induction agents are available, and selection of induction agent and regimen remains controversial. Comparison of agents based on clinical studies can be challenging, given that studies are often conducted in patients of differing immunologic risk and using diverse maintenance immunosuppressive regimens. Comorbid diseases and financial constraints may also vary significantly between patients. These factors should all be considered when selecting the most appropriate induction agent and regimen for renal transplant recipients.

Antibody induction agents are divided into two broad categories, based on their activity on T-lymphocytes, as lymphocyte-depleting antibodies and nondepleting antibodies (Table 1). Lymphocyte-depleting antibodies, including rabbit anti-thymocyte globulin (rATG), equine anti-thymocyte globulin (eATG), monomurab-CD3 (OKT3), and alemtuzumab, are generally recommended in patients at high immunologic risk of rejection. Possible benefits of intense immunosuppression must be balanced with increased risks of infection and malignancy. On the other hand, nondepleting antibodies, including basiliximab and daclizumab, reduce the risk of acute allograft rejection with less intense adverse effects, and are typically used in patients at lower risk of acute rejection. The current Kidney Disease: Improving Global Outcomes guidelines

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Table 1 Lymphocyte depleting and nondepleting induction agents

Agent	Alternative name(s)	Drug class	Proposed mechanism(s) of action	Serious adverse effects
Lymphocyte-depleting				
Anti-thymocyte globulin, rabbit	rATG, Thymoglobulin®	Chimeric (rabbit) polyclonal antibodies	Exact mechanisms unknown; broadly targets and eliminates preactivated, noncycling memory lymphocytes; alters T-lymphocyte activation, homing, and cytotoxic function	Cytokine release syndrome (fever, shivering, myalgia, headache), hypertension, anemia, leukopenia, thrombocytopenia, increased risk of infection
Anti-thymocyte globulin, equine	eATG, Atgam®	Chimeric (equine) polyclonal antibodies		
Alemtuzumab	Campath®	Humanized monoclonal antibody against CD52	Targets most mature some immature lymphocytes; exact mechanism unknown, but may cause antibody-dependent lysis of cells following cell surface binding	
Muromonab-CD3	OKT3, Orthoclone®	Chimeric (murine) monoclonal antibody against CD3	Broadly targets all circulating T-lymphocytes ; promotes antibody-mediated activation of complement and apoptosis of T-lymphocytes	
Lymphocyte nondepleting				
Daclizumab	Zenapax®	Chimeric (murine) monoclonal antibody against CD25	Specifically targets T cells that have been activated by an MHC-antigen stimulus; inhibits T-lymphocyte activity	Cytokine release syndrome (fever, shivering, myalgia, headache), hypertension, anemia, leukopenia, thrombocytopenia, increased risk of infection
Basiliximab	Simulect®	Chimeric (murine) monoclonal antibody against IL-2 receptor		

Abbreviations: eATG, equine anti-thymocyte globulin; IL-2, interleukin-2; MHC, major histocompatibility complex; rATG, rabbit anti-thymocyte globulin; CD, cluster of differentiation.

recommend use of rabbit anti-thymocyte globulin as induction therapy in renal transplant recipients at high immunologic risk for acute allograft rejection.¹ The following review examines the current literature on the efficacy and outcomes of rATG induction and other available/historically significant induction agents in renal transplant recipients (Table 2).

Prevention of rejection

Mechanism of action

rATG (Thymoglobulin®) is a lymphocyte-depleting polyclonal antibody indicated for the treatment of acute renal allograft rejection, and its use in transplant induction is off-label.² The precise mechanisms underlying the therapeutic efficacy of rATG are not entirely known, although T-cell depletion plays a critical role. Both in vitro and in vivo studies have suggested a number of other possible mechanisms, including lymphocyte surface antigen modulation and transcription factor activation.³⁻⁹ rATG may disrupt immune cell processes, such as cytokine production, chemotaxis, endocytosis, stimulation and proliferation, and leukocyte-endothelial cell adhesion. rATG may also promote cell death via induction of apoptosis, antibody-dependent lysis, and complement-mediated lysis of various immune cells (Table 3).^{4,5,8,9} Figure 1 depicts the mechanism of action of alternative induction agents from rATG.

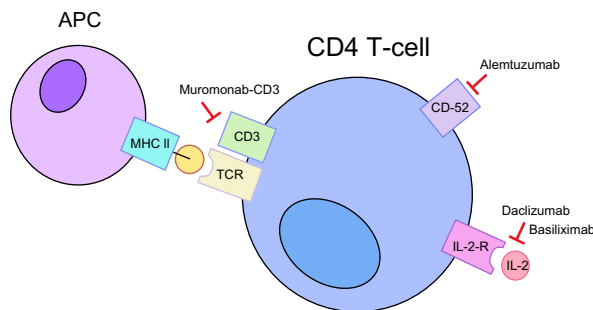


Figure 1 Alternative induction agents and cellular binding sites.

Abbreviations: APC, antigen-presenting cell; MHC II, major histocompatibility complex II; IL-2, interleukin-2; IL-2-R, interleukin-2 receptor; TCR, T-cell receptor; CD, cluster of differentiation.

Dosing and administration

Because use of Thymoglobulin in induction therapy is off-label, and US Food and Drug Administration approval is limited to treatment of acute rejection of renal transplant, the manufacturer’s dosing suggestions are limited to treatment of acute rejection in adults, ie, 1.5 mg/kg/day for 7–14 days.²

Various strategies for rATG induction have been proposed and may vary based on cumulative dose, timing of first dose, and duration of therapy.¹⁰⁻¹² The efficacy of 3-day induction was evaluated by comparing outcomes in 40 renal transplant recipients with a historic group of 48 patients who underwent a 7-day induction.¹⁰ The 3-day course was administered as a single 3 mg/kg intraoperative dose followed by 1.5 mg/kg on postoperative

Table 2 Efficacy outcomes of rATG induction versus alternative regimens

Reference	Treatment (mg/kg/day, unless noted otherwise)	n	Time of assessment (years)	BCAR (%)	Patient survival (%)	Graft survival (%)
Versus noninduction regimens						
Charpentier et al ¹⁷	rATG 1.25 + TAC 0.3 PO ^a	186	0.5	15**	98.4	95.2
	rATG 1.25 + CsA PO	184	0.5	21.2	97.0	90.8
	TAC 0.3 PO	185	0.5	25.4	97.0	95.2
Mourad et al ¹⁸	rATG 1.25 + TAC 0.2 ^a	151	1	15.2**	97.4	92.1
	TAC 0.2	158	1	30.4	96.8	91.1
Versus BAS						
Lebranchu et al ^{5,***}	rATG 1–1.5	50	0.5	8	100	100
			1	8	100	96
	BAS 20 mg on days 0 and 4 ^b	50	5	8	98	96
Mourad et al ²²	rATG 1	53	1	8	98	96
			10	8	98	96
	BAS 20 mg on days 0 and 4 ^b	52	1	8	98	96
Brennan et al ^{21,c}	rATG 1.5	141	1	9.4	98.1	96.2
	BAS 20 mg on days 0 and 4	137	1	9.6	98.1	94.2
Haririan et al ²³	ATG 1.5	36	1.5	15.6*	95.7	90.8
	BAS 20 mg on days 0 and 4	52	1.5	25.5	95.6	89.8
Brennan et al ²⁷	rATG 1.5	48	0.5	14	94	91
			1	4	98	98*
			5	8	85	77*
Hardinger et al ^{25,26,d}	eATG 15	24	0.5	10	75	48
			1	11	75	48
			5	17	96	–
			10	17	96	–
Farney et al ^{29,30,e}	rATG 1.5	50	0.5	25	96	83
	Alemtuzumab 30 mg single dose	48	0.5	34	71	54
				42	67	50
Versus alemtuzumab						
Farney et al ^{29,30,e}	rATG 1.5	50	0.5	20	100	96
	Alemtuzumab 30 mg single dose	48	0.5	0	98	95

Notes: ^atreatment groups received rATG induction and delayed start TAC; ^bafter first dose, subsequent dosage adjustments maintained CD2+ or CD3+ T-cell counts <20/mm³; ^cpatients at high risk of acute rejection or delayed graft function; ^dpatient population was African-American; ^e77% of patients underwent kidney transplants alone, 17% underwent pancreas-kidney transplants, and 4% underwent pancreas after kidney transplant. **P*<0.05 versus comparator(s); ***P*<0.01 versus comparator(s); ***trial was not sufficiently powered to test comparative efficacy.

Abbreviations: BAS, basiliximab; BCAR, biopsy-confirmed acute rejection; CsA, cyclosporine; DAC, daclizumab; eATG, equine anti-thymocyte globulin; MMF, mycophenolate mofetil; n, number of patients; PO, oral; rATG, rabbit anti-thymocyte globulin; TAC, tacrolimus.

days 1 and 2, while the 7-day course consisted of 1.5 mg/kg intraoperatively followed by six additional daily doses of the same size. At one year post transplant, there were no significant differences in frequency of acute rejection episodes, graft survival, or patient survival.¹⁰ However, there was a significantly shorter duration of initial hospital stay (6.1 days versus 8 days) and more sustained lymphocyte depletion with 3-day induction.¹⁰ Intraoperative administration was evaluated in a second, randomized, prospective study of 58 cadaveric renal transplant recipients who received either intraoperative or postoperative rATG induction therapy.¹¹ The total number of rATG doses were equal between the treatment groups, and intraoperative dosing resulted in significantly fewer cases of delayed graft function, lower mean serum creatinine on postoperative days 10 and 14, and a shorter duration of hospital stay (*P*<0.05).¹¹ There was no difference in incidence of cytomegalovirus infection.

rATG regimens ranging from 1 mg/kg to 6 mg/kg per dose for durations from one to 10 days have been studied in clinical settings. In high-risk patients, regimens providing cumulative doses of less than 7.5 mg/kg produced immunosuppressive results similar to regimens providing greater than 7.5 mg/kg, but with lower rates of infection and less development of lymphoma.¹³ At the lower end, cumulative doses of less than 3 mg/kg have been shown to be ineffective at preventing acute rejection.¹¹ The literature suggests that induction totaling 6 mg/kg, administered in divided doses of 1–2 mg/kg over 3–5 days, may provide the best balance of immunosuppression and risk of infection.^{10,11,14–16}

rATG induction versus no induction

Two large, randomized controlled trials have examined rATG induction regimens versus noninduction regimens

Table 3 Mechanisms of action of rabbit anti-thymocyte globulin

Profound lymphocyte depletion	<ul style="list-style-type: none"> • Primary mechanism for rATG immunosuppressive activity • Depletes T-cell via complement-dependent lysis and T-cell activation and apoptosis • Mechanism for this activity is not well understood
Immune cell modulation	<ul style="list-style-type: none"> • Modulates key cell-surface adhesion (CD11a/CD18 integrin) and chemokine receptors • Limits cellular infiltration following post-ischemic reperfusion
Apoptosis/cell lysis	<ul style="list-style-type: none"> • Induces apoptosis in naïve B-cells, activated B-cells, and bone marrow plasma cells • Targets cell surface proteins CD19, CD20, CD80, CD40, CD38, and CD138
Other	<ul style="list-style-type: none"> • Interferes with dendritic cell maturation and migration • Induction of regulatory T-cells and natural killer T-cells by targeting GITR, CTLA-4, and Foxp3

Notes: Unlike monoclonal antibody preparations, polyclonal rATG antibodies target a wide range of immune cell surface antigens, with broad effects on the immune cells; rATG antibodies are known to target T-cells, natural killer cells, B-cells, plasma cells, adhesion molecules, and chemokine receptors.^{3,6,7}

Abbreviations: rATG, rabbit anti-thymocyte globulin; CD, cluster of differentiation; GITR, glucocorticoid-induced tumor necrosis factor receptor; Foxp3, Forkhead box p3; CTLA, cytotoxic T lymphocyte-associated antigen.

in the prevention of renal allograft rejection in adult renal transplant recipients.^{17,18} A three-arm, open-label study compared 555 renal transplant patients who randomly received either tacrolimus triple therapy, ATG induction with tacrolimus, or ATG induction with cyclosporine microemulsion.¹⁷ There were no differences between the treatment groups with regard to mean cold ischemia time, cytomegalovirus status of donor and recipient, or values for human leukocyte antigen mismatch. The number of patients with a panel reactive antibody grade greater than 50% was significantly higher only in the ATG with cyclosporine group ($P=0.044$). All patients received concomitant azathioprine and corticosteroids. Results from this study suggest that addition of ATG induction to tacrolimus immunosuppressive therapy (delayed tacrolimus therapy) leads to significantly fewer cases of biopsy-confirmed acute rejection (BCAR) at 6 months post-transplant.¹⁷ The incidence did not differ significantly between tacrolimus-based therapy with ATG induction and cyclosporine-based therapy with ATG induction, although between these two groups, the incidence of moderate or severe rejection was more common with the cyclosporine-based regimen (13.6% versus 5.4%, $P<0.023$).

A second clinical trial, comparing ATG induction and delayed tacrolimus therapy against immediate tacrolimus-based triple therapy, also found lower rates of BCAR with ATG induction at 12 months post-transplant.¹⁸ However,

neither of these trials reported differences in overall patient or graft survival at 6 and 12 months with ATG induction, and ATG induction did not significantly impact development of delayed graft function or mean serum creatinine levels at 6 and 12 months. Neither study accounted for differences in donor kidneys (living versus deceased) or donor criteria (standard versus expanded) as possible confounding variables.

rATG induction versus nondepleting agents

Two interleukin-2 receptor antagonist induction therapy options, ie, daclizumab (Zenapax[®]) and basiliximab (Simulect[®]). A 2004 meta-analysis of 117 reports of 38 trials examined the efficacy of interleukin-2 receptor antagonist induction therapy.¹⁹ Compared with placebo, interleukin-2 receptor antagonists did not significantly reduce graft loss at one or 3 years post-transplant. Acute rejection was significantly reduced at 6 months (12 trials: relative risk [RR] 0.66, confidence interval [CI] 0.59–0.74) as well as one year (ten trials: RR 0.67, CI 0.60–0.75). Rates of cytomegalovirus infection and malignancy were not significantly reduced at one year. When compared with other antibody therapies, non-interleukin-2 receptor antagonist antibody therapies showed lower rates of biopsy-diagnosed acute rejection, graft loss/death, all-cause mortality, and delayed graft function. Interleukin-2 receptor antagonists were associated with lower rates of adverse effects. The researchers concluded that there was no definite improvement in graft or patient survival and no apparent differences between basiliximab and daclizumab.

In September 2009, Roche announced its voluntary discontinued production of daclizumab due to the availability of alternative induction agents and limited market demand for daclizumab.²⁰

Basiliximab is a chimeric mouse-human monoclonal antibody to the alpha chain of the interleukin-2 receptor of T-cells and is the only nondepleting agent currently on the market. Several studies have shown basiliximab to be less effective than rATG in preventing acute rejection in renal transplant recipients at increased risk of rejection. A prospective, multicenter trial assessed the safety and efficacy of basiliximab (n=137) 20 mg given on postoperative days 0 and 4 versus rATG (n=141) 1.5 mg/kg given on days 0–4 (total 7.5 mg/kg) as induction therapy in renal transplant recipients at high-risk for acute rejection or delayed graft function.²¹ “High-risk” was defined by cold

ischemia time and specific donor/recipient factors. All patients received cyclosporine A (Neoral[®]), mycophenolate mofetil, and corticosteroid taper, with cytomegalovirus prophylaxis given in patients with seropositive donor and/or recipient status. Antifungal and antibacterial prophylaxis was administered as per each center's protocol. At the end of 12 months of follow-up, the overall incidence of first occurrence of biopsy-proven acute rejection (BPAR), delayed graft function, graft loss, or death was similar between the basiliximab and rATG groups (56.2% versus 50.4%, $P=0.34$). The BPAR rate was higher in the basiliximab group (25.5%) than in the rATG group (15.6%), and this difference was statistically significant ($P=0.02$).²¹ In addition, rejection requiring antibody treatment was more common in the basiliximab group than in the rATG group (8.0% versus 1.4%, $P=0.005$).²¹ However, the incidence of delayed graft function was similar between the basiliximab and rATG groups (44.5% and 40.4%, respectively, $P=0.54$). Occurrence of infection was higher in the rATG group when compared with the basiliximab group (85.8% versus 75.2%, $P=0.03$); however, interestingly, the rate of cytomegalovirus-related infections was higher in the basiliximab group when compared with the rATG group (17.5% versus 7.8%, $P=0.02$), which contradicts the findings of previous studies.^{5,22} Leukopenia and thrombocytopenia immediately post-transplant were more common in the rATG group, but rates were similar by day 14. Patient and graft survival rates at one year were similar in both groups. Furthermore, an open-label, prospective French study demonstrated similar patient and graft survival rates in low immunologic risk renal transplant recipients when comparing the safety and efficacy of basiliximab ($n=52$) and rATG ($n=53$).²² In comparing the two cohorts, there was a lower incidence of adverse effects in the basiliximab cohort than in the rATG cohort for the primary endpoints of thrombocytopenia (0% versus 30.2%, $P<0.0001$), leukopenia (19.2% versus 51.0%, $P=0.0007$), and cytomegalovirus infection (21.2% versus 41.5%, $P=0.025$).²² However, this study only reached statistical power for its primary endpoint of adverse event rates.

The benefits of rATG over basiliximab are not as clear in some subsets of the transplant population. A retrospective analysis of rATG and basiliximab induction in 88 African-American renal transplant recipients, a recognized high-risk group, has been completed.²³ At baseline, renal transplant recipients in the rATG group spent a longer time waitlisted, had a longer duration of end-stage renal disease, were more sensitized, and were more likely to receive retransplants when compared with the basiliximab group. The number of human

leukocyte antigen mismatches, allograft cold ischemia time, and donor age and race was similar between the two groups. No difference was found in patient and graft survival, graft function, and incidence of acute rejection and cytomegalovirus infection between the treatment groups.²³

rATG induction versus other depleting agents

Selection of an induction agent is highly dependent upon patient-specific factors along with institution-based preferences and drug availability. In the US, use of lymphocyte-depleting agents has steadily risen over the past 10 years, with lymphocyte-depleting agents reported as the most commonly utilized (60%) induction therapy (25%), and rATG and alemtuzumab (Campath[®]) as the most commonly administered lymphocyte-depleting induction agents.²⁴

Although there are multiple ATG products on the market, utilization of eATG (Atgam[®]) has declined due to the improved tolerability and increased efficacy seen with the rATG product.^{25,26} A single-center, randomized, double-blind trial was conducted to assess the efficacy and safety of rATG versus eATG as an induction agent over a 5-year follow-up period. Seventy-two adult transplant recipients were randomized to receive either rATG ($n=48$) as a 1.5 mg/kg/dose given for up to 7 days or eATG ($n=24$) as a 15 mg/kg/dose given for up to 7 days.²⁶ All patients received cyclosporine A (Neoral), azathioprine, and corticosteroids for maintenance immunosuppression, with the exception of retransplants, patients with severe gout needing allopurinol, and patients with end-stage renal disease secondary to an immunologic cause, who were given mycophenolate mofetil instead of azathioprine. At the end of the follow-up period, "event-free survival" was higher in the rATG group than in the eATG group (73% versus 33%, $P<0.001$).²⁶ There was a significantly higher graft survival seen in the rATG group when compared with the eATG group (77% and 54%, respectively, $P=0.046$). Patient survival was similar between the two arms. At 5 years, rATG patients had a significantly ($P=0.0073$) lower incidence of acute rejection (8%) when compared with eATG patients (34%), but no statistically significant difference in mean serum creatinine was noted between the two groups. Absolute lymphopenia ($<1,000$ cells/mm³) developed rapidly in both groups, and persisted for almost one year in patients receiving rATG and for only 14 days in eATG patients, suggesting more profound lymphocyte depletion with rATG. Furthermore, suppression of CD3, CD5, CD4, and the CD4/CD8 ratio was greater in the rATG group than in the eATG group.²⁶ In addition, there

was a higher incidence of malignancy noted in the Atgam group compared with the Thymoglobulin group (21% versus 6%, $P=0.01$).²⁶

Favorable trends for utilization of rATG over eATG continued at 10-year follow-up in the same study, all indicating increased graft survival and lower rejection rates, with a decreased incidence of malignancy in the rATG cohort when compared with the eATG cohort.²⁵ Similar findings from other studies have led to a significant decline in the use of Atgam as an induction agent, with Thymoglobulin now being the preferred product.²⁷

Alemtuzumab, a humanized anti-CD52 receptor monoclonal antibody targeting CD52 receptors on both B-cells and T-cells, is increasingly being used off-label as renal transplant induction therapy. Optimal dosing and frequency for induction of renal transplant recipients have not been established. Similar patient and graft survival rates were demonstrated in a prospective, randomized, controlled trial comparing alemtuzumab with conventional (rATG or basiliximab) induction therapy in kidney transplant recipients stratified for risk of rejection.²⁸ Patients at low risk of rejection received alemtuzumab or basiliximab induction whereas patients at high risk of rejection received alemtuzumab or rATG induction. All patients received tacrolimus, mycophenolate mofetil, and corticosteroids, with early withdrawal and prophylactic regimens initiated as per institutional protocol. At 12 months' follow-up, the rate of BPAR was lower in the alemtuzumab group when compared with both conventional groups (5% versus 17%, $P\leq 0.001$).²⁸ At 3-year follow-up, a significantly ($P=0.003$) lower rate of BPAR was seen with alemtuzumab (10%) when compared with basiliximab (22%), but no difference was seen between alemtuzumab (18%) when compared with rATG (15%, $P=0.63$).²⁸ Additionally, a prospective trial randomizing kidney alone, pancreas alone, and kidney-pancreas transplant recipients to either alemtuzumab ($n=48$) or rATG ($n=50$) with similar maintenance immunosuppression based on immunologic risk showed similar acute rejection rates.²⁹ When comparing kidney alone transplant recipients, graft survival for the alemtuzumab and rATG cohorts was 95% and 96%, respectively (not statistically significant).²⁹ However, there was a significantly higher number of acute rejection episodes in the rATG group than in the alemtuzumab group ($P=0.007$), with the majority of rATG rejection episodes occurring in standard criteria donor kidney transplants. At 3 years, a larger study of the same group ($n=222$) revealed similar outcomes, with a lower incidence of BPAR episodes in kidney alone transplant patients receiving alemtuzumab than in those receiving rATG (12%

versus 27%, $P=0.03$).³⁰ Significant differences in infectious complications were observed in both studies.²⁸⁻³⁰ Of note, in 2012, Sanofi voluntarily withdrew alemtuzumab from the US and European markets in preparation for an upcoming relaunch with a new indication for treatment of multiple sclerosis, under the trade name Lemtrada®.³¹

OKT3 (muromonab-CD3) was the first biologic agent used in clinical medicine and is the only nonhumanized antibody approved for use in the treatment of acute renal allograft rejection.³ Early evidence suggested that OKT3 was superior to steroids for reversing rejection, which translated into better survival in patients experiencing acute rejection.^{32,33} OKT3 is a mouse-derived monoclonal antibody directed against the CD3 antigen on the surface of T-lymphocytes. The murine monoclonal structure has been shown to promote production of anti-murine antibodies in patients, which can result in tachyphylaxis and anaphylaxis. Immune reactions to OKT3 may be life-threatening, and such reactions can include shock, cardiovascular collapse, cardiac arrest, and respiratory arrest when subsequent doses are administered.³⁴ Initial doses must be administered on an inpatient basis under close supervision and may require prophylaxis with glucocorticoids, antihistamines, and acetaminophen. Because newer induction antibodies are efficacious without the risk of life-threatening immune reactions and cumbersome administration requirements, OKT3 has fallen out of favor in kidney transplant induction. Following a decline in market demand, Janssen discontinued production of OKT3 in 2010.

Special populations

Pediatric renal transplant recipients

Data on the comparative efficacy of rATG and other induction regimens are sparser and less clear in pediatric renal transplant recipients. There is no clear consensus on best induction practices in this population. Two retrospective studies evaluated the relative efficacy of no induction and induction with rATG, eATG, or basiliximab in pediatric patients also receiving combination immunosuppressive therapy.^{35,36} The first of the studies, by Khositseth et al, compared rATG 1.5 mg/kg/day for 10 days with eATG 15 mg/kg/day for 14 days in subjects receiving concomitant corticosteroids, cyclosporine, and mycophenolate mofetil.³⁶ Khositseth et al found that rATG induction was associated with significantly lower rates of BCAR (33% versus 50%, $P=0.02$) up to 3 years after transplantation in these patients. Median time to BCAR and severity of BCAR were not significant between the treatment groups,

nor was there any difference in patient survival at the one-year, 2-year, and 3-year follow-up, or in any other measured endpoint or laboratory marker. Findings from a study by Baron et al suggest that the incidence of BCAR at one year post transplant was not significantly different when comparing no induction, rATG induction, and basiliximab induction. Patient and graft survival rates were comparable at one year, but mean glomerular filtration rate in rATG recipients (42.4 mL per minute) was significantly reduced ($P < 0.05$) versus basiliximab (78.3 mL per minute) or no induction (66 mL per minute).³⁵ Both studies suggest that rATG induction is relatively well tolerated in pediatric patients.^{35,36} There was no difference in incidence of cytomegalovirus infection or post-transplant lymphoproliferative disorder between rATG, eATG, or basiliximab induction, or without induction.³⁶ However, there was a significantly increased likelihood of Epstein–Barr virus infection with rATG induction than with eATG induction (8% versus 3%, respectively, $P = 0.002$).

Elderly renal transplant recipients

The choice of induction immunosuppressive agents in elderly transplant recipients has been a matter of constant debate, given the reduced immunogenicity and high risk of infection in this subset of the transplant population.³⁷ Very few studies have addressed the selection of induction agents in this population. A retrospective registry analysis using the Organ Procurement Transplantation Network/United Network of Organ Sharing database compared induction with rATG ($n = 7,140$), an interleukin-2 receptor antagonist ($n = 6,215$), and alemtuzumab ($n = 1,465$) in four groups of elderly (>60 years) deceased donor kidney transplant recipients categorized according to recipient and donor risk factors.³⁸ Use of rATG was associated with a low risk of rejection and functional graft loss in high-risk recipients (panel reactive antibody >20%, black race, or prior transplant) with high-risk donors (extended criteria donor, donation after cardiac death, or cold ischemia time >24 hours). A lower rejection rate with use of rATG was also noted in low-risk recipients with high-risk donors, but there was no difference in functional graft loss as compared with interleukin-2 receptor antagonists. Prospective comparison of these agents is warranted to compare efficacy versus risk in the elderly population.

HCV-positive renal transplant recipients

Kidney transplantation in hepatitis C virus-seropositive (HCV+) recipients is associated with improved survival

compared with staying on dialysis.³⁹ Concerns about using rATG in HCV+ patients are related to the possibility of progression of HCV infection and associated liver disease following enhanced immunosuppression. In an Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients analysis, Luan et al⁴⁰ showed that induction with either depleting or nondepleting antibodies was associated with a 25% lower risk for mortality in 3,708 HCV+ recipients as compared with those not receiving induction therapy. A significantly reduced hazard ratio (HR) for death among HCV+ renal transplant recipients was apparent 2 years post-transplant (0.75, 95% CI 0.61–0.90, $P = 0.003$). Risk of death-censored graft failure was not affected by induction therapy, neither were rates of delayed graft function, acute rejection, or graft failure in a subgroup analysis. The risk of death with a functioning graft was significantly reduced by induction therapy (HR 0.71, 95% CI 0.58–0.86, $P = 0.0004$). The investigators documented a reduced HR for patient death with the use of depleting antibody induction (OKT3, ATGAM, rATG; HR 0.82, 95% CI 0.69–0.98, $P = 0.03$) and a comparable HR reduction with nondepleting induction (interleukin-2 receptor antagonists; HR 0.79, 95% CI 0.64–0.98, $P = 0.03$).⁴⁰ They noted that the mechanism underlying this reduction in mortality risk was unclear, but was not likely related to differences in kidney graft outcomes, given that no significant differences in rates of acute rejection and death censored graft failure were observed.⁴⁰ Another Scientific Registry of Transplant Recipients analysis observed similar improvements in patient survival among HCV+ recipients given either depleting or nondepleting antibody induction.⁴¹ These studies suggest that HCV seropositivity should not influence selection of induction agents in renal transplant candidates.

Limited studies have examined the long-term outcomes of HCV-related liver disease after kidney transplantation. Despite comparable outcomes with various induction agents on a short-term basis, one retrospective study that analyzed post-transplant biopsies collected every 5 years suggests better outcomes with lymphocyte-depleting induction agents.⁴² A subset analysis ($n = 31$) revealed a pattern of progressive liver fibrosis in HCV+ renal transplant recipients receiving daclizumab induction as compared with OKT-3 or rATG induction.⁴² However, the bulk of the retrospective data obtained to date suggests better patient and death censored graft survival with the use of induction therapy, both depleting and nondepleting, in HCV+ kidney transplant recipients.^{40,41,43}

HIV-positive renal transplant recipients

With the advent of highly active antiretroviral therapy in 1996, the morbidity and mortality associated with human immunodeficiency virus (HIV) infection has decreased dramatically. Historically, HIV was an absolute contraindication to kidney transplantation. However, with increased life expectancy secondary to improved antiretroviral therapy, patients with well managed HIV infection comprise a significant proportion of transplant candidates at many transplant centers. The use of rATG in an HIV-infected individual is controversial. In a prospective observational study of 20 consecutive kidney transplant recipients, profound suppression of CD4+ T-cells from 475 cells per μL to 9 cells per μL was noted after administration of Thymoglobulin in eleven recipients, which successfully reversed rejection.⁴⁴ Use of rATG did not result in a significant increase in opportunistic infections or progression to acquired immunodeficiency syndrome or death, but led to an increased risk of bacterial infection requiring hospitalization. Similarly, in a prospective study of 150 HIV-infected kidney transplant recipients, Stock et al⁴⁵ found that patients who received rATG had about twice as many serious infections per follow-up year than patients who did not (0.9 versus 0.4, $P=0.002$). In addition, the risk of graft loss (HR 2.5, CI 1.1–5.6) was marginally higher for patients who received rATG. The optimal induction agent needs to be very carefully selected in this population because not only are they at an increased risk of rejection but there is also a concern about an increase in infectious complications. The currently available data suggest restricting rATG to patients at high immunological risk of rejection.

Safety and monitoring

rATG is generally well tolerated, with adverse reactions ranging in severity but most often manageable and reversible.^{46–49} Acute hypersensitivity reactions and anaphylaxis to rATG are rare, with the primary risk factor being allergy to the rabbit component of the drug. Serum sickness, on the other hand, has a delayed onset, and may occur 1–3 weeks after administration, with a reported frequency of 7%–27%.⁴⁶ This delayed immune response can present as fever, arthralgia, pruritus, and swelling at the injection site because of a reaction to the protein content of the rabbit serum component of rATG.⁴⁶ Some patients may experience cytokine release syndrome with primary exposure to an rATG dose. The mechanism behind this reaction is thought to be related to a rapid rise in inflammatory cytokines such as interleukin-8 and tumor necrosis factor-alpha on first exposure to monoclonal and polyclonal antibodies such as rATG.⁴ Patients may develop

mild to severe flu-like symptoms, including fever, rash, shivering, nausea, vomiting, diarrhea, malaise, and in severe cases, respiratory failure. Most institutions now routinely premedicate with corticosteroids, diphenhydramine, and acetaminophen to circumvent these reactions.

A central line infusion is the preferred route of administration for rATG due to the risk of venous thrombosis associated with peripheral administration. This risk has been found to be significantly reduced by adding hydrocortisone and heparin to the rATG infusion solution,⁵⁰ facilitating utilization of the drug without central line placement and in outpatient settings. To minimize possible reactions to rATG, the duration of drug infusion is typically 4 hours or longer. Transplant centers that have administered infusions in 4 hours or less have reported a higher incidence of “first-dose syndrome”, including adverse events such as dyspnea, shivering, and nausea.²⁷

There are no known drug interactions established with rATG. However, as with other immune globulin products, in patients receiving concomitant plasmapheresis and rATG, it should be noted that plasmapheresis may remove the rATG drug product.^{49,51} The percentage of total dose removed is currently unknown; however, administration after a plasmapheresis session may provide the most effect of an rATG dose.

Leukopenia and thrombocytopenia are commonly observed adverse reactions to administration of rATG, given the profound lymphocyte depletion seen with this drug. Concomitant therapy with drugs known to cause hematologic toxicity, including mycophenolate mofetil and valganciclovir (Valcyte[®]), can potentiate this risk. Daily monitoring of white blood cell, T-cell, and platelet counts is warranted, with dose adjustment based on the level of depletion. Routine utilization of immune function monitoring assays such as ImmuKnow[®] is not yet validated. Several studies have suggested an increased risk of cytomegalovirus disease with use of rATG. However, changes in prophylactic agents and regimens for cytomegalovirus may help to minimize this risk.

The Scientific Registry of Transplant Recipients reviewed 41,686 renal transplant recipients for incidence of post-transplant lymphoproliferative disorder over a follow-up period from January 1, 1996 to February 28, 2002. Patients received either no induction therapy or induction therapy with monoclonal or polyclonal antibodies (eATG, rATG, OKT3, daclizumab, basiliximab, Nashville rabbit ATG, or T10B9). There was a significantly increased risk of developing post-transplant lymphoproliferative disorder in those receiving induction therapy compared with those receiving no induction therapy (RR 1.78, $P<0.001$).⁵² The incidence of

post-transplant lymphoproliferative disorder in rATG patients was 5.7% (RR 3.00, $P=0.001$) versus 9% in eATG patients (RR 1.50, $P=0.1$).⁵² Similar findings have been reported from other US databases.^{53,54} However, it should be noted that these databases included all agents, including the older induction agents such as OKT3, and may not necessarily reflect current practice. However, the reported incidence of post-transplant lymphoproliferative disorder in patients receiving rATG is still low, and similar to that for other induction agents.^{22,25,26} In the pediatric population, a higher rate of Epstein–Barr virus infection was found with rATG, but this did not increase the risk of post-transplant lymphoproliferative disorder.³⁵ It is imperative to note that several variables, including recipient-specific risk factors, concomitant disease states and drug therapy, and post-transplant medical management may alter this risk. Xenogeneic anti-rabbit antibody formation may occur after exposure to rATG. A few studies have suggested lower drug concentrations secondary to neutralizing antibodies against the drug; however, this has not been shown to affect treatment outcomes or patient and graft survival.^{53,54}

During recent years, the kidney transplant population has witnessed an upward trend in incidence of BK virus (BKV) nephropathy, which currently affects approximately 7.5% of renal transplant recipients.^{55–57} While upwards of 90% of the general population are benign latent carriers of BKV, reactivation of BKV in immunosuppressed patients often results in clinically relevant BKV-related disease, including BKV nephropathy.^{57,58} An estimated 50%–90% of renal transplant recipients experience allograft loss within one year of BKV infection progressing to BKV nephropathy, making BKV nephropathy a significant risk factor for poor allograft prognosis.^{55–57}

Increasing potency of the immunosuppressive agents since the mid-1990s has paralleled the growing incidence of BKV-associated nephropathy in transplant patients.^{57,59} Immunosuppression is presumed to create a more permissive environment for viral replication. However, the relative potency of an immunosuppressive agent alone should not be used to predict its impact on BKV infection.^{55,57,60} Kidney grafts are infected by BKV more frequently than native kidneys, suggesting that factors other than immunosuppression contribute to the pathogenesis of BKV in renal epithelial cells.⁶⁰ The influence of individual induction agents on development of BKV-associated nephropathy has been explored in numerous studies.^{61–66}

Two retrospective registry analyses found that rATG induction significantly increased the frequency of BKV

treatment versus no induction.^{61,62} Along the same lines, a prospective study found higher rates of BKV replication at 6 months post-transplant versus no induction.⁶¹ However, the data available for the effects of ATG on BKV replication have been inconsistent.^{16,62–66} A prospective, single-arm study found that, when used in the treatment of acute rejection, ATG did not influence BKV markers for replication or development of nephropathy.⁶⁶ One registry analysis found that exposure to human ATG was not associated with a greater need for treatment of BKV.⁶² A number of other studies could not identify ATG as an independent risk factor for BKV viremia, BKV viremia, or BKV nephropathy.^{16,64–67} While the data suggest that rATG induction may increase the incidence of BKV-associated disease, additional investigation is warranted.

In the largest alemtuzumab and BKV nephropathy outcomes study performed to date, Theodoropoulos et al retrospectively followed 666 simultaneous pancreas-kidney transplant patients and found that 4.7% of those who underwent induction with alemtuzumab developed BKV nephropathy.⁶⁸ This rate of BKV nephropathy did not differ significantly from that observed in patients who underwent less potent induction regimens with basiliximab, rATG, or steroids alone.⁶⁸ Previous studies of alemtuzumab induction and risk of BKV nephropathy have yielded both supporting and conflicting data.^{29,68–74} However, unlike most of the earlier studies, Theodoropoulos et al analyzed BKV nephropathy as a coprimary endpoint (along with onset of BK viremia or BK viremia), which strengthens the validity of their findings.⁶⁸ Data from registry analysis and retrospective review indicate that induction with nondepleting agents such as basiliximab and daclizumab does not significantly impact the risk of developing BKV.^{55,57,62,70,75}

Cost-effective strategies with thymoglobulin induction

Optimizing rATG induction regimens can have significant financial implications. The average wholesale price for a five-dose course of rATG is estimated at \$12,750.00 (1.5 mg/kg \times 5 doses for a 70 kg patient).⁷⁶ Marfo et al conducted a retrospective review of 84 deceased donor kidney transplant recipients who received either short-course rATG of 1.5 mg/kg for a total of three doses ($n=28$; total mean dose 4.6 mg/kg) or standard rATG induction therapy of 1.5 mg/kg for a total of five doses ($n=32$; total mean dose 7.3 mg/kg).⁷⁷ At 6 months post-transplant, neither BCAR (17.8% versus 12.5%) nor serum creatinine concentration (1.56 mg/dL versus 1.85 mg/dL) differed significantly

between the short-course and standard-course rATG groups, suggesting that shorter-course rATG induction offers cost savings of up to 30% (\$2,548 per patient in 2011), without negatively impacting rates of graft survival or acute rejection. Moreover, short-course induction appeared to reduce the prevalence of therapy-related leukopenia compared with standard-course induction, although this finding was not statistically significant. CD3+ cell count monitoring has been proposed as a means of determining the minimum necessary cumulative dose of rATG.^{14,77,78} The efficacy of rATG is dependent on T-lymphocyte depletion and functional alteration, and there is evidence of successful dosing and cost minimization guided by CD3+ cell counts.^{14,78} In 2004, eight cardiac transplant recipients were treated with dose-adjusted rATG for induction and acute rejection, to maintain absolute CD3+ cell counts less than 25 cells/mm³.⁷⁸ Researchers observed a 60% reduction in the total dose of rATG administered and a 58% reduction in total cost. Another study examined the outcomes and pharmacoeconomics of intermittent administration of rATG doses as induction therapy in high-risk kidney and kidney-pancreas transplant recipients.¹⁴ The first doses of induction therapy were administered intraoperatively, and repeat doses were not given until CD3+ cell counts surpassed 20 cells/mm³. A calcineurin inhibitor was not initiated as part of the maintenance immunosuppression regimen until serum creatinine levels decreased by at least 25% from pretransplant levels, and rATG doses were discontinued once serum calcineurin inhibitor concentrations reached the therapeutic target range. This intermittent dosing schedule resulted in average savings of 46% and 68%, respectively, when compared with standard 6-day and 10-day rATG induction regimens.¹⁴ Unfortunately, there is no standard threshold for CD3+ cell counts in rATG dose adjustment. Depending on the literature consulted, adjustments may be made based on percent T-cell count from 10% to 20% or absolute T-cell counts ranging from 10 cells/mm³ to 100 cells/mm³.^{14,78} Because of this lack of consistency, monitoring of CD3+ cell count has not become standard practice in rATG induction therapy.

Conclusion

rATG is a lymphocyte-depleting polyclonal antibody that, when used as induction therapy, effectively reduces rates of BCAR in renal transplant recipients. rATG promotes intense immunosuppression that may be particularly beneficial in patients at high risk for acute allograft rejection, but benefits should be balanced with potential risks. rATG is not approved by the US Food and Drug Administration

for transplant induction, and current strategies for use vary widely based on cumulative dose, timing of first dose, and duration of therapy. Alternative induction agents may be broadly categorized as lymphocyte-nondepleting agents (daclizumab and basiliximab) or lymphocyte-depleting agents (eATG and alemtuzumab). Head-to-head comparisons suggest that rATG is more effective than basiliximab at preventing acute rejection in patients at high risk for acute rejection and delayed graft function, with some increased risk of infection. Compared with alternative depleting agents, rATG is better tolerated and more efficacious than eATG; rATG and alemtuzumab equally promote long-term graft survival, but the risk of acute graft rejection and BPAR may be elevated with rATG.

The debate on best practices in special populations is ongoing. rATG appears to be well tolerated in pediatric patients, although there is increased risk of Epstein–Barr virus infection in this population. Elderly patients have reduced immunogenicity and are at greater risk of post-transplant infection, and rATG induction may be best limited to recipients at high risk for rejection and with high-risk donors. Induction therapy of any kind has been shown to substantially improve survival in HCV-positive renal transplant recipients. rATG profoundly suppresses CD4+ T-cells in HIV-infected patients and should be restricted to use in patients at high immunologic risk for rejection.

rATG is well tolerated and adverse reactions are typically manageable and reversible. Immune reactions are common and may be serious, so most institutions premedicate with corticosteroids, diphenhydramine, and acetaminophen. Administration via central line infusion bypasses the risk of venous thrombosis; however, pretreatment with hydrocortisone and heparin also addresses this risk with outpatient peripheral infusion. Due to the risk of leukopenia and thrombocytopenia, white blood cell and platelet counts should be monitored daily, and rATG doses should be adjusted based on the level of depletion. Concomitant cytomegalovirus prophylaxis is recommended due to an increased risk of infectious complications.

rATG induction therapy is relatively expensive. Short-course therapy and intermittent dosing regimens have provided cost savings with no negative impact on graft survival or risk of acute rejection. CD3+ cell count monitoring has been proposed as a means to guide dose minimization; however, there are no established thresholds for CD3+ monitoring at this time. A cost-effective strategy in a kidney transplant protocol design including rATG induction should have emphasis on tailoring rATG doses based on the

renal transplant recipient's immunologic risk for rejection to balance efficacy with treatment-associated risks, such as infection and malignancy.

Disclosure

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