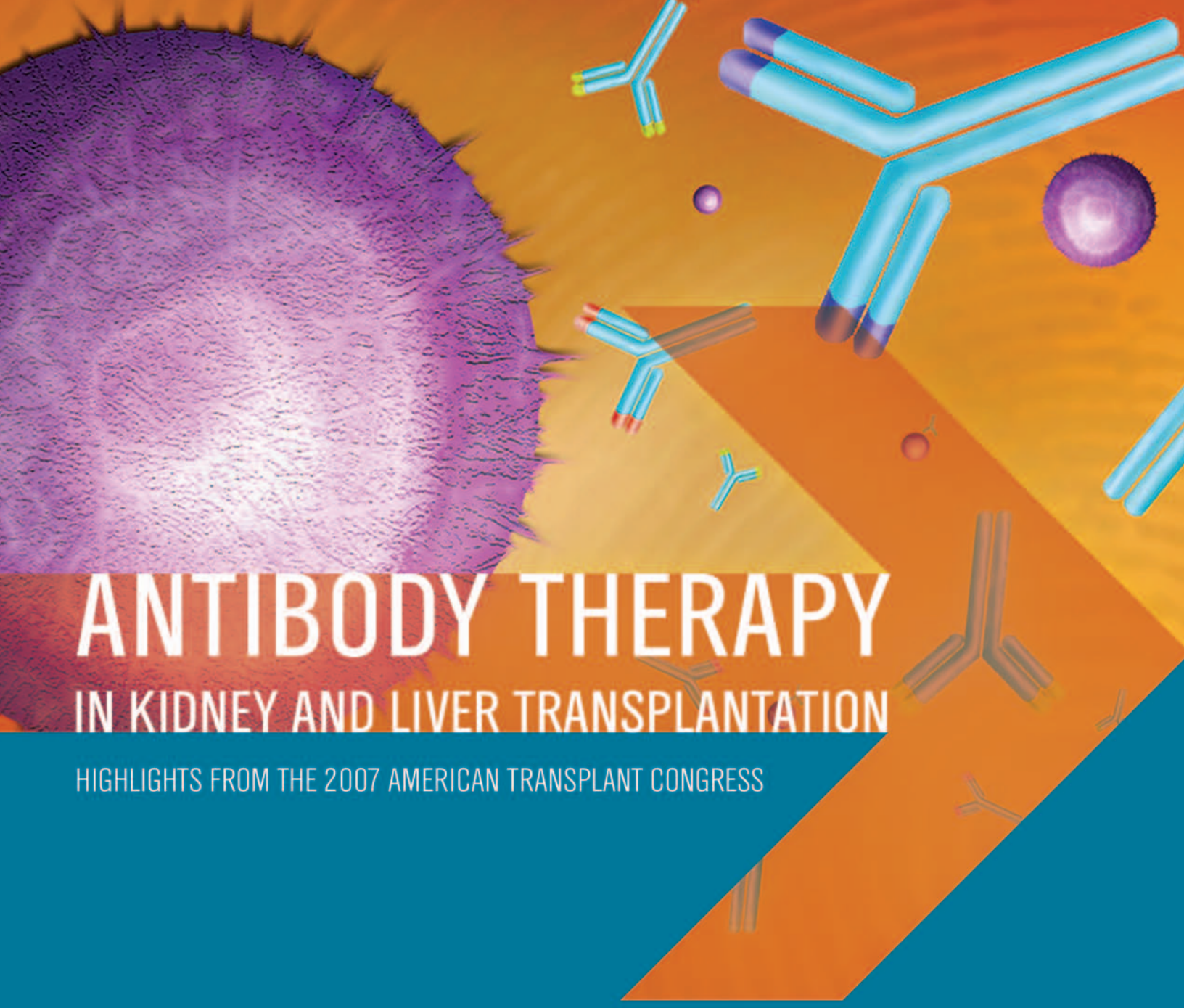

ANTIBODY THERAPY
IN KIDNEY AND LIVER TRANSPLANTATION

HIGHLIGHTS FROM THE 2007 AMERICAN TRANSPLANT CONGRESS

Robert S. Gaston, MD
Medical Director of Kidney and Pancreas Transplantation
Professor of Medicine: Division of Nephrology
Professor of Surgery: Division of Transplantation
University of Alabama at Birmingham
Birmingham, Alabama

William H. Marks, MD, PhD
Robert B. McMillen Chair and Director
Department of Organ Transplantation
Swedish Medical Center
Seattle, Washington

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ANTIBODY THERAPY
IN KIDNEY AND LIVER TRANSPLANTATION

2007 AMERICAN TRANSPLANT CONGRESS MEETING HIGHLIGHTS

ANTIBODY THERAPY IN KIDNEY AND LIVER TRANSPLANTATION

Abstract Review, San Francisco, CA, May 5 - 9, 2007

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Robert S. Gaston, MD
Medical Director of Kidney and Pancreas Transplantation
Professor of Medicine in the Division of Nephrology
Professor of Surgery in the Division of Transplantation
University of Alabama at Birmingham
Birmingham, Alabama

William H. Marks, MD, PhD
Robert B. McMillen Chair and Director
Organ Transplantation
Swedish Medical Center
Seattle, Washington

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It is the policy of the University of Kentucky to ensure balance, independence, objectivity and scientific rigor in all of its scientific activities. In accordance within the policy of the University of Kentucky, faculties are asked to disclose any affiliation or financial interest that may affect the content of their presentation. Faculty reported the following:

Robert S. Gaston, MD has received consultation fees from Novartis, Astellas, Roche, Pfizer and Genentech. He has received contract research support from Astellas and Roche Laboratories. Dr. Gaston is a member of a paid speaker's bureau with Astellas Pharma, US and Roche Laboratories.

William H. Marks, MD, PhD has no financial relationship with commercial interest of healthcare products or services that relate to the content of this CME activity.

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2007 AMERICAN TRANSPLANT CONGRESS MEETING HIGHLIGHTS

ANTIBODY THERAPY IN KIDNEY AND LIVER TRANSPLANTATION

Abstract Review
San Francisco, CA
May 5-9, 2007

The present CME activity summarizes the results of state-of-the art use of induction therapy in kidney and liver transplantation, as presented at the 2007 American Transplant Congress (ATC).

TARGET AUDIENCE

The activity is designed to meet the educational needs of transplant surgeons, physicians, nurses and pharmacists.

NEEDS ASSESSMENT

The trend to minimize the use of calcineurin inhibitors (CNIs) and corticosteroids (CSs) has contributed to an increase in the use of antibody induction therapy in kidney and liver transplantation. Significant comorbid conditions associated with historical maintenance immunosuppressive regimens consisting of CNIs and CSs have resulted in a paradigm shift in clinical practice. Identification of immunosuppressive regimens that both reduce long-term immunosuppressive load, and minimize immunosuppressive agent-specific toxicities, such as cardiovascular disease (CVD), new onset diabetes mellitus (NODM), and nephrotoxicity, has been a central focus for transplant clinicians over the past two decades.

Additionally, donor characteristics including advanced age, cardiac death, and extended cold ischemia time all put a patient at risk of poor long-term outcomes, and are factors that should be considered when making decisions about immunosuppressive regimens. More liver and kidney transplant recipients are also at high immunological risk, including those that are re-transplanted, sensitized, or African American, and therefore may require alterations to traditional regimens in an attempt to overcome these challenges.

Novel approaches to the use of existing antibody induction agents are the current focus of multiple clinical trials in kidney and liver transplantation. This summary of the most up-to-date clinical data regarding antibody induction, as presented at the 2007 American Transplant Congress, is offered to transplant clinicians to help support making critical decisions in this regard for individual patients.

EDUCATIONAL OBJECTIVES

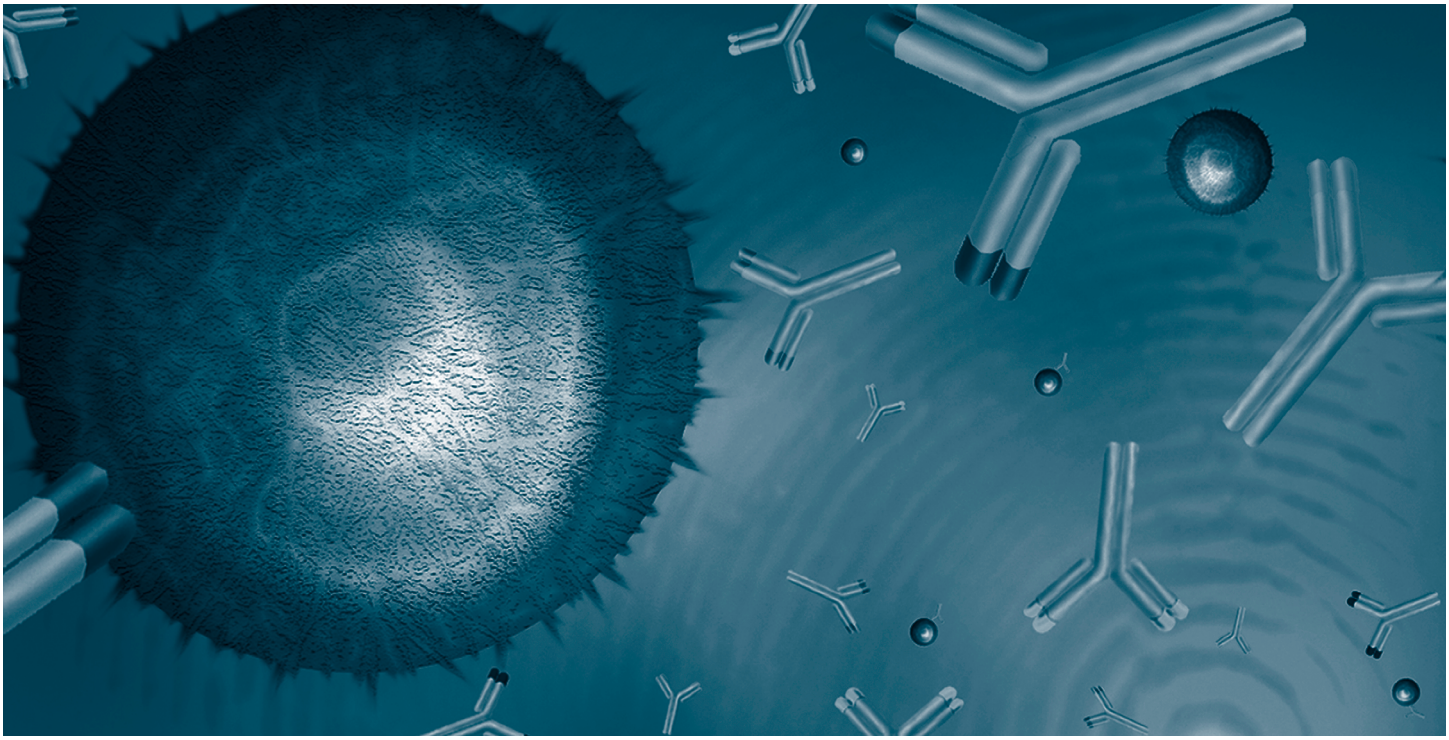
Following their review of the CME activity, transplant professionals will be able to:

1. Describe current safety and efficacy outcomes following the use of T-cell depleting polyclonal antibodies, T-cell depleting monoclonal antibodies, and non-depleting antibodies in kidney or liver transplantation
2. Describe novel approaches for the minimization of long-term maintenance immunosuppression
3. Identify unique management issues related to patient risk profiles

OFF-LABEL USE

The studies summarized in this report include investigator-driven use of immunosuppressive antibodies for indications not approved by the Food and Drug Administration (FDA). Drugs used outside labeled indications include alemtuzumab (Campath®, marketed by Bayer HealthCare Pharmaceuticals, Montville NJ), basiliximab (Simulect®, Novartis, East Hanover NJ), daclizumab (Zenapax®, Roche, Nutley, NJ), and rabbit anti-thymocyte globulin (rATG, Thymoglobulin®, Genzyme, Cambridge, MA).

Campath® is not currently indicated for organ transplantation.



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PROGRAM BACKGROUND

Over the past two decades, advances in immunosuppressive regimens have resulted in an improvement in both patient and graft survival for kidney and liver transplant recipients. Historically, standard triple therapy maintenance immunosuppressive regimens have consisted of a calcineurin inhibitor (CNI) [tacrolimus (TAC) or cyclosporine (CsA)], an antiproliferative agent [mycophenolate mofetil (MMF) or azathioprine (AZA)], or a target of rapamycin inhibitor [sirolimus (SRL)], and corticosteroids (CSs). As noted previously, these standard maintenance immunosuppressive regimens have been associated with substantial comorbid conditions in kidney and liver transplant recipients, including cardiovascular disease (CVD), new onset diabetes mellitus (NODM), nephrotoxicity, and gastrointestinal complications. Significant improvements in outcomes over the past 20 years have resulted in a transition of clinical focus from the traditional transplantation endpoints of acute rejection, graft survival, and patient survival, to attempts to minimize chronic immunosuppressive-related adverse events, while further decreasing acute rejection rates and improving overall survival.

Effective clinical management of kidney and liver transplant recipients has been further impacted by the introduction of new immunosuppressive agents and protocols. As will be demonstrated within this program review, a myriad of institution-specific and physician-specific immunosuppressive strategies exist in current clinical practice. Each strategy is somewhat unique due to varying patient populations, transplant center size, and, often times, existing institutional standards of care. It is the intent of this program to summarize results from retrospective patient analysis, single-center investigator-initiated trials, and multi-center, industry-supported experiences, so as to capture and report current clinical transplant immunosuppressive management practices, as presented at the 2007 American Transplant Congress (ATC).

Due to the large volume of data, differences in study design and patient population, as well as disparity in data reporting, it is a challenge to standardize nomenclature and terminology throughout the report. Wherever possible, definitions of endpoints have been provided. Due to the heterogeneity of these reports, the reader should be made aware that some conclusions and data interpretation are the result of a generalized summation of reported data, and may require further interpretation based upon individual needs and clinical experience.

ANTIBODY INDUCTION OVERVIEW

Induction therapy is usually interpreted as the utilization of a supplemental potent immunosuppressive agent during the early post-transplant period. Traditionally, this implies the administration of therapeutic antibodies (biologic agents) to minimize early rejection while avoiding concomitant usage of nephrotoxic agents, such as CNIs. More recently, primary goals of antibody induction therapy have evolved to include minimization or elimination of maintenance immunosuppressive agents, including CNIs and CSs, and their associated comorbidities.

Antibody induction agents include both monoclonal and polyclonal antibodies. Daclizumab (Zenapax®) and basiliximab (Simulect®) are humanized monoclonal antibodies that inhibit binding of interleukin-2 to its receptor while leaving overall lymphocyte populations relatively intact. Alternatively, alemtuzumab (Campath®), an anti-CD52 monoclonal, and, to a lesser extent, muromonab-CD3 (OKT3®) are depleting antibodies that result in reduction in absolute lymphocyte counts. Polyclonal antibodies include rATG and ATGAM®, both of which are T-cell depleting agents. The use of rATG, ATGAM, and alemtuzumab have all been associated with prolonged lymphopenia, which may account for the much lower frequency of acute rejection episodes when compared to Interleukin-2 receptor antagonists (IL-2RAs).[1]

KIDNEY TRANSPLANTATION

In 2006, the Organ Procurement and Transplantation Network (OPTN) reported the use of antibody induction therapy in 74% of US kidney transplant recipients.[2] Amongst those receiving kidney transplants in the US, 39% were administered rATG, 28% received either basiliximab or daclizumab, 9% received alemtuzumab, and <2% were treated with OKT3 or ATGAM. Since 2004, only the use of rATG and alemtuzumab has increased. Antibody induction regimens are utilized for a variety of recipient populations, including those with increased immunological risk factors, such as sensitized recipients, retransplants, and African American recipients. In addition, antibody induction regimens are utilized in patients to avoid or minimize CNIs or CSs. Wide ranges of rejection rates associated with these antibody induction agents were reported at the 2007 ATC, due to the varying study designs, patient populations and concurrent immunosuppressive regimens (Figure 1).

Figure 1

2007 American Transplant Congress Data Acute Rejection Rates Reported (+/- Antibody Induction Therapy)	
Alemtuzumab	~6% - 22%
IL-2 Receptor Antagonists	~25%
Rabbit ATG (rATG)	~9 - 21%
No Induction	~30 - 35%

EFFICACY OF ANTIBODY INDUCTION THERAPY IN KIDNEY TRANSPLANTATION

The 2007 ATC provided a forum for investigators to report both confirmatory data and long-term analysis regarding the efficacy of rATG and IL-2RAs in kidney transplant recipients, with follow-up ranging from 9-48 months post-transplant. Several abstracts reported shorter efficacy follow-up data in recipients treated with alemtuzumab, ranging from 9-12 months post-transplant. The results summarized in Table 1 are an overview of a larger body of efficacy data presented at the 2007 American Transplant Congress.

Long-term efficacy data from randomized, controlled clinical trials on the use of antibody induction therapy are scarce. One novel approach at this meeting reported long-term data on patients who participated in a multi-center controlled study that compared the safety and efficacy of rATG and basiliximab therapy.[3] The results reported were obtained by linking clinical trial data with OPTN data. Four year results are summarized in Abstract #334. Kidney transplant recipients treated with rATG experienced a significantly lower incidence of the triple composite endpoint of acute rejection (AR)/graft loss/death, than recipients treated with basiliximab, 37.3% vs. 49.5%, respectively (p=0.047). This study, based on eligibility criteria that quantitated high-risk, was reported by the author to be representative of nearly 50% of all deceased donor transplants in the US. In addition, this analysis demonstrated that rATG compared to basiliximab resulted in a significant difference in a quadruple composite endpoint of delayed graft function (DGF)/AR/graft loss/death, 58.5% vs. 72.1%, respectively (p=0.005). The same trial data were used to prospectively compare cost between the two antibody induction agents. The authors reported that the average per-patient cost is approximately $35,563 less for patients receiving rATG than those receiving basiliximab, primarily reflecting reduction in the need for treatment of adverse outcomes.[326]

A novel approach of administrating rATG was reported by Stevens and colleagues.[1449] A single infusion of rATG (6mg/kg) over 24 hours resulted in an acute rejection rate equivalent to patients who received 4 divided doses (1.5mg/kg for 4 doses to a target of 6mg/kg), with well-preserved renal function associated with the single infusion, particularly among recipients of kidneys from deceased donors.

Meta-analysis of studies published through October 2006 revealed that the IL-2RAs, basiliximab and daclizumab, reduce the risk of acute rejection, DGF, and graft failure (comparator not specified).[1467] The investigators noted, however, that the meta-analysis could not assess outcomes in African American recipients, due to lack of published studies, and that further studies were warranted.

Compared to treatment with alternate antibodies (rATG, OKT3 and ATGAM), basiliximab use in recipients of living donor kidneys resulted in a higher

Table 1. Efficacy of Antibody Induction Therapy in Kidney Transplantation

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#334 Brennan DC et al Novel Approach to Obtain Long-Term Outcomes of Patients in a Randomized Trial Comparing Thymoglobulin and Basiliximab in Kidney Transplant Using Registry Data. Washington University St. Louis	Review of US patient data through OPTN records matched to those from the randomized, multi-center, multinational trial comparing rATG and basiliximab	rATG n=91 Basiliximab n=92	Not specified Follow-up: 4 years
#326 Schnitzler MA et al Cost-Effectiveness of Thymoglobulin Compared to Basiliximab in Kidney Transplant Using Multicenter Randomized Trial Data. Washington University St. Louis	Prospective cost analysis of the US component of the randomized, multi-center, multinational trial comparing rATG and basiliximab	rATG n=91 Basiliximab n=92	Not specified Follow-up: 1 year
#1449 Stevens RB et al Improved Renal Graft Function Following Single Dose rATG (6mg/kg/24h) Induction University of Nebraska Medical Center	Prospective randomized trial Single center	rATG x 1 dose (6mg/kg) n= 61 rATG x 4: alternate day dosing (6mg/kg) n=63	TAC/SRL Follow-up: 12 months

incidence of acute rejection and a higher incidence of delayed or slow graft function.[1457] This occurred in a setting of increased exposure to tacrolimus, and more prevalent CS avoidance amongst basiliximab treated recipients. Taber and colleagues evaluated a large single center cohort of patients and reported acute rejection in 9%, 24% and 34% of recipients treated with rATG, IL-2RA or no induction (p<0.001). In addition, this study evaluated risk factors for developing acute rejection and found that use and type of induction therapy was the only variable that was independently associated with acute rejection.[1205]

The efficacy of alemtuzumab was evaluated in a number of clinical studies.[333, 330, 1463] In short-term follow-up of a European, prospective, multi-center, clinical trial, alemtuzumab treatment and tacrolimus monotherapy resulted in a numerically lower incidence of acute rejection, compared to no antibody treatment, 21.5% vs. 30.3%, respectively (p value not reported).[333] At 9 months of follow-up in a single-center study, Farney and colleagues reported similar patient and graft survival, initial length of stay, delayed graft function, major infections and incidence of post-transplant lymphoproliferative disease (PTLD), in a comparison of recipients treated with rATG vs. alemtuzumab. Acute rejection rates were acceptable in both groups, however, there was a decreased incidence of acute rejection in the alemtuzumab vs. rATG treated recipients, 6% vs. 21%, respectively (p = 0.01).[330]

TABLE 1 SUMMARY

EFFICACY OF ANTIBODY INDUCTION THERAPY IN KIDNEY TRANSPLANTATION

- Both rATG and alemtuzumab induction result in excellent one year patient and graft survival
- In kidney recipients maintained on tacrolimus and sirolimus maintenance therapy, a single infusion (6mg/kg) of rATG is as effective and may provide additional benefits in renal function compared with the same dose (6mg/kg) divided over 4 infusions
- Overall costs associated with caring for patients administered rATG were significantly lower than those treated with basiliximab. Results attribute savings to improved clinical outcomes following rATG treatment

Clinical Endpoints				Comments
	rATG	**Basiliximab**	***P*-value**	The methodology uses the transplant registry to provide long-term follow-up data on recipients followed in shorter term clinical trials
Acute rejection/graft loss/death	37.3%	49.5%	0.047	The use of rATG reduces the risk of acute rejection, DGF, graft loss and death
DGF/acute rejection/graft loss/death	58.5%	72.1%	0.005	Acute rejection and return to dialysis are significant predictors of graft loss and patient death, respectively
Hazard ratio determination: For graft loss: Acute rejection=3.77; P<0.0001 For death: Return to dialysis=22.2; P<0.0001				
	rATG	**Basiliximab**	***P-value***	Savings attributed to the use of rATG at the end of one year = $7,599
BPAR/ return to dialysis/death	19.8%	31.5%	0.07	Use of rATG, compared to basiliximab results in significantly less: 1. BPAR/return to dialysis/deaths (FDA triple endpoint) 2. DGF/AR/return to dialysis/deaths (trial composite endpoint)
Average cost per pt*	$143,269	$178,832	NR	
DGF/acute rejection/ return to dialysis/death	48.4%	62.0%	0.06	The average per-patient cost is $35,563 less for patients receiving rATG than those receiving basiliximab, reflecting a reduction in the need for treatment of adverse outcomes
Average cost per pt*	$222,678	$322,368	NR	
*Free of endpoint				
Renal function among recipients administered single dose rATG: - Predischarge: superior - P<0.05 - Beyond 1 month post-transplant: numerically superior - P<0.13 (result not reported) No differences in complications between groups No patient or graft losses reported No differences in acute rejection rates between groups				Overall, renal function was superior in patients who received single dose rATG

Table 1. Efficacy of Antibody Induction Therapy in Kidney Transplantation (Cont.)

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#1463 Hartmann E et al Short-term Outcomes in Transplant Recipients over Age 60 Randomized to either Campath or Thymoglobulin Induction Therapy. Wake Forest University	Prospective randomized trial Single center Posthoc subanalysis of data collected on patients >60 years of age	Alemtuzumab n=15 rATG n=16	TAC/MMF/±CS Median follow-up: 9 months
#1467 McGee J et al A Meta-Analysis of IL-2 Receptor Antagonists in Renal Transplantation: What We Still Do Not Know. Tulane University	Meta-analysis 11 RCT published 1966-October 2006	Basiliximab Daclizumab N=1,989	Not specified
#1457 Cooper M et al Impact of Induction Agents on Renal Recipient Outcomes of the First 1000 Laparoscopic Donor Nephrectomies at a Single Institution. University of Maryland	Retrospective single center review Recipients of living donor kidneys 1996-2005	Basiliximab n=256 Alternate antibody therapy n=232 - rATG n=158 - OKT3 n=40 - ATGAM n=34 None n=463	Various regimens Higher use of TAC among patients receiving basiliximab, compared to those receiving alternate antibody induction therapy (96.8% vs 78.2%; P<0.0001) CS avoidance more prevalent among basiliximab treated patients (81.7% vs 3.7%; P<0.0001) Follow-up: results at 1 year reported
#1205 Taber DJ et al A Large-Scale Long-Term Single Center Analysis of the Use of Induction Therapy in Kidney Transplant Recipients. Medical University of South Carolina	Retrospective single center analysis Patients transplanted 2001-2004	rATG n=81 IL-2RA - not specified n=136 No antibody induction therapy n=76	Not specified Follow-up: 1 year
#333 Margreiter R et al Alemtuzumab (Campath-1H) Induction Followed by Tacrolimus Monotherapy vs. Tacrolimus Based Triple Drug Immunosuppression in Cadaveric Renal Transplantation - Results of a Multicenter Trial. University Hospital Innsbruck, Australia, et al	European prospective randomized trial	Alemtuzumab n=65 No antibody n=66	Alemtuzumab: TAC No antibody: TAC/MMF/CS Follow-up: 12 months
#330 Farney A et al Alemtuzumab versus Rabbit Antithymocyte Globulin Induction in Kidney and Pancreas Transplantation: A Prospective Randomized Study. Wake Forest University	Prospective randomized trial Single center	Alemtuzumab n=64 rATG n=58	TAC/MMF CS early elimination by risk stratification Median follow-up: 9 months

BPAR - biopsy-proven acute rejection; CS - corticosteroid; DGF - delayed graft function; eGFR - estimated glomerular filtration rate; GFR- glomerular filtration rate; LOS - length of stay; MDRD - modification of diet in renal disease equation; MMF - mycophenolate mofetil; NODM - new onset diabetes mellitus; NR - not reported; rATG - rabbit antithymocyte globulin; RCT - randomized controlled trial; SCr - serum creatinine; SGF - slow graft function; SRL - sirolimus; TAC - tacrolimus

Clinical Endpoints				Comments
	Alemtuzumab	**rATG**	***P*-value**	The use of T-cell depleting antibody induction therapy in older kidney transplant recipients results in acceptable safety and efficacy
Patient survival	93%	100%	NS	
Graft survival	93%	84%	NS	
Rejection	7%	17%	0.41	
Incidence of infection, rate of hospitalization for infection similar among patients >60 years of age, and those aged 28-59 years				
Efficacy of IL-2RA:	**Odds ratio**	**95%CI**		Basiliximab and daclizumab reduce the incidence of acute rejection, DGF and graft failure The author states that the effectiveness of IL-2RA in African American transplant recipients cannot be assessed from these results and further studies are warranted
Acute rejection	0.51	0.42-0.62		
DGF	0.74	0.57-0.96		
Graft failure	0.71	0.52-0.97		
- Comparator not specified - African American outcomes reported in only 1 trial				
	Basiliximab	**Alternate antibody**	***P*-value**	Recipients of laparoscopic living donor transplants treated with basiliximab are at greater risk of developing acute rejection and delayed or slow graft function, even after adjusting for confounding factors, than those treated with rATG, OKT3 and ATGAM
Acute rejection*	25.5%	15.7%	<0.0001	
MDRD eGFR (mL/min/1.73m^2)	55.6±19.8	52.8±20.9	NS	
DGF/SGF	22%	14.3%	0.005	
*Relative risk adjusted for CS avoidance, TAC usage, demographic variables=2.7 (95% CI 1.78-4.4; P<0.0001)				
	rATG	**IL-2RA**	**No antibody**	***P*-value**	Recipients treated with rATG developed significantly less acute rejection, compared to recipients treated with IL-2RA, or no antibody A significant decrease in BPAR was identified in recipients treated with rATG, despite having significant demographic risk factors for the development of acute rejection
BPAR	9%	24%	34%	<0.001	
Sole risk factor for development of BPAR, identified in multivariate analysis: Antibody treatment - Odds Ratio=0.34 (95% CI 0.21-0.55; P<0.001)				
	Alemtuzumab	**No antibody**		Alemtuzumab and a TAC monotherapy maintenance regimen resulted in a lower incidence of rejection compared to a standard TAC/MMF/CS regimen with no antibody induction therapy
Treated rejection	21.5%	30.3%		
Graft loss	3.1%	9.1%		
SCr (mg %)	1.6 (0.9-3.0)	1.6 (0.9-3.2)		
Patient survival	100%	98.5%		
Graft survival	96.9%	90.9%		
P-values NR				
	Alemtuzumab	**rATG**	***P*-value**	Both alemtuzumab and rATG treatment result in excellent one year patient and graft survival Alemtuzumab therapy is associated with a lower incidence of acute rejection at 9 months and lower drug acquisition cost
Patient survival	95%	100%	NR	
Kidney survival	93%	94%	NR	
Acute rejection	4 (6%)	14 (21%)	0.01	
Antibody cost	$1466	$4728	<0.001	
Median LOS* (d)	7(3-53)	6(4-46)	NR	
Patients off CS	56%	50%	NR	
*Total charges for initial LOS similar between groups				

SAFETY OF ANTIBODY INDUCTION THERAPY IN KIDNEY TRANSPLANTATION

The decision on the use and the type of antibody induction therapy requires assessment of both immunological risk factors and a patient's potential tolerance for treatment-related adverse events. Opportunistic infections and post-transplant malignancies are common consequences of all immunosuppression. So, how much immunosuppression is enough? How much is too much? What is acceptable? How can infectious complications be minimized? The answers to these questions remain elusive; however several approaches have been reported by investigators to address these questions.

In a retrospective analysis, approximately 50% of recipients treated with alemtuzumab developed infections over a two year follow-up period, comparable to infection rates noted with other management strategies. Sixty-five percent of infections were bacterial, mostly consisting of simple urinary tract infections. Viruses accounted for 30% of infections (cytomegalovirus [CMV] 12%), and 5% of infections were fungal in etiology. Most of the infections occurred before day 30 or after day 180 following transplantation.[1389]

In another retrospective analysis, of patients transplanted between 1994 and 2005 at a large single center, the use of alemtuzumab (primarily in multidose regimens) was identified as a significant risk factor for the development of CMV in patients not receiving valganciclovir prophylaxis. This report spanned a lengthy period of time, during which immunosuppression (cyclosporine, tacrolimus, mycophenolate, and sirolimus) and prophylaxis (acyclovir, ganciclovir, valganciclovir) evolved significantly. Nonetheless, the investigators reported compromised survival at two years among recipients treated with alemtuzumab who developed CMV disease within the first year post-transplant.[1396]

A retrospective analysis of the OPTN registry reported the risk of PTLD based on antibody induction therapy.[332] Despite concern regarding alemtuzumab's depletional mechanism of action and duration of effect, there was no increased risk of PTLD compared to recipients receiving no induction at all. The investigators also described a higher risk of PTLD associated with rATG induction, although the analysis was not adjusted for rATG dose. Overall, however, the incidence of PTLD remained below 1% for patients treated with any induction agent.

Table 2. Safety of Antibody Induction Therapy in Kidney Transplantation

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
Infectious Complications / Lymphopenia			
#336 Srinivas TR et al Total Rabbit ATG Dose is a Risk Factor for Onset of BK Viremia in Kidney Transplant Recipients. University of Florida	Prospective single center Comparison of 5 dose and 3 dose regimens of rATG	rATG n=158	Not specified Follow-up: 6 months
#1453 Guerra G et al Rabbit ATG Dose: Risk Factor for Opportunistic Infection in Renal Transplant Recipients. University of Florida	Prospective single center Comparison of infectious outcomes in patients receiving 3 different cumulative doses of rATG	rATG n not specified **Low dose:** <4.65 mg/kg **Mid dose:** 4.65 to <5.82 mg/kg **High dose:** >5.82 mg/kg	Not specified Follow-up: 6 months

Two reports from the University of Florida examined infectious risks associated with dosing of rATG. Srinivas and colleagues reported several significant risk factors for BK viremia, including recipient age, recipient race, donor age, obesity, deceased donor and total dose of rATG >500 mg.[336] Guerra and coworkers also examined the risk of infectious complications at their institution based on low, mid or high dose rATG induction. (<4.65mg/kg, 4.65 - 5.82mg/kg or >5.82mg/kg). They found that recipients who received greater than 5.82 mg/kg of rATG had a 41% incidence of opportunistic infections, compared to 25% and 30% in the low and mid dose groups, respectively. However, the type of infections, the use of antimicrobial or antiviral prophylaxis, and concomitant immunosuppressive agents were not reported.[1453]

TABLE 2 SUMMARY

SAFETY OF INDUCTION THERAPY IN KIDNEY TRANSPLANTATION

- Increased overall immunosuppressive load may increase the risk of infectious complications, an aphorism known in transplantation since its inception
- Overall rates of infection with alemtuzumab appear comparable to previously published reports with other agents
- The results of a OPTN registry analysis revealed a low incidence of PTLD (<1%) associated with the use of any antibody induction agent
- Higher doses of rATG (>5.82 mg/kg) may be related to a higher incidence of opportunistic infection

Clinical Endpoints			Comments
		Incidence of BK Viremia	A single center prospective analysis identified the following as significant risk factors for BK Viremia: · Recipient age · Recipient race · Donor age · BMI · Transplant type · rATG dosing These data provide a rationale to prospectively study body weight adjusted dosing for rATG in a large scale trial
Total rATG dose	>500 mg	26%	
	<500 mg	16%	
Recipient age	>50 years	32%	
	<50 years	7%	
Donor age	>50 years	29%	
	<50 years	15%	
Recipient race	African American	27%	
	Caucasian	12%	
Obese vs non obese		32% vs 15%	
Deceased vs living donor		17% vs 27%	
- *P*-values for all comparators significant - No correlation with risk of BK viremia: Dosing by mg/kg (<5 vs >5), recipient gender, donor race, DGF, number of HLA-DR mismatches			
Dose:	**Low**	**Mid**	**High**	***P*-value**	A single center prospective analysis comparing 3 different cumulative doses of rATG in an unspecified number of recipients demonstrated that a higher dose of rATG is associated with increased risk for opportunistic infections following renal transplantation Prospective studies of different rATG doses are required to establish comprehensive risk-benefit data
Infection Rates	25%	30%	41%	0.03	
- Higher rATG dose associated with shorter time to infection (P=0.002) - Adjusted hazard ratio for post-transplant opportunistic infection: - Mid dose: 1.5 (95% CI 0.8-2.6) - High dose: 2.2 (95% CI 1.3-3.8)					

Table 2. Safety of Antibody Induction Therapy in Kidney Transplantation (Cont.)

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
Infectious Complications / Lymphopenia			
#1389 Walker JK et al Infectious Complications After Renal Transplantation Utilizing Alemtuzumab Induction. Northwestern Memorial Hospital	Retrospective single center chart review Patients transplanted 2002-2004	Alemtuzumab n=301	TAC/MMF No corticosteroids Mean follow-up 26±9 months
#1396 Zachariah M et al Anti-Lymphocyte Antibody Agent as a Risk Factor for CMV Infection in the Current Era of Immunosuppression. University of Wisconsin, Madison	Retrospective single center analysis Patients transplanted 1994-2005	Alemtuzumab n=710 ATG n=158 Other antibodies n=1,926 - 51% IL-2RA - 49% OKT3	Not specified Follow-up: 1 year
Malignancy / PTLD			
#332 Cherikh W et al Updated Analysis of Dissociation of Depletion and PTLD in Kidney Recipients Treated With Alemtuzumab Induction Therapy. UNOS Member Institutions	Retrospective analysis of OPTN database Patients transplanted 2000-2004	Alemtuzumab n=1,691 rATG n=13,110 Basiliximab n=14,182 Daclizumab n=7,511 No antibody induction therapy n=23,066	Not specified Follow-up: 730d

ATG – antithymocyte globulin; BMI – body mass index; BKV – BK virus; CMV – cytomegalovirus; D+/R- – donor positive/recipient negative; IL-2RA – Interleukin 2 receptor antagonist; MPA – mycophenolic acid; OPTN – Organ Procurement and Transplantation Network; PTLD-post-transplant lymphoproliferative disease; rATG – rabbit antithymocyte globulin

Clinical Endpoints	Comments
Overall incidence of infection: 48.5% of patients experienced 246 infections **Proportion of all infections:** Bacterial=65% / Viral=30% (12% CMV; 2% BKV) / Fungal=5% **Timing:** Most infections occurred before 30 days, and after 180 days following transplantation	A single center retrospective chart review analysis, of recipients receiving alemtuzumab to assess the incidence of infection: • 48.5% of alemtuzumab treated recipients experienced infections
Significant risk factors for CMV (antigenemia/infection/disease not specified): **D+/R- CMV status** — Hazard ratio 2.9; P<0.0001 **Alemtuzumab use** — 1.93; P<0.0001 - Graft survival at 1 year: alemtuzumab 90% vs 92% for patients treated with other antibodies (*P*=0.0013) - Patients treated with alemtuzumab who developed CMV experienced reduced survival at 2 years (data not reported; *P*=0.02) - Effect of prophylaxis – valganciclovir had a protective effect against CMV in patients treated with alemtuzumab; however, the benefit was lost by 2 years of follow-up	A single center, retrospective analysis of alemtuzumab use did not result in significantly compromised survival At 2 yrs post-transplant, 40% of alemtuzumab treated recipients developed primary CMV compared to 25% of those patients treated with ATG A higher mortality rate was seen in alemtuzumab treated recipients experiencing CMV during the first year
Incidence of PTLD **Alemtuzumab** 6 (0.35%) **rATG** 79 (0.60%) **Basiliximab** 50 (0.35%) **Daclizumab** 23 (0.31%) **No antibody therapy** 90 (0.39%) *P*<0.01 **Risk factors for PTLD:** — Relative risk — *P*-value **Alemtuzumab** 1.15 0.74 **Basiliximab** 0.84 0.33 **Daclizumab** 0.64 0.06 **Thymoglobulin** 1.63 <0.01 * Analysis is based on use of antibody agent. rATG is the only agent that is indicated and used for treatment of rejection	A retrospective, analysis of the OPTN registry indicated that alemtuzumab treatment is not associated with an increased incidence of PTLD, compared to treatment with rATG or no antibody induction therapy The overall incidence of PTLD remained below 1% for patients treated with any induction agent

USE OF ANTIBODY INDUCTION THERAPY TO MINIMIZE CORTICOSTEROID EXPOSURE IN KIDNEY TRANSPLANTATION

The inclusion of antibody induction agents at the time of transplantation is thought essential in the attempt to minimize, or even avoid, the associated toxicities and side effects of long-term maintenance immunosuppressive agents. Glucose intolerance, hyperlipidemia, hypertension, weight gain, and osteoporosis are established side effects related to long-term CS use. Their frequency and intensity have clearly diminished with modern protocols that involve more limited dosing. Nonetheless, there remains substantial enthusiasm for even further minimization or discontinuation. CS withdrawal protocols typically imply discontinuation of steroids weeks to months after transplantation. CS avoidance generally infers that CSs are avoided altogether, or are administered for only a few days post-transplant. The latter approach is currently thought to be most effective. While definitions vary by institution, previously published data, and data reported at the 2007 ATC, indicate this approach to be relatively safe, with the potential for substantial benefit in kidney transplant recipients.

Multiple abstracts reporting CS minimization/avoidance/withdrawal protocols are included in Table 3. CS minimization strategies differed with respect to the antibody induction agent, the schedule of CS minimization, and the maintenance immunosuppressive regimens.

Woodle and colleagues reported data after four years of follow-up in a multicenter, randomized, controlled, blinded trial of early CS withdrawal (post-transplant day 7) utilizing either rATG or IL-2RAs as antibody induction therapy involving almost 400 recipients. No difference was noted at 4 years in the primary endpoint (composite of death, graft loss or severe acute rejection requiring antibody treatment). In addition, 4 year biopsy proven acute rejection (BPAR) rates (10.8% and 17.3%, respectively) did not differ for chronic CS vs. CS withdrawal (CSWD). No difference was noted in renal function. Recipients in the CSWD group experienced better lipid profiles, reduced requirement for insulin to treat new onset diabetes mellitus (NODM) and fewer bone disorders. However, in for-cause biopsies, more recipients in the CSWD group were noted to demonstrate chronic allograft nephropathy (CAN). This study will remain blinded to patients and investigators for five years, allowing additional assessment of differences between groups in upcoming reports.[1704]

Early results from another multicenter, randomized study were reported by Hanaway and colleagues.[1703] In this trial involving 477 subjects, patients were stratified into low- and high-risk groups by immunologic risk. Among low-risk patients, alemtuzumab was associated with substantially less acute rejection (2.0% vs. 19.5%, $p<0.05$) and comparable infectious risks when compared to basiliximab in an early steroid withdrawal (ESWD) protocol. In high-risk patients, rATG and alemtuzumab induced comparable rejection rates (9.6% and 6.7%, respectively), with fewer infections in those patients on alemtuzumab.

Table 3. Use of Antibody Induction Therapy to Minimize Corticosteroid Exposure in Kidney Transplantation

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#1704 Woodle ES et al A Randomized Double Blind, Placebo-Controlled Trial of Early Corticosteroid Cessation Versus Chronic Corticosteroids: Four Year Results. University of Cincinnati	Randomized controlled trial	rATG IL-2RA (not specified)	TAC/MMF CS WD d7 n=191 CS maintenance n=195 - Follow-up: 5 years, total - Report of 4 year data - Study still blinded
#445 Malat G et al One-Year Outcome of Early Steroid Withdrawal and Basiliximab Induction in Kidney Recipients with Retransplantation. Drexel University	Retrospective analysis	Basiliximab n=248 Primary transplants n=202 Retransplants n=46	CNI/MMF or SRL CS- withdrawn on post-transplant day 2 Follow-up: 1 year

Several single center studies assessed early CSWD in various subgroups of patients. A retrospective analysis of early CSWD in kidney transplant recipients receiving basiliximab antibody induction therapy, revealed a significant increase in the incidence of BPAR at 1 year in repeat kidney transplant recipients compared to primary transplant recipients.[445] A prospective, noncomparative trial assessed alemtuzumab antibody induction therapy in 32 high-risk kidney recipients, in a CNI monotherapy protocol.[1173] CSs were weaned by 8 weeks post-transplantation. Patient death with a functioning graft was reported in 4/32 cases and graft failure in 2/32. Of the 26 recipients alive with a functioning graft at time of analysis, 17 were maintained on CNI monotherapy. A protocol modification study assessing CSWD in African American and high-risk caucasian kidney recipients demonstrated that the use of rATG antibody induction therapy provided sufficient immunosuppression to allow for CS withdrawal at 3 weeks post-transplant in most high-risk kidney recipients.[1462]

Alemtuzumab, rATG, and IL-2RAs have all been used to minimize CS exposure with varying efficacy and safety data. However, the overall results of these studies suggest that each patient's risk factors for acute rejection, infection, and other immunosuppression related complications should be considered when implementing a CS minimization protocol.

TABLE 3 SUMMARY

USE OF ANTIBODY INDUCTION THERAPY TO MINIMIZE CORTICOSTEROID EXPOSURE IN KIDNEY TRANSPLANTATION

- Protocols vary widely with respect to antibody induction therapy, schedule of CS minimization, and choice of maintenance immunosuppressive agents
- Depending on the immunologic and comorbidity risk profile of the patient population, alemtuzumab, rATG or IL-2RAs have been used successfully to minimize CSs in kidney transplant recipients
- rATG induction therapy was associated with effective CS withdrawal in both African American and high-risk caucasian kidney transplant recipients
- Patient follow-up in most studies is short (one year or less). Lessons from earlier CS withdrawal trials suggest that recipients should be followed for at least five years to determine the full effects of CS minimization[4]
- In a randomized, double-blind, placebo controlled, multicenter study, CSWD patients experienced an absolute increase of CAN at 4 years, compared to recipients on chronic CS maintenance therapy
- CNI monotherapy may be possible in some patient populations selected for CS minimization

Clinical Endpoints				Comments
CS	**WD**	**Maintenance**	*P*-value	Approximately 2/3 of study recipients received rATG
Treatment failure*	16.8%	12.3%	NS	CSWD at 4 years in recipients receiving antibody induction therapy is associated with improvement in triglyceride levels, an absolute increase in the incidence of CAN, reduced requirement for insulin to treat new onset diabetes and fewer bone disorders
Death	4.7%	5.1%	NS	
Graft loss	4.7%	3.6%	NS	
BPAR	17.3%	10.8%	0.08	
CAN† <1 month	9.9%	4.1%	0.03	
>1month	8.9%	4.1%	0.064	
Mean SCr (mg/dL)	1.6±1.0	1.5±0.7	NS	
CrCl (mL/min/1.73m2)	58.5±19.3	604±20.8	NS	
Triglycerides (mg/dL)	-56.1	+6.2	0.002	
New insulin use	3.6%	11.3%	0.03	
Bone disorders‡	3.7%	9.7%	0.02	
*Death/graft loss/severe acute rejection †For cause biopsy specimens ‡Fractures/avascular necrosis				

	Primary	**Retransplants**	*P*-value	Use of basiliximab for induction therapy in kidney transplant recipients undergoing retransplantation with CS withdrawal results in a significant increase in BPAR at 1 year when compared to primary transplant recipients 15% of the retransplant recipients required antibody treatment for BPAR Anti IL-2RA therapy may be less useful than rATG or alemtuzumab in high risk patients
BPAR	5.4%	32.6%	0.00	
CAN	28.2%	32.6%	0.55	
SCr (mg/dL)	2.1±1.3	2.3±1.4	0.164	
CrCl (mL/min)	60.26±31.1	43.94±21.73	0.42	
1 year patient and graft survival were equivalent in primary and retransplant patients				

Table 3. Use of Antibody Induction Therapy to Minimize Corticosteroid Exposure in Kidney Transplantation (Cont.)

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#1462 Gurk-Turner C et al Steroid Withdrawal in African American and High-Risk Caucasian Recipients of Renal Allografts with Thymoglobulin Induction Therapy. University of Maryland	Review of center protocol modification	rATG African American patients n=24 High-risk Caucasian patients n=25 - Sensitized - CIT>24h	TAC/MMF CS tapered off by 21d, except in patients with PRA>40, and retransplants Follow-up: 1 year
#1464 Baez Y et al Experience with Alemtuzumab (Campath 1H) Induction Followed by Non-Steroid Maintenance in Kidney Transplants Recipients. Columbiana de Transplantes, Bogata Columbia	Retrospective analysis Patients transplanted 2005-2006	Alemtuzumab n=100	CNI/MPA CS - 1 dose day of transplant C2 CsA target - 400-600 ng/dL TAC target - 4-7 ng/dL Median follow-up: 6 months (range 1-12 months)
#1703 Hanaway M et al Results of a Multicenter, Randomized Trial Comparing Three Induction Agents (Alemtuzumab, Thymoglobulin and Basiliximab) with Tacrolimus, Mycophenolate Mofetil and a Rapid Steroid Withdrawal in Renal Transplantation. University of Alabama, Birmingham	Open label randomized trial	Based on risk High-risk*: Alemtuzumab (30 mg) or rATG (6.0 mg over 4 doses) Low risk†: Alemtuzumab or basiliximab *African American / PRA >20 / Retransplants †Non-African American / PRA <20 / Primary transplants	TAC/MMF/rapid CSWD Follow-up: 6 months
#1173 Potdar S et al Campath-1H Induction and Maintenance Monotherapy in High Risk Kidney Transplant Recipients. Geisinger Medical Center	Prospective noncomparative single center trial High-risk patients: CIT >24h / donation after cardiac death / retransplant / PRA >20 / >3 HLA mismatches	Alemtuzumab n=32	TAC CS weaned off by 8 weeks Mean follow-up: 31.2 months (range 24-42 months)
#203 Aull MJ et al Steroid Sparing Immunosuppression Provides Numerous Benefits to Hepatitis C Positive Kidney Transplant Recipients. NY Presbyterian Hospital	Single center review HCV+ kidney transplant recipients	CS sparing n=18 16 rATG 2 Basiliximab CS maintenance n=11 1 rATG 1 Basiliximab	TAC/MMF Follow-up: 5 years

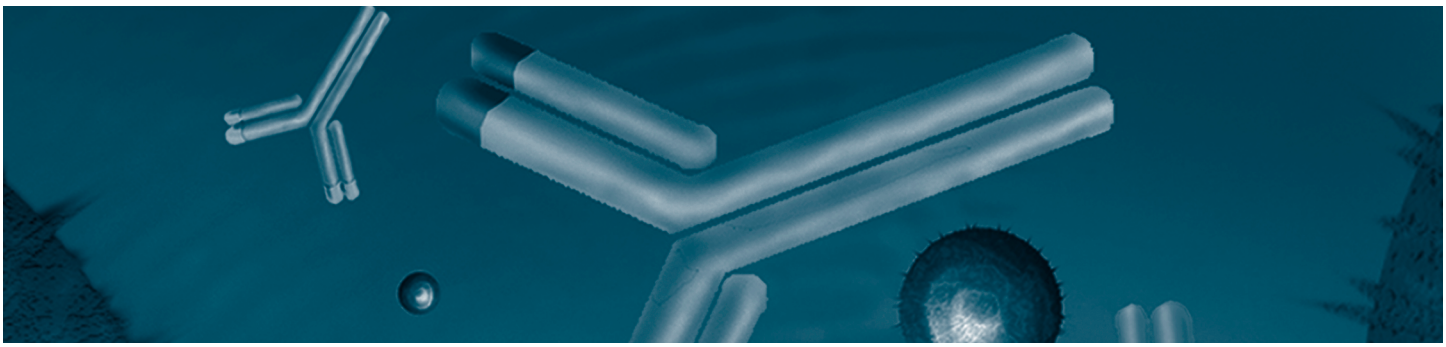
Clinical Endpoints	Comments
<table><tr><th></th><th>African American</th><th>Caucasian</th><th>*P*-value</th></tr><tr><td>**DGF**</td><td>56%</td><td>21%</td><td>0.02</td></tr><tr><td>**Rejection**</td><td>16%</td><td>17%</td><td>NS</td></tr><tr><td>**Successful CS WD**</td><td>53%</td><td>88%</td><td>NS</td></tr><tr><td>**Median SCr** (mg/dL)</td><td>1.5</td><td>1.2</td><td>NS</td></tr></table> Patient and graft survival were equivalent	rATG induction therapy supported CS withdrawal in both African American and high-risk caucasian kidney transplant recipients Authors reported that DGF rates in AA recipients are comparable to historical rate in recipients treated with basiliximab rATG induction therapy and maintenance immunosuppressive regimens in AA recipients resulted in equivalent rejection rates and renal function at one year of follow-up when compared to caucasian recipients
BPAR at 12 months: 13% **Graft loss (return to dialysis): n=3** **Infectious complications:** 23%; 3 fatal incidents	Long-term follow-up is required to confirm the ability of alemtuzumab antibody induction therapy to support a CS sparing maintenance regimen
High-Risk No difference in BPAR between alemtuzumab and rATG (6.7% vs. 9.6%) **Low-Risk** Significantly higher frequency of rejection episodes, and episodes requiring treatment, in low risk recipients treated with basiliximab compared to alemtuzumab: ·BPAR: 19.5% vs. 2.0% ·Treated rejection: 24.2% vs 4.4% *P*-values <0.05	rATG and alemtuzumab induction therapy result in comparable BPAR rates and requirement for treatment of rejection in high-risk kidney transplant recipients At one year, there were fewer infections in the high-risk group receiving alemtuzumab vs. rATG Compared to basiliximab, alemtuzumab may provide better protection against acute rejection in low risk kidney allograft recipients
Death: n=4 (12.5%) **Graft failure:** n=2 (6%) **Acute cellular rejection:** 19% **Mean SCr:** 1.3 mg/dL **DGF:** 7% **TAC monotherapy:** 17/26 **TAC/CS/MMF:** 5/26 **MMF monotherapy:** 4/26	Alemtuzumab and tacrolimus monotherapy can be safely used in high-risk kidney transplant recipients 4/32 patient deaths (12.5%)
Significantly better rejection free survival in CS sparing group at 6 months (data not reported; graph suggests 100% vs ~62%; *P*<0.01) Patient survival at 3 years and graft survival at 5 years equivalent between CS sparing and maintenance groups Improvements in CS sparing group: **NODM:** 0 vs. 22% (*P* NR) **HCV load** (data not reported for maintenance group) - Stable - increase < 1 log: 58.4% - Increased >1 log: 33.3% - Remained undetectable: 8.3%	CS sparing in combination with rATG induction therapy may benefit HCV+ kidney transplant recipients by reducing the risk of early acute rejection and NODM In this study, there did not appear to be detrimental effects associated with the use of antibody induction therapy in HCV+ kidney transplant recipients

Table 3. Use of Antibody Induction Therapy to Minimize Corticosteroid Exposure in Kidney Transplantation (Cont.)

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#338 Tan HP et al Rejection Characteristics of 266 Living Donor Kidney Only Transplants Using Alemtuzumab Induction and Tacrolimus Monotherapy. University of Pittsburgh	Review of consecutive living donor kidney transplants at single center	Alemtuzumab n=266	TAC monotherapy; weaning protocol Mean follow-up: 21.6±12.2 months
#838 Chan, K et al Steroid Sparing Regimens and Monoclonal Antibody Induction Reduces the Incidence of Infection in Renal Transplant Recipients. Hammersmith Hospital, London UK	Retrospective single center review of 502 recipients	No antibody n=147 No antibody n= 107 Alemtuzumab n=114 Daclizumab n=134	**CS regimen:** No antibody: TAC/CS/MMF or AZA (1996-2000) **CS sparing regimens:** No antibody: TAC/MMF Alemtuzumab: TAC Daclizumab: TAC/MMF Mean follow-up: 404±35.2 months
#815 Badosa, F et al Steroid-Withdrawal at Day 2 After Kidney Transplantation With Two-Dose Daclizumab Induction. Lankenau Hospital	Review of consecutive kidney transplants at single center	Daclizumab (LD) or rATG (DD) n=55 Daclizumab n=53	**CS regimen:** Daclizumab or rATG: TAC/MMF/CS Mean follow-up: 45 months **CS sparing regimen:** Daclizumab: TAC/MMF/CS on d0, d1 only Mean follow-up: 20 months
#1190 Peddi VR et al Comparison of Basiliximab and Thymoglobulin Induction in an Early Steroid Cessation Protocol in Renal Transplant Recipients. California Pacific Medical Center	Single center review Patients at low immunological risk (not defined)	Basiliximab n=19 rATG n=28	MMF/TAC Early CSWD (not specified) Mean follow-up: 300d

AA- African American; AZA – azathioprine; BMI – body mass index; BPAR – biopsy proven acute rejection ; CAN – chronic allograft nephropathy; CIT – cold ischemia time ; CNI – calcineurin inhibitor; CrCl – creatinine clearance; CS – corticosteroid; CsA – cyclosporine; CSWD- corticosteroid withdrawal; DD – deceased donor; DGF – delayed graft function; EC – extended criteria donor; HCV – hepatitis C virus; LD – living donor; MMF – mycophenolate mofetil; MPA – mycophenolate acid; NODM - new onset diabetes mellitus; PNF –primary non-function; PCP – Pneumocystic Carinii pneumonia; PRA – panel reactive antibody; rATG – rabbit antithymocyte globulin ; SCr – serum creatinine; SRL – sirolimus; TAC – tacrolimus; TB- tuberculosis; UTI – urinary tract infection; WD – withdrawal

Clinical Endpoints	Comments
Graft loss: n=11 (4%) **Acute cellular rejection:** 7.1% (12 months) 11.7% (24 months) **Mean SCr (mg/dL):** 1.46±0.51 (12 months) 1.49±0.71(latest follow-up) Patients weaned to spaced TAC dosing: 37.4% Patients CS free from time of transplant: 87%	Alemtuzumab with a TAC monotherapy maintenance regimen was safe and effective in living donor kidney transplant recipients
Graft survival: 5 years - 90.1%; 10 years - 76.8% **UTIs:** 61.8% of all infections - More frequent in CS regimen: 57.1% vs 30.8%; ·***P*=0.0157** **Wound infection significantly lower in CS sparing regimens:** ·3.4% vs 8.2%; P=0.02 **Wound infections and bacteremia significantly lower in CS sparing regimens:** ·***P*=0.04** (data not reported)	A CS sparing regimen and a monotherapy antibody was associated with less infection UTI is the most common cause of infection post-transplant Prophylaxis for CMV, PCP and TB is highly effective
Expanded criteria donors in each regimen: 30% **Cardiac death donors in each regimen:** 21% **No statistically significant differences between CS / CS sparing regimens in:** Graft / patient survival at 1 year Acute cellular rejection: 2% vs 10% (no increase in African American patients or recipients of DD kidneys) DGF : 31% vs 41%	Aggressive use of DD and EC donors has resulted in a high incidence of PNF and DGF Rapid CS withdrawal under a daclizumab regimen provides excellent 1 year patient and graft survival Full evaluation of the potential benefits of a CS sparing regimen using daclizumab require longer term follow-up
Freedom from acute rejection: Basiliximab 84%; rATG 92%; *P*-value 0.29 **Freedom from rejection and infection**: Basiliximab 73.7%; rATG 80.8%; *P*-value 0.32 - No graft loss or patient death	Basiliximab or rATG supports early CSWD There may be a tendency for a higher frequency of acute rejection in recipients treated with basiliximab, and for more serious infections in patients treated with rATG



USE OF ANTIBODY INDUCTION THERAPY TO MINIMIZE CALCINEURIN INHIBITOR EXPOSURE IN KIDNEY TRANSPLANTATION

In the current era, it has become generally accepted that long-term toxicities, renal and non-renal, associated with CNIs pose a significant problem for transplant recipients.[5] Unfortunately, these agents remain for most clinicians as the cornerstone of therapy, with significant reluctance to alter their use. The previously described benefits of antibody induction therapy in minimizing CS exposure in kidney transplant recipients has also been examined in the effort to minimize CNI usage without increasing the risk of acute rejection. (see Table 4).

Leventhal and colleagues at Northwestern evaluated a CNI conversion (TAC/MMF → SRL/MMF) and a CNI-free regimen (SRL/MMF) in combination with alemtuzumab induction therapy, in a living donor kidney transplant patient population. The overall patient and graft survival at 1 year was 100% and 93%, respectively. Acute rejection incidence was similar at 13% in both CNI conversion and CNI free groups; however in the CNI-free group, antibody mediated rejection posed a significant problem.[725] These investigators offer the hope that immunologic monitoring might help identify patients at lower risk of rejection in a CNI-free protocol.

In another report of a small series from the same Northwestern group, alemtuzumab was used to delay the administration of tacrolimus for 14 days in a steroid-free protocol. At 4 years of follow-up, 70% of recipients with a functioning graft remained CS free. However, the investigators concluded

Table 4. Use of Antibody Induction Therapy to Minimize Calcineurin Inhibitor Exposure in Kidney Transplantation

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#237 Amundsen B et al Steroid Avoidance and Delayed Introduction of Tacrolimus Using Alemtuzumab Induction in Kidney Transplantation: Five-Year Follow-Up. Northwestern University	Retrospective analysis Patients transplanted 2001-2002	Alemtuzumab n=33	MMF/perioperative CS only Delayed TAC: Median time to initiation 14d Median follow-up: 58 months
#1452 Knight RJ et al Four year Outcomes Comparing Thymoglobulin and Basiliximab in Combination with Sirolimus and Reduced dose Cyclosporine for High versus Low Risk Immune Responders. University of Texas	Retrospective single center review High immune responders: African American patients; retransplants; PRA >30% Low immune responders: All other patients	rATG n=120 Basiliximab n=156	SRL/CS Delayed CsA Median follow-up: 21 months (range 1-81 months)
#233 Stevens RB et al Successful CNI Discontinuation Following Early Steroid Withdrawal in Recent Allograft Recipients Is Associated with Reduced Chronic Allograft Nephropathy, Improved Renal Function without Increased Risk of Rejection. University of Nebraska	Prospective, randomized single center trial	rATG; single infusion vs 4-dose schedule n=124 First 22/34 patients withdrawn from TAC were compared to patients who were not withdrawn	CS free regimen/CNI withdrawal (CNIWD): CNI withdrawal (TAC): SRL/TAC first 6 months Mean follow-up: - 12.7±9.4 months - CNI withdrawal: 7.5±0.9 months
#725 Leventhal JR et al CEL220: A Randomized Prospective Trial of Steroid and Calcineurin Inhibitor Free Immunosuppression Using Alemtuzumab Induction: Interim Analysis of Patient Immune Status and Clinical Outcomes. Northwestern University	Single center prospective trial Living donor kidney transplant recipients	Alemtuzumab	**Group 1:** TAC/MMF; converted to SRL post-transplant (time not specified) n=15 **Group 2:** SRL/MMF n=12 Follow-up: 12 months

CAN – chronic allograft nephropathy; CNI – calcineurin inhibitor; CNIWD – calcineurin inhibitor withdrawal; CS – corticosteroid; CsA – cyclosporine; GFR – glomerular filtration rate; MMF – mycophenolate mofetil; rATG – rabbit antithymocyte globulin; SCr – serum creatinine; SRL – sirolimus; TAC – tacrolimus; WD – withdrawal

that the regimen, in which patients received only MMF for two weeks after alemtuzumab, was associated with a high incidence of acute rejection and graft loss, 36% and 27%, respectively.[237]

In a small, single-center, prospective, randomized trial of rATG administered as either a single infusion, or as a divided dose infusion, data supported a CS-free, CNI withdrawal regimen. In this study, the incidence of chronic allograft nephropathy (CAN) was significantly higher in the CNI-based group, when compared to recipients on a CNI withdrawal regimen.[233]

In another retrospective analysis, delayed administration of CsA was evaluated in an induction regimen with either rATG or basiliximab, in which all patients received sirolimus. The incidence of acute rejection among high-risk recipients treated with rATG was significantly lower than low-risk recipients treated with basiliximab (19% vs. 28%, respectively).[1452]

TABLE 4 SUMMARY

USE OF ANTIBODY INDUCTION THERAPY TO MINIMIZE CALCINEURIN INHIBITOR EXPOSURE IN KIDNEY TRANSPLANTATION

- Rabbit ATG (rATG), in conjunction with sirolimus, was more effective in preventing acute rejection and minimizing CNIs when used in high-risk recipients, when compared to basiliximab when used in low-risk recipients
- As noted in Table 3, Tan et al and Potdar et al have found alemtuzumab induction to facilitate CNI minimization in some patients
- Overall, CNI minimization and/or avoidance remains challenging regardless of which antibody is chosen for induction

Clinical Endpoints	Comments
1 year / **4 years** **Rejection** 30.3% / 36% **Graft survival** 88% / 73% **Patient survival** 97% / 91% **Mean SCr** (mg/dL) 1.58±0.6 / 148±0.6 **Mean GFR** (mL/min) 65.9±20.8 / 76.2±32.2 **Remaining off CS** 70%	Use of alemtuzumab to eliminate CS use and delay CNI was associated with increased risk of rejection and graft loss 1/3 of recipients experienced an infectious complication
Group 1: rATG in high immune responders **Group 2:** Basiliximab in low immune responders **Group 1** / **Group 2** / *P*-value **Acute rejection** 19% / 28% / <0.05 **Graft survival at 4 years** 70% / 73% / NS **Mean SCr** (mg/dL) **at 4 years** 1.7±0.6 / 1.6±0.8 / NS	Compared to a basiliximab regimen in low risk recipients, rATG and a delayed CsA regimen in high-risk recipients, resulted in a lower acute rejection incidence and equivalent graft survival at 4 years of follow-up
Group 1: Single infusion rATG; SRL/TAC n=30 **Group 2:** 4-dose rATG; SRL/TAC n=31 **Group 3:** Single infusion rATG; SRL/MMF n=31 **Group 4:** 4-dose rATG; SRL/MMF n=32 - CNI withdrawal outcomes compared **CNIWD** / **No WD** / *P*-value **CAN** 7% / 41% / 0.01 GFR improved 3 months following CNIWD (values not reported; ***P*=0.04**)	Successful avoidance of CNI and CS with a single or divided-dose rATG resulted in successful short-term outcomes Use of rATG for antibody induction therapy in CNIWD group resulted in improved GFR at 3 months, compared to recipients who were maintained on CNIs CNIWD resulted in decreased incidence of CAN, compared to recipients who were maintained on CNIs
CNI Conv. Group 1 / **CNI Avoid Group 2** **Rejection** 2/15 / 2/12 **Patient & Graft Survival** 100% / 93% - Profound depletion of CD4+ cells - Significant increases in: CD19+CD38+ plasma cells - Increased frequency of CD8+CD28- cells	CNI conversion or CNI avoidance regimens in combination with alemtuzumab induction was effective in living donor kidney transplant recipients Both rejection episodes in CNI avoidance groups were antibody mediated

USE OF ANTIBODY INDUCTION THERAPY IN AT-RISK KIDNEY TRANSPLANT RECIPIENTS

In recent years, more patients on the kidney waiting list are considered high immunological risk candidates, at greater risk of mounting an immunological response to a donor kidney than low-risk candidates. In an attempt to equitably distribute donor kidneys to all individuals on the transplant waiting list, including those that are at high immunological risk, transplant clinicians are attempting to optimize existing protocols through the incorporation of antibody induction therapy to prevent acute rejection.

Several abstracts analyzing the results of antibody induction therapy in high-risk-recipients were presented at the 2007 ATC meeting. High-risk was defined variably as African American recipients, patients who developed DGF, retransplanted patients, and presensitized patients (PRA >20; PRA>40; PRA >50). Recipients of donor organs with cold ischemia time (CIT) >24h, recipients of extended criteria donor (ECD) organs, or recipients of organs donated after cardiac death (DACD), were also cited as factors contributing to the risk of AR or DGF.

Besides African American race, several risk factors for acute rejection, including age, body mass index (BMI), peak PRA > 20%, DGF, and the use of sirolimus, were identified in a single center retrospective analysis of African American recipients treated with rATG.[1198]

A single-center, retrospective analysis comparing alemtuzumab and rATG treatment, suggested equivalent outcomes between the two induction agents in high-risk recipients maintained on triple therapy regimens.[1455] Two separate studies confirmed the superiority of rATG in reducing the incidence of acute rejection, when compared to an IL-2RA (daclizumab or not specified) or to no antibody induction therapy in at-risk patient populations.[331, 1206] In a single center retrospective review, rATG was identified as a significant factor protecting against the occurrence of acute rejection.[1206]

Table 5. Use of Antibody Induction Therapy in At-Risk Kidney Transplant Recipients

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#1198 Patel SJ et al Differences in Risk Factors for Acute Rejection between African American and Non-African American Renal Transplant Recipients under Antithymocyte Globulin Induction. Methodist Hospital, Houston	Retrospective single center analysis	rATG n=231	CS + two of the following: MPA/TAC/SRL Comparison of results in African American (n=157) vs non-African American (n=71) recipients
#1455 Lipshutz GS et al Alemtuzumab vs Antithymocyte Globulin for High-Risk Kidney Recipients: 1-Year Outcomes at a Single Center. UCLA	Retrospective single center review Patients transplanted 2004-2005 High-risk: - Long CIT - ECD - DACD - Elevated donor SCr	Alemtuzumab n=100 rATG n=54	Non-minimization triple immunosuppression (not specified) Follow-up: 1 year
#331 Noel C et al Daclizumab versus Thymoglobulin in Renal Transplant Recipients with a High Immunological Risk: A French and Belgian Prospective Randomized Trial. CHRU de Lille, France	Prospective multi-center randomized trial (France, Belgium) High-risk: - Peak PRA >50% or PRA at time of transplant >30% - 3rd or 4th retransplant - Immunologic loss of first kidney <2 years	rATG n=113 Daclizumab n=114	TAC/MMF/low dose CS Follow-up: 12 months

A prospective, multi-center, randomized trial of high immunological risk recipients in France and Belgium, demonstrated that acute rejection rates of kidney transplant recipients receiving rATG antibody induction therapy were significantly lower when compared to recipients treated with daclizumab[331] . Alternatively, a group at the University of Maryland found the greatest benefit of rATG induction to be in less sensitized patients, with compromised efficacy of both rATG and basiliximab in highly sensitized recipients.[1451] In a separate short-term follow-up study in at-risk patients, daclizumab administered on a 2-dose schedule was found to be equivalent to basiliximab, with respect to efficacy and safety.[1456]

TABLE 5 SUMMARY

USE OF ANTIBODY INDUCTION THERAPY IN AT- RISK KIDNEY TRANSPLANT RECIPIENTS

- A variety of recipient demographic factors and donor organ characteristics define the at-risk kidney transplant recipient
- Antibody agents are effective at reducing the incidence of acute rejection in many at-risk kidney transplant recipients. Rabbit ATG (rATG) and alemtuzumab appear to be the most effective agents

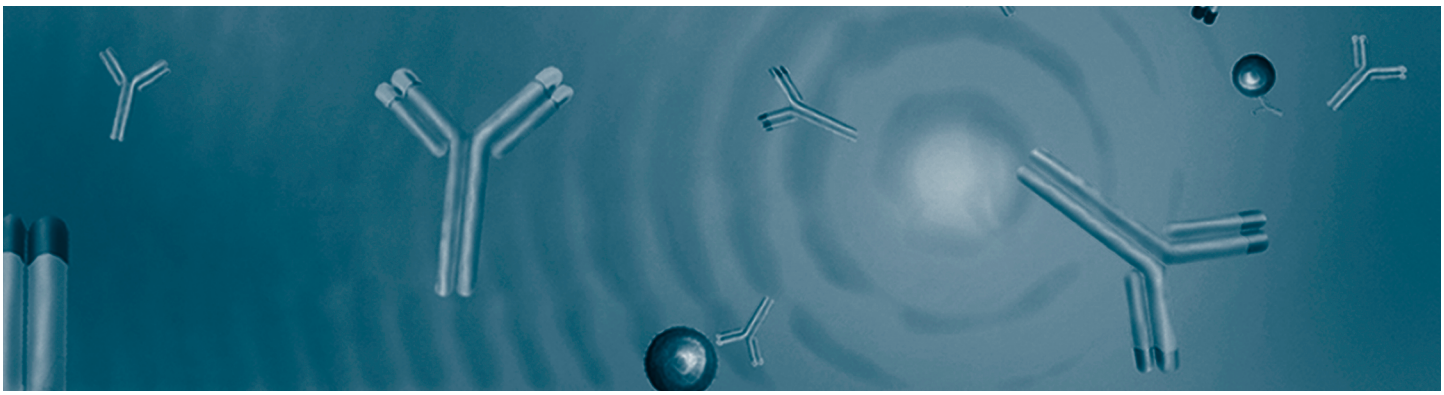
Clinical Endpoints	Comments
<table><tr><th></th><th>African American</th><th>Non African American</th><th>*P*-value</th></tr><tr><td>**Rejection**</td><td>27(17%)</td><td>5(7%)</td><td>0.04</td></tr></table>	African American kidney transplant recipients are at higher risk of acute rejection than non African American recipients A number of risk factors are associated with acute rejection in African American recipients including - Older age - Higher BMI - Peak PRA >20% - Delayed graft function - Use of SRL
Equivalent: - Patient and graft survival – >95% and >90%, respectively - DGF – 21.7% vs 30.7% - Serious fungal infections – 6.5% vs 5.6% - Urinary BKV – 10.9% vs 7.6% - CMV – 17.4% vs 17.0% - Rejection – 10.9% vs 16.7% - humoral rejection more prevalent among rATG treated recipients (data not reported) All values alemtuzumab vs rATG	In high-risk renal transplant recipients, either alemtuzumab or rATG supports a triple therapy maintenance regimen safely and effectively
<table><tr><th></th><th>rATG</th><th>Daclizumab</th><th>*P*-value</th></tr><tr><td>**BPAR**</td><td>19.5%</td><td>29.8%</td><td>0.043</td></tr><tr><td>**MDRD eGFR**</td><td>49.3±17.9</td><td>50.9±17.2</td><td>NS</td></tr><tr><td>**Graft survival**</td><td>84.1%</td><td>95.6%</td><td>NR</td></tr><tr><td>**Patient survival**</td><td>86.0%</td><td>96.5%</td><td>NR</td></tr></table>	High-risk recipients receiving rATG antibody induction therapy were at lower risk of acute rejection, compared to those treated with daclizumab There were no significant differences in graft or patient survival, or renal function, at one year of follow-up

Table 5. Use of Antibody Induction Therapy in At-Risk Kidney Transplant Recipients (Cont.)

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#1206 Hammond EB et al Thymoglobulin Induction Significantly Reduces Acute Rejection Compared to Either IL-2 Receptor Antagonists or No Induction in African American Kidney Transplant Recipients. Medical University of South Carolina	Retrospective single center review High-risk: African American patients	rATG n=47 IL-2RA n=78 No antibody n=37	Not specified Follow-up: 1 year
#1451 Philosophe B et al Differential Effects of Thymoglobulin (Thymo) Depletion and Basiliximab Induction in Sensitized Patients Undergoing Renal Transplantation. University of Maryland	Retrospective single center review Patients transplanted 2004-2006 High-risk: - Sensitized - peak PRA >40% - Unsensitized - peak PRA <20%	n=527 rATG n not specified Basiliximab n not specified Sensitized n=98 Unsensitized n=353	Not specified Follow-up: 2 years
#1456 Harris MT et al Two-Daclizumab vs Two-Dose Basiliximab in High-Risk Kidney and Kidney-Pancreas Transplant. Duke University	Retrospective single center analysis Patients transplanted 2004-2006 High-risk: - African American patients - Positive crossmatch - Second transplant - Long CIT - ECD	Basiliximab n=53 Daclizumab n=20	CNI (TAC or CsA)/MMF or SRL/CS Follow-up: 6 months

BPAR - biopsy proven acute rejection; BKV - BK virus; BMI - body mass index; CI - confidence interval; CIT - cold ischemia time; CMV - cytomegalovirus; CNI - calcineurin inhibitor; CS - corticosteroid; CsA - cyclosporine; DACD - donation after cardiac death; DGF - delayed graft function; ECD - extended criteria donor; eGFR - estimated glomerular filtration rate; GFR- glomerular filtration rate; IL-2RA - Interleukin 2 receptor antagonist ; MDRD - modification of diet in renal disease equation; MMF - mycophenolate mofetil; MPA - mycophenolic acid; NR - not reported; NS - not significant; OR - odds ratio; PRA - panel reactive antibody; SCr - serum creatinine; SRL - sirolimus; TAC - tacrolimus

Clinical Endpoints	Comments
rATG Group – significantly higher demographic risk for acute rejection (rATG vs. IL-2 RA/No antibody) - PRA>10% – 45% vs 13% - Retransplant – 43% vs 3%; ***P*<0.001** **BPAR** - rATG vs no antibody – 11% vs 41%; ***P*<0.0017** - rATG vs IL-2RA – 11% vs 24%; ***P*<0.066** - IL-2RA vs no antibody – 24% vs 41%; ***P*<0.076** Significant multivariate risk factor for BPAR: - Use of rATG- Odds ratio=0.17; (95% CI 0.05-0.55); ***P*<0.003** - Factors identified as nonsignificant – gender, donor source, PRA >10%, DGF, choice of CNI	Despite higher demographic risk for acute rejection, African American kidney transplant recipients treated with rATG experienced a significantly lower incidence of BPAR, compared to those who did not receive antibody induction therapy Use of rATG was identified as a significant protective factor against the occurrence of BPAR
rATG / **Basiliximab** / ***P*-value** **Cumulative rejection** - Unsensitized patients: 6% / 21% / 0.031 - Sensitized patients: 31% / 25% / NS **Graft survival** - Sensitized patients: 76% / 100% / 0.007 - Patients with rejection: 38%* / 96% - Patients with no rejection: 94%* / 96% **P*<0.0001	The efficacy of rATG may be affected by the sensitization status of the transplant recipient, and by the occurrence of rejection Antibody-mediated (humoral) rejection and graft loss among recipients who experience rejection may occur more frequently under rATG antibody therapy in sensitized recipients
Basiliximab / **Daclizumab** / ***P*-value** **BPAR**: 7.5% / 20% / 0.2 **Acute humoral rejection**: 0 / 10% / 0.07 - No difference in SCr (data not reported) - Equivalent patient (≥93%) and graft (kidney ≥97%; pancreas ≥92%) survival	Daclizumab and basiliximab were safe and effective induction regimens in high-risk renal or pancreas transplant recipients



LIVER TRANSPLANTATION

In 2005 (the latest year for which data are available), the OPTN reported that 21% of all liver allograft recipients were treated with antibody induction therapy, compared to 74% of all kidney transplant recipients.[6] IL-2RAs were used most frequently (11%), followed by rATG (7%), and alemtuzumab (2%). The data reflect a 21% increase in antibody use in 2004-2005, compared to 1994. The increasing clinical interest in the use of antibody therapy in liver transplantation translated into several interesting abstracts presented at the 2007 ATC.

EFFICACY AND SAFETY OF ANTIBODY THERAPY FOLLOWING LIVER TRANSPLANTATION

Corticosteroid and/or CNI sparing following liver transplantation was a prominent topic at the 2007 ATC.

CNI maintenance therapy after liver transplantation may result in renal insufficiency.[5] While CS sparing in liver transplantation has been widely practiced, a need for further optimization of immunosuppressive regimens to diminish the nephrotoxic effects of CNIs remains.

A retrospective single center study in patients with renal dysfunction utilizing rATG or no antibody therapy was presented by Bajjoka and colleagues from Detroit. This study assessed the impact of delayed CNI initiation on renal function. Patient survival and graft survival were similar at 1 year between the groups and BPAR was lower in the rATG group than in the control group, 13% vs. 26%, respectively. Importantly, renal function was better at 1 year in rATG treated patients than controls. There was also no increase in infections or HCV recurrence observed in rATG treated patients.[168]

Two other groups presented experience with rATG compared to no antibody therapy in a delayed CNI protocol. While their approaches were somewhat different, both concluded that use of rATG therapy was safe and effective in liver transplant recipients, resulted in a low incidence of rejection, and in some cases improved renal function.[1578, 172]

A retrospective evaluation of 391 liver transplant recipients in Vienna who were given 3 doses of ATG and delayed CNI introduction (n=262) vs. no antibody therapy and immediate CNI therapy (n=129) demonstrated a lower incidence of acute rejection and improved renal function early post-transplant in the delayed CNI cohort.[176] Another retrospective analysis conducted at Northwestern evaluated the use of alemtuzumab (n=104) vs. unspecified

Table 6. Efficacy and Safety of Antibody Therapy Following Liver Transplantation

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#168 Bajjoka I et al Comparing Thymoglobulin Induction and Delayed Calcineurin Inhibitor Initiation with No Antibody Induction and Early Calcineurin Inhibitor Initiation in Liver Transplantation. Henry Ford Hospital	Prospective Single center Patients with renal dysfunction, defined as SCr >1.5 mg/dL at transplantation	**Group 1:** rATG n=120 **Group 2:** No antibody therapy n=80	**Group 1:** - Delayed CNI until renal function improved - MMF plus CS x 6 months **Group 2:** - CNI within 48h - MMF plus CS x 3 months Follow-up: 1 year
#634 Eason JD et al Rabbit ATG Induction as a Calcineurin Inhibitor-Sparing Protocol in Steroid-Free Liver Transplantation. University of Tennessee	Prospective Single center Noncomparative	rATG: Two doses; intraoperatively + d2 One dose of CS prior to first dose of rATG n=100	- MMF - Low dose TAC delayed 2 days - SRL *if* SCr >2.5 mg/dL or oliguria >d7 Follow-up: 3 months
#176 Burghuber CK et al Short-term Induction Therapy with Antithymocyte Globulin and Delayed use of Calcineurin Inhibitors in Orthotopic Liver Transplantation Medical University Vienna, Austria	Retrospective analysis	**Group 1:** ATG x 3d n=262 **Group 2:** No antibody n=129	**Group 1:** CNI delayed to d3 **Group 2:** CNI immediately post-transplant Follow-up: 5 years

antibody agents (n=182) and reported similar incidence of acute rejection, and patient and graft survival. The alemtuzumab recipients, who were also taking MMF, experienced a significant increase in neutropenia, infections and CMV.[198]

Eason and colleagues presented a retrospective, single center study utilizing a 2 dose regimen of rATG in a CS minimization regimen. Short term follow up demonstrated excellent patient and graft survival, 94% and 91%, respectively, and a low incidence of acute rejection (20%). Only 7% of patients with acute rejection required CS treatment.[634]

TABLE 6 SUMMARY

EFFICACY AND SAFETY OF ANTIBODY THERAPY IN LIVER TRANSPLANTATION

- Antibody induction therapy is being used to minimize the use of CSs, to delay the use of CNIs, or to support CNI monotherapy following liver transplantation
- The use of rATG may be effective in both limiting acute rejection, and in preserving renal function
- The use of rATG in liver transplant recipients with Hepatitis C and renal dysfunction did not result in an increase in HCV recurrence and has the potential to improve renal function

Clinical Endpoints				Comments
	Group 1	**Group 2**	***P*-value**	Use of rATG to delay CNIs is associated with lower incidence of acute rejection, better renal function, and a lower incidence of infection There was no increase in HCV recurrence
Patient survival	90%	89%	NS	
Graft survival	88%	86%	NS	
BPAR at 30d	13%	26%	0.021	
SCr (mg/dL)				
- Baseline	2.6	2.2	0.044	
- 6 months	1.3±0.6	1.6±04	0.001	
- 12 months	14±0.5	1.7±0.5	<0.001	
HCV recurrence	40%	64%	0.146	
Infection	37%	51%	0.04	
Patient survival	94%			Following liver transplantation, rATG may be used effectively as part of a renal sparing regimen to reduce exposure to both CSs and CNIs
Graft survival	91%			
Acute rejection	20% ; 7% CS-treated			
SCr	Pre-transplant - 1.4 mg/dL d3 - 1.5 mg/dL 1 month - 1.3 mg/dL 3 months - 1.4 mg/dL			
	Group 1	**Group 2**	***P*-value**	A short course of ATG results in a lower incidence of acute rejection, and improved renal function early post-transplant
Overall survival	70.1%	74.3%	>0.05	
Graft survival	68.0%	71.8%	>0.05	
Acute rejection	14.5%	31.8%	0.0008	
- Treated	7.3%	23.3%	0.001	
SCr (mg/dL)				
- Baseline	1.14	1.18	>0.05	
- 1 year	1.26	1.37	0.015	
eGFR (mL/min)	81	75	0.02	

Table 6. Efficacy and Safety of Antibody Therapy Following Liver Transplantation (Cont.)

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#1578 Cantarovich M et al Long-Term Renal Function in Liver Transplant Patients with Post-Operative Renal Dysfunction Receiving Anti-Thymocyte Globulin Induction and Delayed Calcineurin Inhibitors. McGill University, Montreal	Retrospective Analysis Patients with renal dysfunction defined as SCr >150 µmol/L on POD 1-2	**Group 1:** ATG* (every 3-5 days) n=112 **Group 2:** ATG* (daily) n=209 **Group 3:** No antibody therapy n=58 *Maximum dose 6mg/kg	**Group 1:** Delayed, low dose CNI **Group 2:** Delayed, low dose CNI **Group 3:** Delayed, standard dose CNI Follow-up: 7 years
#172 Mangus RS et al Induction Immunosuppression in 698 Consecutive Adult, Cadaveric Liver Transplant Recipients. Indiana University	Retrospective review Patients transplanted 2001-2006	**Group 1:** Intraoperative rATG n=166 **Group 2:** Delayed rATG (48h) n=259 **Group 3:** Delayed rATG (48h) + rituximab (72h) n=273	TAC/CS Median follow-up 33 months
#198 Stosor V et al Alemtuzumab (Campath) is Associated with High Risk of CMV Infection after Liver Transplant (LT). Northwestern University	Retrospective cohort study Patients transplanted 2003-2005	**Group 1:** Alemtuzumab n=104 **Group 2:** Other antibody agents (not specified) n=182	MMF/CS/(no CNIs specified) Results at 1 year follow-up reported

Clinical Endpoints					Comments
	Group 1	**Group 2**	**Group 3**		Use of ATG to delay CNI introduction and reduce CNI dose in liver transplant recipients is associated with a low incidence of CKD and subsequent requirement for dialysis, without increasing acute rejection rates
Patient survival					
Year 1	73%	83%	84%		
Year 5	55%	70%	72%		
Year 7	46%	63%	69%		
Acute rejection					
(year 1)	36%	23%	43%		
CKD Requiring Dialysis					
Year 1	2.0%	0%	0%		
Year 5	3.4%	0.9%	3.3%		
Year 7	9.8%	2.0%	3.3%		
	Survival at 1 year				Antibody therapy is safe in adult liver transplant recipients, with good efficacy and minimal immunosuppression related side effects
	Group 1	**Group 2**	**Group 3**		
Overall					
Graft	84.3%	82.2%	85.1%		
Patient	87.3%	83.8%	86.1%	*P*=NS	
HCV+					
Patient	90.8%	85.1%	87.9%	*P*=NS	
HCC					
Patient	85.7%	87.2%	86.0%	*P* NR	
·Acute rejection < 5%					
·No CS-resistant rejection					
·PTLD - 0.3% (2 patients)					
	Group 1	**Group 2**	***P*-value**		Alemtuzumab treatment is a risk factor for the development of clinically significant CMV infection following liver transplantation, in the setting of antiviral prophylaxis
Overall survival	86.5%	84.1%	0.574		
Graft survival	94.2%	93.4%	0.782		
Rejection	14.4%	20.9%	0.176		
Neutropenia	30.8%	12.1%	<0.001		
CMV					
- Prophylaxis	96.2%	99.5%	0.051		
- Interruption*	27.9%	11.5%	<0.001		
- Infections	20.2%	8.2%	<0.001		
- Viremia	13.5%	1.1%	<0.001		
- End organ disease	3.8%	0.5%	041		
- Hospitalization	8.6%	1.1%	<0.001		
Multivariate risk factors for CMV infection :					
- Alemtuzumab: *P*<0.001					
- Low dose valganciclovir prophylaxis: *P*=0.022					
- Neutropenia: *P*=0.046					
*Low WBC count					

Table 6. Efficacy and Safety of Antibody Therapy Following Liver Transplantation (Cont.)

Abstract / First Author / Title	Study Design	Antibody Therapy	Maintenance Therapy Follow-up
#70 Bajjoka I et al Safety of Thymoglobulin Induction in HCV Liver Transplant Recipients. Henry Ford Hospital	Retrospective review	**Group 1:** rATG=54 patients with renal dysfunction, defined as SCr ≥ 1.5 mg/dL **Group 2:** No antibody treatment n= 54	CNI/MMF x 6 months/CS x 3 months Delayed CNI to patients in Group 1 Group 1 follow-up: 681±448 d Group 2 follow-up: 805±395 d
#629 Mazariegos G et al Long-Term Outcome with rATG Induction and Steroid-Free Immunosuppression in Pediatric Liver Transplantation (PLTX). Children's Hospital, Pittsburgh	Retrospective review Pediatric liver transplant recipients; median age 5.3 years (1.4 months - 21.7 years)	rATG (4-5 mg/kg) n=119	TAC monotherapy Mean follow-up: 24.2±16.3 months

AZA: azathioprine; BPAR – biopsy-proven acute rejection; CKD – chronic kidney disease; CMV – cytomegalovirus; CNI – calcineurin inhibitor; CS – corticosteroid; eGFR – estimated glomerular filtration rate; HCC – hepatocellular carcinoma; HCV – hepatitis C virus; HTN – hypertension; MMF – mycophenolate mofetil; NODM – new onset diabetes mellitus; NR – not reported; NS – not significant; POD – post operative day; PTLD – post-transplant lymphoproliferative disease; rATG – rabbit antithymocyte globulin; SCr – serum creatinine; SRL – sirolimus; TAC – tacrolimus; WBC – white blood cell

INDIVIDUALIZING ANTIBODY THERAPY IN KIDNEY AND LIVER TRANSPLANTATION: SUMMARY

Thus, data presented at the 2007 American Transplant Congress provide additional information for transplant clinicians to consider in their management of the kidney and liver transplant recipient. Historical endpoints such as graft survival, patient survival and acute rejection rates were compared and contrasted in multiple immunosuppressive regimens, in both prospective and retrospective studies, and novel approaches to minimize the use of toxic maintenance immunosuppression were evaluated. The implications of study design, patient population, and institutional standard of care should all be considered before making conclusions regarding changes in practice and patient care.

To summarize, studies presented at the 2007 ATC continue to expand our understanding of antibody induction protocols in kidney and liver recipients, confirming the advantages noted by many clinicians in adopting induction therapy.

- In a meta-analysis consisting of 11 randomized, controlled trials, basiliximab and daclizumab reduced the incidence of DGF, acute rejection and graft failure (comparator not specified).[1457]
- In a prospective, randomized multi-center OPTN trial, comparing the use of rATG antibody induction therapy vs. basiliximab in kidney transplant recipients, rATG significantly reduced the risk of the composite endpoint (DGF/AR/graft loss/death).[334] Antibody induction therapy in kidney transplant recipients treated with either rATG or alemtuzumab result in excellent one-year patient and graft survival rates.[330, 1455]
- Despite higher risk for acute rejection, African American kidney transplant recipients treated with rATG experienced a lower incidence of BPAR compared to no antibody induction therapy.[1206]

Clinical Endpoints				Comments
	Group 1	Group 2	*P*-value	Use of rATG in liver recipients with renal dysfunction resulted in improved renal function, with no measurable impact on HCV recurrence
Patient survival	83%	78%	0.465	
Acute rejection	48%	61%	0.121	
HCC	1.8%	9.3%	0.093	
HCV recurrence	76%	76%	NS	
SCr (mg/dL)				
- Baseline	2.61±1.1	1.0±0.5	<0.001	
- Latest follow-up	1.5±0.5	1.4±0.4	NS	
- % change	-38.1%	+50.1%	<0.001	
Patient survival	95.8%			Treatment with low dose rATG may reduce the requirement for maintenance CS, and reduce the incidence of immunosuppression related complications following pediatric liver transplantation
Graft survival	92.7%			
CS treated rejection	n=36 (30.3%)			
Mean creatinine	0.6±0.36 mg/dL			
PTLD	n=3			
CMV disease	n=2			
Post-transplant HTN	6.1%			
NODM	n=1			
- 8 patients converted to SRL to minimize potential long-term CNI toxicity - 69.7% patients CS free at time of report				

Appropriate antibody induction therapy in kidney and liver transplantation can provide adequate immunosuppression in the perioperative period, facilitating CS avoidance or withdrawal, and minimization of CNI use.

- CNI and CS withdrawal can be achieved, even in high immunological risk recipients, with the appropriate individualization of immunosuppressive therapy.
- Anti IL-2RA therapy may be less useful than rATG or alemtuzumab in higher risk patients.[445]
- rATG and alemtuzumab antibody induction therapy result in comparable BPAR rates, and were significantly lower than basiliximab, in kidney transplant recipients on a CSWD regimen.[1703]
- Rabbit ATG (rATG) antibody induction therapy in high-risk kidney transplant recipients, when compared to basiliximab in a low-risk recipient population, supported a delayed CNI regimen.[1452]
- Use of rATG antibody induction therapy to facilitate CNI withdrawal may result in improved GFR and reduction in CAN.[233]

These data provide a compelling rationale for inclusion of antibody induction therapy as a critical component in the immunosuppressive armamentarium in kidney transplantation, and provide further clinical evidence regarding the benefit of antibody therapy in liver transplantation. Doubtless, next year's meeting will provide updates on many of these same studies, as well as additional data to allow the astute clinician to make informed choices regarding the best immunosuppressive therapies for his or her patients.

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