TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

REVIEW

Induction therapy in lung transplantation

Stuart C. Sweet

Pediatric Lung Transplant Program, Washington University School of Medicine, St. Louis, MO, USA

Keywords
immunosuppression, induction, lung clinical, tolerance.

Correspondence
Stuart C. Sweet MD, PhD, Pediatric Lung Transplant Program, Washington University School of Medicine, One Children's Place, Campus Box 8116-NWT, St. Louis, MO 63110, USA.
Tel.: 314-454-2694;
fax: 314-454-2515;
e-mail: sweet@wustl.edu

Conflicts of interest
No conflict of interest.

Received: 31 December 2012
Revision requested: 13 February 2013
Accepted: 20 April 2013
Published online: 23 May 2013

doi:10.1111/tri.12115

Abstract

Strategies for induction in lung transplant recipients typically mirror those used in other solid organ transplant recipients. Polyclonal (Atgam, RATG) and monoclonal (OKT3) T-cell depleting agents, IL-2 Receptor antagonists (basiliximab and daclizumab) have been used most commonly. In spite of evidence from ISHLT registry reports that induction reduces acute rejection and has a small benefit in freedom from bronchiolitis obliterans and long-term survival, other studies have been less convincing in terms of long-term benefit. Future iterations of induction strategy for lung transplant recipients will hopefully utilize tolerogenic approaches currently being tested in renal transplantation.

The role of induction

The evolution of induction immunosuppression strategies for lung transplantation has typically been similar to those used in other solid organ transplantation. In general, baseline targets for immunosuppression are higher than those used in other solid organ transplants, particularly during the first several months after transplantation. This is likely because of multiple factors. Transplanted lungs contain significant numbers of donor dendritic cells capable of stimulating T cells via direct allorecognition. These cells diminish in number during the first several months post-transplant [1]. Allograft injury associated with donor brain death and the ischemia reperfusion response provide a proinflammatory milieu that enhances the T-cell response [2–4]. The lung is continually exposed to exogenous pathogens and toxins capable of stimulating innate and adaptive responses that may in turn increase T-cell responses via indirect allorecognition. Finally, the fact that the lung receives the entire cardiac output increases the likelihood of matching circulating T cells with a cognate antigen present in the lung. Thus, maximizing effective immunosuppression must be an important consideration for lung transplant recipients in the immediate post-transplant period. Nonetheless, enthusiasm for aggressive early immunosuppression must be tempered by the potential for infection for which exposure to the outside world places the lung allograft at particular risk.

Thus, many lung transplant centers use an induction agent in the peri-transplant period to provide enhanced immunosuppression during this critical period. Because, in the absence of a positive crossmatch, early allograft injury is felt to be primarily because of T-cell responses, induction strategies are focused on T-cell inhibition. Strategies fall into two general categories, both involving the use of antibodies. In the first strategy, monoclonal or polyclonal antibodies with reactivity against one or more lymphocyte surface antigens are used to deplete T cells (and other immune cells). In the second, monoclonal, chimeric antibodies directed against the IL-2 receptor are

Table 1. Agents Commonly Used for Induction in Lung Transplantation.

Agent	Composition	Activity	Major Side Effects
Antithymocyte Globulins (ATG)	Polyclonal antibodies raised in horse (Atgam) and rabbit (RATG)	Interacts with thymocyte surface proteins, leading to lysis, diminished function, and prolonged T-cell depletion	Cytokine-release syndrome, cytopenia, serum sickness, anaphylaxis
Murmonab CD3 (OKT3)	Monoclonal antibody	Interacts with CD3 surface protein, leading to activation and, cytokine release, followed by reduced function, lysis, and T-cell depletion	Severe, cytokine release syndrome, pulmonary edema, aseptic meningitis, seizures, renal failure
Alemtuzumab (Campath)	Monoclonal antibody directed against CD52 (present on all B and T cells, most monocytes, macrophages, and natural killer cells)	Binds to CD52 on circulating leukocytes leading to cell lysis and prolonged depletion	Mild cytokine-release syndrome, cytopenia, paroxysmal nocturnal hematuria
IL-2 Receptor Antagonists	Chimeric (basiliximab) or Humanized (daclizumab) monoclonal antibody against CD25 (IL-2 receptor α chain)	Binds to CD25 molecule on activated T cells, leading to interference with IL-2-dependent T-cell activation	Hypersensitivity reactions (uncommon); otherwise generally well tolerated

used to inhibit IL-2-dependent T-cell proliferation (Table 1).

Lymphocyte depleting agents

Therapies intended to deplete circulating T cells fall into two general categories based on the antibody type: polyclonal versus monoclonal.

The polyclonal agents include antilymphocyte (ALG) and antithymocyte (ATG) globulin. Antithymocyte globulin is the most commonly used of these and is produced by inoculating animals with human thymocytes, collecting and filtering the resulting immunoglobulin. The resulting preparation contains antibodies specific for lymphocytes. Two ATG preparations are available. Thymoglobulin (RATG) is derived from rabbit serum and Atgam is derived from equine serum [5]. Both agents are dosed on a daily basis for up to 14 days with thymoglobulin having a longer half-life than Atgam (30 days vs. 5.7 days). Administration of the antibodies leads to indirect depletion of cytotoxic T cells through depletion of circulating lymphocytes. Multiple mechanisms including Fc-dependent, complement-mediated lysis and opsonization with clearance via the reticuloendothelial system are responsible [6]. Side effects of ATG preparations include a cytokine-release syndrome consisting of fevers and rigors, with occasional anaphylaxis, usually worst during initial dosing. For this reason, acetaminophen, diphenhydramine, and steroids are used to blunt these responses. Leukopenia and thrombocytopenia are not uncommon. Late complications include immune complex-related serum sickness and glomerulonephritis. Because the risk of anaphylaxis increases with multiple courses, most centers limit the use of these agents to a single course (Table 1).

Antibodies contained in these polyclonal γ-globulin preparations may also induce anergy or tolerance through blockade of costimulatory signals [7] In addition, recent reports suggest that treatment with ATG can lead to regulatory T-cell (T-reg) expansion *in vitro* and relative T-reg sparing *in vivo* [8,9].

In terms of monoclonal antibodies, muromonab-CD3 (OKT3) is considered the prototype agent. OKT3 is a murine-derived monoclonal antibody directed against the ε chain of the T-cell receptor-CD3 complex. Binding of OKT3 to T cells leads initially to activation and subsequently to depletion of circulating T cells [10–12]. Similar to ATG, patients receiving OKT3 may have a cytokine-release syndrome, rarely leading to circulatory collapse. As such, patients typically receive acetaminophen, diphenhydramine, and steroid prophylaxis [13]. Other, less frequent side effects of OKT3 include pulmonary edema, aseptic meningitis, renal insufficiency, and seizures. OKT3 is dosed on a daily basis starting on the day of transplant and continuing for up to 7 days post-transplant. As with ATG, treatment with OKT3 relatively spares T-reg cells [8,9]. OKT3 was voluntarily withdrawn from the United States market in 2009.

Finally, alemtuzumab is a more recently approved humanized monoclonal antibody directed against the CD52 antigen (present on the cell surface of B and T cells as well as monocytes, macrophages, NK cells, and thymocytes). Alemtuzumab causes depletion of leukocytes through Fc/complement-mediated cytolysis, antibody-medicated cellular cytotoxicity, and induction of programmed cell death. It was originally prescribed in chronic lymphocytic leukemia and lymphoma and introduced in renal transplantation in the late 1990s [14]. Use in lung transplant has been reported by the Pittsburgh Group

Table 2. Studies of induction in lung transplant recipients.

Study	Description	Key Results
ISHLT Registry Reports [33,35–39]	Retrospective analyses of data submitted to the ISHLT registry for heart and lung transplantation reports	Decreased incidence of BOS Benefit when 14-day conditional survival considered IL2RA with lower incidence of acute rejection OKT3 with increased and IL2RA decreased risk for 5-year mortality in 2012 registry report [33]
Hachem *et al.* [34]	Independent, retrospective multivariate analysis of data submitted to the ISHLT registry.	4-year survival in patients receiving IL2RA and ATG was better than without induction No difference in BOS between IL2RA and no induction groups
Palmer *et al.* [41] Hartwig *et al.* [42]	Single center, prospective, randomized comparison of RATG versus no induction	The initial study showed reduced acute rejection and a trend toward reduced BOS with RATG. The follow-up study confirmed a reduction in early rejection but showed no difference in survival at 8 years.
Mullen *et al*. [43]	Single center, prospective, randomized comparison of RATG and daclizumab	No difference in acute rejection, BOS or survival Higher incidence of CMV in daclizumab group (also had higher CMV mismatches)
Brock [44]	Single center, prospective, randomized comparison of OKT3, RATG and daclizumab	No difference in acute rejection, BOS or 2-year survival. OKT3 had the highest and daclizumab had the lowest incidence of infection.
Shyu *et al.* [16]	Single center, retrospective analysis of alemtuzumab induction compared with historical controls receiving no induction, daclizumab or RATG.	Five-year survival, freedom from acute rejection, lymphocytic bronchitis, OB, and BOS were better in the alemtuzumab group PTLD incidence was no different across groups

[15,16]. Alemtuzumab causes prolonged depletion of inflammatory cells beyond its 12-day half-life. Recovery of monocytes, B cells, and T cells occurs at 3 months, 12 months, and 36 months, respectively [17]. Side effects include a cytokine "storm" similar to, but typically milder than that observed with T-cell depleting agents. Paroxysmal nocturnal hematuria may also be seen with alemtuzumab [18]. Similar to the agents above, alemtuzumab treatment is less effective at depletion of regulatory T cells. Memory T cells are also relatively spared [9,18].

IL-2 Receptor antagonists

Rather than depletion, daclizumab and basiliximab are chimeric monoclonal antibodies directed against the α(tac) subunit of the IL-2 receptor (CD25). Daclizumab, which is no longer available in the US, is a "humanized" monoclonal antibody, consisting of 90% human and 10% murine IgG [19]. Basiliximab is a glycoprotein obtained from fermentation of an established mouse myeloma cell line genetically engineered to express plasmids containing the human heavy and light chain constant region genes and mouse heavy and light chain variable region genes encoding an antibody that binds selectively to CD25 [20]. Through interaction with the IL-2 receptor, these antibodies inhibit T-cell proliferation and differentiation but do not lead to significant T-cell depletion. Because of a larger percentage of murine versus human components, basiliximab has a shorter half-life (13 days) and effective IL-2 receptor saturation (30 days) than daclizumab (20–40 days and 120 days, respectively) [21,22]. Basiliximab is dosed at 20 mg on the first and fourth days post-transplant. Daclizumab is dosed at 1 mg/kg within the first 24 h post-transplant and then every 2 weeks for four additional doses [19,20]. Because they are largely composed of human amino acid sequences, IL-2R antagonists generally have minimal side effects although basiliximab has rarely been

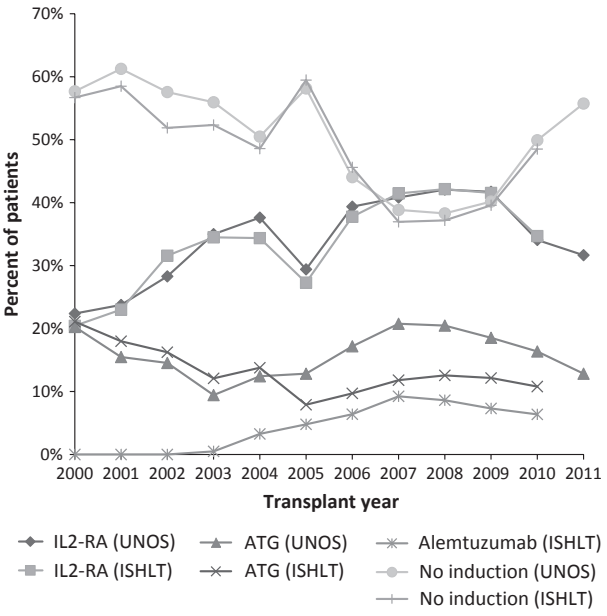

Figure 1 Use of induction agents in lung transplantation by Year. Data from [33,52].

reported to cause pulmonary edema and an ARDS-like syndrome [23]. Based on their effectiveness in reducing acute rejection in renal [24,25] and cardiac transplant [26,27], and favorable side effect profiles, these agents became the most common form of induction in lung transplant recipients shortly after their introduction in the late 1990s [28,29] (Fig. 1). Nonetheless, in contrast to T-cell depleting agents, IL-2R antagonists appear to reduce and/or prevent development of T-regs [9,30].

Efficacy

Evidence in renal and cardiac transplants that induction can reduce the incidence of acute rejection and prolong graft survival [24–27,31,32], provides a strong rationale for their use in lung transplantation. Moreover, there are potential secondary benefits including renal protection related to delaying initiation of calcineurin inhibitor (CNI) until the postoperative effects of hypovolemia and cardiopulmonary bypass can be overcome and a longer window to achieve adequate CNI levels. However, during more than half of the past 12 years, at least 50% of lung transplant recipients did not receive induction [29,33] (Fig. 1). In addition to concerns about the increased risk of infection associated with induction [34], demonstration of clear benefit of induction in lung transplant recipients has been difficult to obtain (Summarized in Table 2).

Reports from the registry of the International Society of Heart and Lung Transplantation (ISHLT) in the recent era have consistently shown a decreased incidence of BOS and survival benefit (when patients not surviving at least 14 days are excluded from the analysis) for those receiving induction agents [33,35–39] (Fig. 2). In the most recent report, induction with OKT3 showed an increased risk for 5-year mortality in a multivariable analysis of adult lung transplant recipients surviving at least 1 year. In the same analysis, IL2-R antagonist induction reduced the 5-year mortality risk [33]. These reports have also indicated a decreased incidence of acute rejection in patients treated with IL-2R antagonists as compared with no induction, or ALG/ATG [33,37–39]. Patients receiving alemtuzumab had lower incidence of acute rejection in the 2010 report, but not in more recent reports [37]. The ISHLT heart and lung transplant registry includes data from nearly 400 participating centers. Although roughly 15% of these submit data manually through a web-based entry system, the majority of the data is obtained through data sharing agreements with several "Data Collectives" including the United Network for Organ Sharing (UNOS), Eurotransplant, and UK Transplant. Hence, for the majority of the data, the ISHLT registry primarily depends on the data collectives for ensuring accuracy [40]. It is also important to emphasize that these reports include the disclaimer "however, these findings should be interpreted with caution because they may be confounded by contraindications to induction therapy and are not adjusted for age, diagnosis category, center, or other potentially confounding factors" in relation to the findings about induction.

Another study utilizing nearly 4000 patients from the ISHLT registry who received transplants between 2000 and 2004 attempted to address some of these potential confounding factors. Consistent with the registry reports, the authors found that survival at 4 years was better in the IL2-R antagonist (64%) and polyclonal ATG (60%) groups than the no induction group (57%). They were also able to demonstrate that the use of these agents remained a statistically significant predictor of survival in a multivariable Cox analysis model using multiple other recipient and donor factors including diagnosis, HLA matching, donor age, and center volume. Interestingly, the survival difference could not be explained by a difference in BOS, as the IL2-R

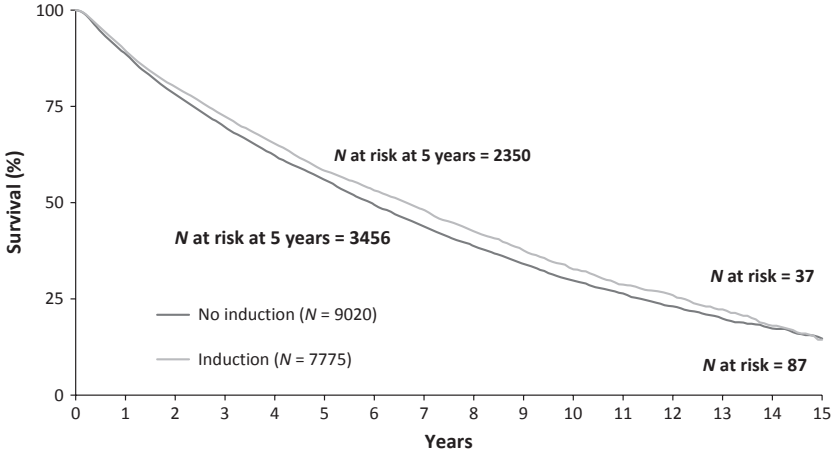

Figure 2 ISHLT Registry Data: Survival by Induction Usage Conditional on Survival to 14 Days (Transplants: April 1994 – June 2010).

antagonist group had similar freedom from BOS compared with the no induction group and better freedom from BOS than the polyclonal ATG group [34].

Although single center studies may also be able to address some of the potential confounders present in the registry studies, they are limited by power and, in most cases, their retrospective natures. Moreover, results from such studies have been contradictory.

In two studies from the Duke program, the first demonstrated a reduced incidence of acute rejection and a trend toward reduced BOS in patients receiving RATG induction [41]. However, a follow-up study from the same group did not confirm those findings. Although early rejections were reduced, overall acute rejection and, more importantly, survival at 8 years was no different [42].

IL-2R antagonists have been evaluated in two prospective controlled trials. In the first, comparing daclizumab and antithymocyte globulin induction, no difference in acute rejection was observed. The daclizumab group had a higher incidence of CMV infections. That group also had a higher percentage of CMV mismatches [43]. In the second study, daclizumab was compared with OKT3 and antithymocyte globulin. There was no difference in acute rejection frequency, freedom from BOS or 2-year survival. However, daclizumab had the lowest incidence of infection [44].

Other small retrospective studies involving comparisons of specific induction agents have been published with conflicting results. In one study, daclizumab was superior to ATG in terms of acute rejection, BOS, and mortality [45]. Another demonstrated a lower rejection rate with daclizumab [46]. However, two others demonstrated increased acute rejection and BOS with daclizumab or basiliximab rather than antithymocyte globulin induction [47,48].

In a single center, retrospective study, Moffatt and colleagues concluded that patients receiving RATG induction had significantly improved survival and freedom from acute rejection, BOS, and infection when compared with OKT3 [49].

Two small studies suggest that the timing of induction may be important. In a single center, retrospective study, patients who received the first dose of basiliximab prior to implantation had a lower cumulative rejection score compared with those who received the first dose of basiliximab prior to implantation or no induction [50]. Similarly, in a small retrospective study of pediatric lung transplant recipients, RATG administered prior to reperfusion of the first lung had a low (5.2%) incidence of grade A2 or greater acute rejection in the first 6 months post-transplant compared with 25–50% in other published studies [51].

Data regarding alemtuzumab in lung transplantation have come primarily from the group at the University of Pittsburgh. One report compared early outcomes of patients receiving alemtuzumab induction followed by reduced maintenance immunosuppression (tacrolimus with target level 10 ng/ml, mycophenolate mofetil (MMF) 250 mg bid, and prednisone 7.5 mg daily) to historical controls who received standard immunosuppression but no induction. No difference was observed in patient and graft survival, acute rejection (AR), and infection rate [15]. More recently, investigators from Pittsburgh published 5-year retrospective data. Patients receiving alemtuzumab had 5-year patient survival comparable to those receiving thymoglobulin and better than those receiving daclizumab or no induction. Five-year graft survival was nearly 60% in the alemtuzumab group compared with less than 50% in the thymoglobulin, daclizumab, or no induction groups. Five-year freedom from acute rejection, lymphocytic bronchitis, OB, and BOS were best in the alemtuzumab group. Freedom from BOS was 54% in the alemtuzumab group compared with thymoglobulin (27%), daclizumab (43%), and no induction (46%). The incidence of PTLD in this population was no different among groups. Although infection as a cause of death was no different across the induction groups, incidence of infection was not reported [16].

It would be reasonable to conclude, based on consistent evidence of reduced BOS and slightly better survival, coupled with reduced acute rejection that IL-2R antagonists would be the best compromise. Indeed, the ISHLT and UNOS registry reports show increased use of IL-2R antagonists up until 2010 [33,52]. It is not surprising that, given the limitations of registry studies, and the lack of convincing data from more carefully controlled studies, and more recently raised concerns that IL-2R antagonists my impair the development of T-regs, [9,30] that use of induction agents overall has waned in the recent past [33,52].

Future

Although all of the induction agents used in lung transplantation appear to have some benefit in terms of early acute rejection and potential for a modest long-term benefit in terms of freedom from BOS and patient survival, it seems clear that none of the currently utilized induction approaches are going to lead to long-term outcomes comparable to those obtained with other solid organ transplants.

To achieve that goal, initial immunosuppression strategies for lung transplantation will likely need to be adapted based on an evolving understanding of mechanisms of tolerance development including the role of humoral immunity, the importance of regulatory T and B Cells and the potential benefit of costimulatory blockade.

Successful strategies will probably involve one of the strategies currently being investigated in renal transplantation, either by inducing mixed chimerism [53] or involving

the use of costimulation blockade agents such as belatacept [54].

Yet, to date, there are no data regarding the use of these strategies in human lung transplant. Animal studies are mixed regarding the potential befit for lung transplant recipients. In a study using cynomolgus monkeys, in spite of the successful induction of mixed chimerism in recipients of fully MHC-mismatched lung allografts, the lung recipients rejected their allografts significantly earlier than kidney recipients [55]. In a study in murine orthotopic lung transplant, blockade of the CD28/B7 costimulatory pathways reduced acute cellular rejection in the absence of CD4 + T cells, but did not affect acute rejection when CD4 + T cells were present [56]. However, another murine orthotopic lung transplant study demonstrated that CD154/CD40 costimulation blockade was sufficient to significantly reduce allospecific effector T-cell responses including acute cellular rejection and facilitate development of CD4 + T regulatory cells [57]. Thus, these strategies do not appear to be ready to use in clinical transplantation.

In summary, the literature does not provide clear guidance regarding the use of induction in lung transplant. Until more clearly effective regimens are available, decisions regarding induction will probably be patient- and center-dependent, balancing the risk of infection against the need to limit the incidence of acute rejection in the early post-transplant period. More effective tolerogenic induction strategies remain to be elucidated.

Disclaimer

The data and analyses reported in the Annual Data Reports of the Organ Procurement and Transplantation Network and the US Scientific Registry of Transplant Recipients have been supplied by the Arbor Research Foundation or the Minneapolis Medical Research Foundation and UNOS under contract with HHS/HRSA. The authors alone are responsible for reporting and interpreting these data; the views expressed herein are those of the authors and not necessarily those of the US Government.

Funding

No funding.

References

1. Game DS, Lechler RI. Pathways of allorecognition: implications for transplantation tolerance. *Transpl Immunol* 2002; **10**: 101.
2. Avlonitis VS, Fisher AJ, Kirby JA, Dark JH. Pulmonary transplantation: the role of brain death in donor lung injury. *Transplantation* 2003; **75**: 1928.
3. Rostron AJ, Cork DM, Avlonitis VS, Fisher AJ, Dark JH, Kirby JA. Contribution of Toll-like receptor activation to lung damage after donor brain death. *Transplantation* 2010; **90**: 732.
4. Andrade CF, Waddell TK, Keshavjee S, Liu M. Innate immunity and organ transplantation: the potential role of toll-like receptors. *Am J Transplant* 2005; **5**: 969.
5. Deeks ED, Keating GM. Rabbit antithymocyte globulin (thymoglobulin): a review of its use in the prevention and treatment of acute renal allograft rejection. *Drugs* 2009; **69**: 1483.
6. Taniguchi Y, Frickhofen N, Raghavachar A, Digel W, Heimpel H. Antilymphocyte immunoglobulins stimulate peripheral blood lymphocytes to proliferate and release lymphokines. *Eur J Haematol* 1990; **44**: 244.
7. Merion RM, Howell T, Bromberg JS. Partial T-cell activation and anergy induction by polyclonal antithymocyte globulin. *Transplantation* 1998; **65**: 1481.
8. Demirkiran A, Hendrikx TK, Baan CC, van der Laan LJ. Impact of immunosuppressive drugs on CD4 + CD25 + FOXP3 + regulatory T cells: does in vitro evidence translate to the clinical setting? *Transplantation* 2008; **85**: 783.
9. Yeung MY, Sayegh MH. Regulatory T cells in transplantation: what we know and what we do not know. *Transplant Proc* 2009; **41**: S21.
10. Todd PA, Brogden RN. Muromonab CD3. A review of its pharmacology and therapeutic potential. *Drugs* 1989; **37**: 871.
11. Caillat-Zucman S, Blumenfeld N, Legendre C, *et al.* The OKT3 immunosuppressive effect. In situ antigenic modulation of human graft-infiltrating T cells. *Transplantation* 1990; **49**: 156.
12. Hong JC, Kahan BD. Immunosuppressive agents in organ transplantation: past, present, and future. *Semin Nephrol* 2000; **20**: 108.
13. Halloran PF. Immunosuppressive drugs for kidney transplantation. *New Engl J Med* 2004; **351**: 2715.
14. Ciancio G, Burke GW 3rd. Alemtuzumab (Campath-1H) in kidney transplantation. *Am J Transplant* 2008; **8**: 15.
15. van Loenhout KC, Groves SC, Galazka M, *et al.* Early outcomes using alemtuzumab induction in lung transplantation. *Interact Cardiovasc Thorac Surg* 2010; **10**: 190.
16. Shyu S, Dew MA, Pilewski JM, *et al.* Five-year outcomes with alemtuzumab induction after lung transplantation. *J Heart Lung Transplant* 2011; **30**: 743.
17. Magliocca JF, Knechtle SJ. The evolving role of alemtuzumab (Campath-1H) for immunosuppressive therapy in organ transplantation. *Transpl Int* 2006; **19**: 705.
18. Weaver TA, Kirk AD. Alemtuzumab. *Transplantation* 2007; **84**: 1545.
19. Zenapax Prescribing Information [12/27/12]. Available at: http://www.gene.com/download/pdf/zenxapax_prescribing.pdf.

20. Simulect Prescribing Information [12/27/12]. Available at: http://www.gene.com/download/pdf/zenxapax_prescribing.pdf.
21. Onrust SV, Wiseman LR. Basiliximab. *Drugs* 1999;**57**:207.
22. Wiseman LR, Faulds D. Daclizumab: a review of its use in the prevention of acute rejection in renal transplant recipients. *Drugs* 1999; **58**: 1029.
23. Lake KD. Immunosuppressive drugs and novel strategies to prevent acute and chronic allograft rejection. *Seminars in respiratory and critical care medicine* 2001; **22**: 559.
24. Vincenti F, Kirkman R, Light S, *et al.* Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group [see comments]. *New Engl J Med* 1998; **338**: 161.
25. Kahan BD, Rajagopalan PR, Hall M. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. *Transplantation* 1999; **67**: 276.
26. Beniaminovitz A, Itescu S, Lietz K, *et al.* Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody [see comments]. *N Engl J Med* 2000; **342**: 613.
27. Mehra MR, Zucker MJ, Wagoner L, *et al.* A multicenter, prospective, randomized, double-blind trial of basiliximab in heart transplantation. *J Heart Lung Transplant* 2005; **24**: 1297.
28. Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1995-2004. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD, 2005. Available at: http://optn.transplant.hrsa.gov/data/citing.asp.
29. Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1999-2008. U.S. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD; 2009. Available at: http://optn.transplant.hrsa.gov/data/citing.asp.
30. Rech AJ, Vonderheide RH. Clinical use of anti-CD25 antibody daclizumab to enhance immune responses to tumor antigen vaccination by targeting regulatory T cells. *Ann N Y Acad Sci* 2009; **1174**: 99.
31. Opelz G. Efficacy of rejection prophylaxis with OKT3 in renal transplantation. Collaborative Transplant Study. *Transplantation* 1995; **60**: 1220.
32. Szczech LA, Berlin JA, Aradhye S, Grossman RA, Feldman HI. Effect of anti-lymphocyte induction therapy on renal allograft survival: a meta-analysis. *J Am Soc Nephrol* 1997; **8**: 1771.
33. Christie JD, Edwards LB, Kucheryavaya AY, *et al.* The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. *J Heart Lung Transplant* 2012; **31**: 1073.
34. Hachem RR, Edwards LB, Yusen RD, Chakinala MM, Alexander PG, Trulock EP. The impact of induction on survival after lung transplantation: an analysis of the International Society for Heart and Lung Transplantation Registry. *Clin Transplant* 2008; **22**: 603.
35. Trulock EP, Christie JD, Edwards LB, *et al.* Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult lung and heart-lung transplantation report-2007. [Review] [0 refs]. *J Heart Lung Transplant* 2007; **26**: 782.
36. Christie JD, Edwards LB, Aurora P, *et al.* Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult lung and heart/lung transplantation report–2008. *J Heart Lung Transplant* 2008; **27**: 957.
37. Christie JD, Edwards LB, Kucheryavaya AY, *et al.* The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report–2010. *J Heart Lung Transplant* 2010; **29**: 1104.
38. Christie JD, Edwards LB, Kucheryavaya AY, *et al.* The Registry of the International Society for Heart and Lung Transplantation: twenty-eighth Adult Lung and Heart-Lung Transplant Report–2011. *J Heart Lung Transplant* 2011; **30**: 1104.
39. Christie JD, Edwards LB, Aurora P, *et al.* The Registry of the International Society for Heart and Lung Transplantation: twenty-sixth Official Adult Lung and Heart-Lung Transplantation Report-2009. *J Heart Lung Transplant* 2009; **28**: 1031.
40. ISHLT International Registry for Heart and Lung Transplantation [cited 2013 4/1]. Available at: http://www.ishlt.org/registries/heartLungRegistry.asp.
41. Palmer SM, Miralles AP, Lawrence CM, Gaynor JW, Davis RD, Tapson VF. Rabbit antithymocyte globulin decreases acute rejection after lung transplantation: results of a randomized, prospective study. *Chest* 1999; **116**: 127.
42. Hartwig MG, Snyder LD, Appel JZ, 3rd, *et al.* Rabbit antithymocyte globulin induction therapy does not prolong survival after lung transplantation. *J Heart Lung Transplant* 2008; **27**: 547.
43. Mullen JC, Oreopoulos A, Lien DC, *et al.* A randomized, controlled trial of daclizumab vs anti-thymocyte globulin induction for lung transplantation. *J Heart Lung Transplant* 2007; **26**: 504.
44. Brock MV, Borja MC, Ferber L, *et al.* Induction therapy in lung transplantation: a prospective, controlled clinical trial comparing OKT3, anti-thymocyte globulin, and daclizumab. *J Heart Lung Transplant* 2001; **20**: 1282.
45. Ailawadi G, Smith PW, Oka T, *et al.* Effects of induction immunosuppression regimen on acute rejection, bronchiolitis obliterans, and survival after lung transplantation. *J Thorac Cardiovasc Surg* 2008; **135**: 594.
46. Garrity ER Jr, Villanueva J, Bhorade SM, Husain AN, Vigneswaran WT. Low rate of acute lung allograft rejection after

the use of daclizumab, an interleukin 2 receptor antibody. *Transplantation* 2001; **71**: 773.
47. Hachem RR, Chakinala MM, Yusen RD, *et al.* A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. *J Heart Lung Transplant* 2005; **24**: 1320.
48. Burton CM, Andersen CB, Jensen AS, *et al.* The incidence of acute cellular rejection after lung transplantation: a comparative study of anti-thymocyte globulin and daclizumab. *J Heart Lung Transplant* 2006; **25**: 638.
49. Moffatt SD, Demers P, Robbins RC, *et al.* Lung transplantation: a decade of experience. *J Heart Lung Transplant* 2005; **24**: 145.
50. Swarup R, Allenspach LL, Nemeh HW, Stagner LD, Betensley AD. Timing of basiliximab induction and development of acute rejection in lung transplant patients. *J Heart Lung Transplant* 2011; **30**: 1228.
51. Goldfarb SB, Gaynor JW, Fuller S, *et al.* Induction therapy with antithymocyte globulin before reperfusion. *Ann Thorac Surg* 2010; **90**: 1110.
52. Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). OPTN/SRTR 2011 Annual Data Report.: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2012 [12/26/12]. Available at: http://srtr.transplant.hrsa.gov/annual_reports/2011/pdf/2011_SRTR_ADR.pdf.
53. Fehr T, Sykes M. Clinical experience with mixed chimerism to induce transplantation tolerance. *Transpl Int* 2008; **21**: 1118.
54. Vincenti F, Larsen CP, Alberu J, *et al.* Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. *Am J Transplant* 2012; **12**: 210.
55. Aoyama A, Ng CY, Millington TM, *et al.* Comparison of lung and kidney allografts in induction of tolerance by a mixed-chimerism approach in cynomolgus monkeys. *Transplant Proc* 2009; **41**: 429.
56. Gelman AE, Okazaki M, Lai J, *et al.* CD4 + T lymphocytes are not necessary for the acute rejection of vascularized mouse lung transplants. *J Immunol* 2008; **180**: 4754.
57. Dodd-o JM, Lendermon EA, Miller HL, *et al.* CD154 blockade abrogates allospecific responses and enhances CD4(+) regulatory T-cells in mouse orthotopic lung transplant. *Am J Transplant* 2011; **11**: 1815.

