

# Induction Therapy in Lung Transplantation

José María Borro<sup>1</sup> and Amparo Solé<sup>2</sup>

<sup>1</sup>Department of Thoracic Surgery and Lung Transplantation, Hospital Universitario de La Coruña, La Coruña, Spain; <sup>2</sup>Pulmonary Transplant Unit, Hospital Universitario la Fe, Valencia, Spain

## Abstract

**Lung transplantation has become a real alternative for some patients with end-stage lung disease to improve their quality of life and long-term survival.**

**The emergence of powerful immunosuppressants that operate in different ways of alloimmune response has been one of the factors responsible for the progressive improvement of survival. However, the favorable results of other organs have not been corroborated in lung transplantation, where acute and chronic rejection rates are high and are one of the most important factors responsible for the morbidity and mortality.**

**The two major complications associated with lung transplantation are rejection and infection. Both complications can cause death, highlighting the importance of an adequate immunosuppressive therapy to improve medium and long-term survival. Therefore, the key for successful lung transplantation is to achieve the suitable level of immunosuppression that allows preventing rejection without increasing infections or other side effects. From the existing data on induction therapy in lung transplantation it seems to be a good option to prevent or reduce acute and chronic rejection and to decrease the nephrotoxicity related to the use of calcineurin inhibitors. Nowadays, induction therapy seems to be a good option to prevent or reduce acute and chronic rejection and to decrease the nephrotoxicity related to the use of calcineurin inhibitors.** (Trends in Transplant. 2011;5:196-204)

Corresponding author: José María Borro, Jose.MA.Borro.Mate@sergas.es

## Key words

**Lung transplantation. Induction therapy. Immunosuppression. Allograft rejection.**

## Introduction

Currently, lung transplantation is an accepted modality of treatment for patients with

end-stage lung disease. Since the 1990s, more than 25,000 procedures have been performed worldwide<sup>1</sup>. For patients with severe functional disability and short life expectancy, lung transplantation offers the possibility to improve quality of life and survival. The treatment is remarkably successful, and more than 80% of patients survive the first year and more than 50% of patients survive after five years. The number of patients on the waiting list for a lung transplant in the USA has increased due to its indication as a therapy for end-stage lung disease and progressive improvement of

### Correspondence to:

José María Borro  
Departamento de Cirugía Torácica y Trasplante Pulmonar  
Hospital Universitario de La Coruña  
Xubias, 84  
15006 La Coruña, España  
E-mail: Jose.MA.Borro.Mate@sergas.es

the outcomes in relation to the progress made in donor management, surgical techniques, immunosuppression, and patient postoperative care<sup>2</sup>.

However there are still many areas of improvement. In fact comorbidities related to immunosuppression are very high.

According to the 2011 International Society of Heart and Lung Transplantation (ISHLT) Registry, the most frequent comorbidities in lung transplant patients are hypertension (52.3 and 83.7%), renal dysfunction (23.9 and 33.3%), hyperlipidemia (24.7 and 57.5%), diabetes (26.2 and 39.6%) and bronchiolitis obliterans syndrome (9.5 and 37.9%) at one year and five years posttransplantation, respectively<sup>5</sup>.

The two main causes of death reported in the ISHLT registry between January, 1992 and June, 2010 during the first month and up to the first year are graft failure and non-cytomegalovirus (CMV) infections. After the first year, the most common causes of death are bronchiolitis obliterans syndrome (BOS), graft rejection, and non-CMV infections<sup>5</sup>.

## **GAP areas in lung transplantation**

### **Rejection**

The first barrier to long-term graft and patient survival is transplant rejection. The high incidence of acute rejection after lung transplantation may be explained by different reasons. First, no donor-recipient human leukocyte antigen (HLA) matching is performed. Second, the lung graft is constantly in contact with the external environment and exposed to various inhaled agents, such as fumes, toxins, and infectious agents, which may potentially cause local inflammation and favor non-immunological rejection. Finally, the lung graft contains a huge amount of donor antigen-presenting cells constantly processing and presenting HLA

alloantigens to recipient lymphocytes that initiate a process of immune recognition<sup>6</sup> and frequent infections in these recipients.

We can find different types or categories of rejection depending on the time when it occurs: hyperacute rejection, acute rejection, and chronic lung allograft dysfunction<sup>7,8</sup>.

### **Hyperacute rejection**

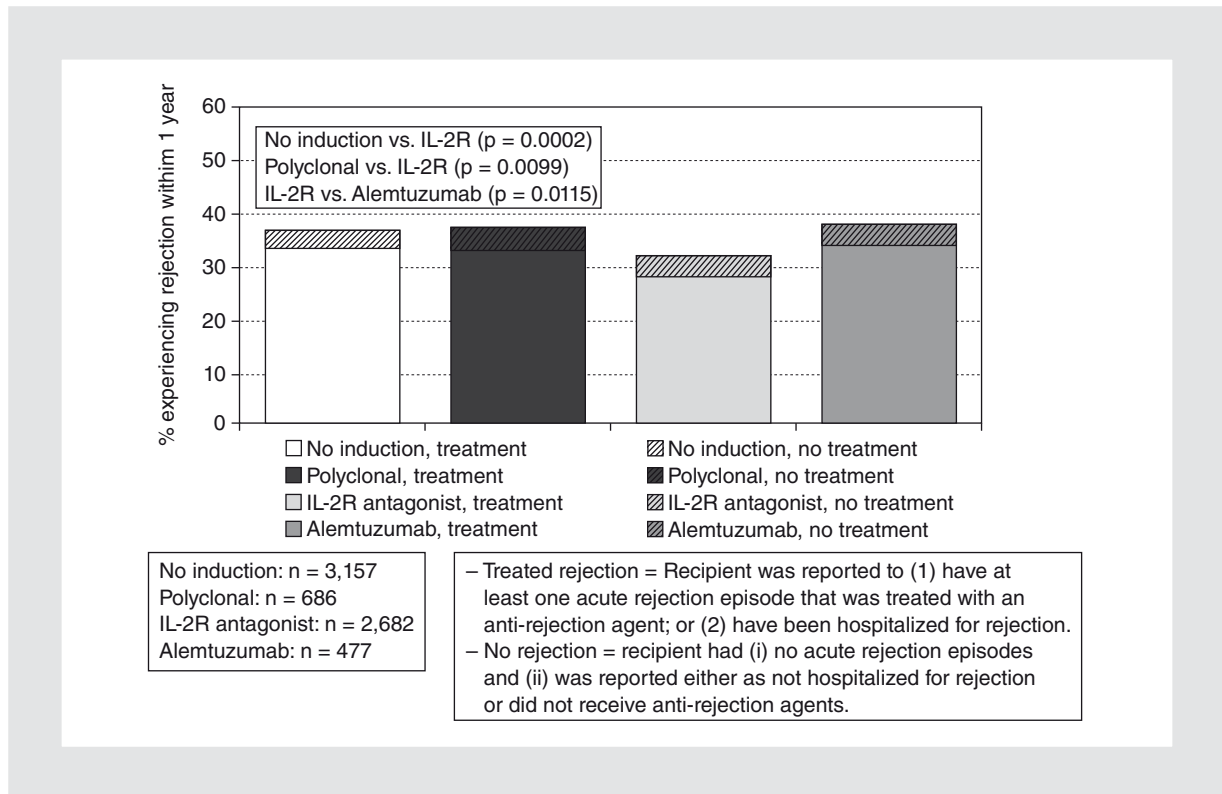
Immediate response after transplantation: it is an antibody reaction in response to blood group antigens, HLA, and other antigens that cause cell injury<sup>9</sup>.

### **Acute rejection**

Cellular rejection is an immunological response of T-cell-mediated inflammation to HLA of the donor; it is very common in first 100 days posttransplantation. Rejection rates reduce over time, but acute rejection can appear at any point in the evolution of the patient. Humoral rejection can also occur, but, to date, its diagnostic criteria are not well-defined. Nowadays it is known that the intensity of acute rejection and its recurrence are risk factors for chronic rejection. Hence, an immunosuppressant regimen that reduces the incidence of acute rejection presumably would reduce the chronic rejection and improve survival (Fig. 1).

### **Chronic rejection or chronic lung allograft dysfunction**

This is the most important cause of morbidity and mortality in lung transplantation. Recently, two very distinct forms of this post-transplant complication have been defined. One is BOS, and correlates with the histologic diagnosis of obliterative bronchiolitis and shows irreversible obstructive changes in pulmonary function. The other form of chronic lung allograft



**Figure 1.** Reported rejection between discharge and the 1-year follow-up for adult lung transplant follow-up assessments from July 2004 through June 2010, stratified by type of induction therapy. Rejection is classified as treated (solid) or untreated (hatched). Analysis is limited to patients who were alive at the time of the discharge. IL-2R: interleukin-2 receptor. (adapted from Christie, et al.<sup>5</sup>).

dysfunction is the restrictive allograft syndrome, representing 30% of it<sup>7,8</sup>. It is characterized by a restrictive fibrotic pulmonary process with worse impact on survival. Both disorders are possibly the result of different etiological factors, including the response of the host, but currently it cannot be predicted which form of chronic lung allograft dysfunction will appear or when it will appear. The only treatment aimed at stopping chronic lung allograft dysfunction that has shown effectiveness in the short to medium term is azithromycin in patients with BOS associated with neutrophilic inflammation.

## Infections

Opportunistic infections are a common cause of morbidity and mortality in lung transplant recipients. The rate of infection in lung transplant recipients is higher than in recipients

of other organs as a consequence of the exposure of the allograft to the external environment<sup>6,10,11</sup>.

Common opportunistic infections<sup>12,13</sup> seen in lung transplant recipients include: bacterial, mainly gram-negative infections, CMV, and fungal infections<sup>14</sup>.

## Tumors or lymphomas

Malignancies are common after lung transplantation: 13% of surviving recipients reported at least one malignancy at five years after transplantation and 27% at 10 years after transplantation<sup>5</sup>. The most common tumors in lung transplant patients are skin cancer and lymphomas<sup>13</sup>. The majority of lymphomas are diagnosed after the first posttransplant year. Lung transplant patients (mainly cystic fibrosis

receptors) show the highest cancer relative risk among different types of organ transplants<sup>15</sup>.

### **Acute renal failure and chronic kidney disease**

There is a high incidence of acute renal failure in lung transplants in the immediate postoperative period, and a positive correlation between the degree of kidney failure at one month and that observed at six and 12 months after the transplant<sup>16</sup>. Chronic kidney disease (CKD) is a common complication after lung transplantation. According to the ISHLT Registry, 23.9% of transplant recipients surviving at one year develop renal dysfunction and up to 33.3% at five years. In a Spanish retrospective study, Paradela de la Morena, et al. reported a CKD incidence at one year of 50.7%, 63.9% at two years and 68.6% at five years<sup>17</sup>. In addition, recipients who developed CKD at one year after transplantation showed a stronger association with mortality than did patients who did not develop it ( $p = 0.001$ ).

In another Spanish observational, multicenter, longitudinal study of 113 consecutive patients with lung transplantation with at least two years of evolution, the CKD prevalence was 58.4%, but this was underestimated in 21.2% of cases<sup>18</sup>.

Taking all these data into consideration, strategies aiming to reduce early renal injury, such as calcineurin inhibitor (CNI) sparing or delayed introduction by means of induction therapy, should be considered.

Taking in account all these frequent comorbidities the goal for induction therapy in lung transplant is triple first to try reduce incidence of rejection. Second, to give comfortable time-frame to achieve target levels of calcineurin inhibitors without exposing the patient to the risk of early acute rejection. Third, induction therapy allows renal function

to recover from operative stresses, such as hypovolaemia or negative effects of cardiopulmonary bypass without being exposed to the toxic effects of calcineurin inhibitors. However, the fear of increased post-transplant infections, especially cytomegalovirus (CMV) infection, and posttransplant malignancies, both events very frequent in lung transplantation precludes its use in half of world centers.

### **Immunosuppression and induction therapy in lung transplantation**

As mentioned before, lung transplantation is a real alternative for patients with end-stage lung diseases to improve their quality of life and prolong survival. But, currently, the challenge is to achieve medium and long-term survival with good quality of life.

In order to prevent allograft rejection and subsequent damage to the new lung or lungs, recipients must take a regimen of immunosuppressive drugs (Table 1). A common immunosuppression regimen used consists in CNI, antiproliferative agents, and corticosteroids with or without induction therapy. It is not known as to which is the best immunosuppressive regimen to improve medium and long term outcomes. Induction therapy is administered differently depending on the working groups, and its use is intended to minimize complications such as acute rejection or renal impairment, contributing to ameliorate long-term results.

The ISHLT Registry has reported tacrolimus as the most commonly used compared with cyclosporin A (CsA) both at one and five years after lung transplantation. In the same way, mycophenolate mofetil (MMF) is prescribed more commonly than azathioprine at one and five years after lung transplantation<sup>5,19</sup>.

Currently, the most common combination immunosuppressive therapy is tacrolimus and

**Table 1. Immunosuppressive drugs, their mechanisms of action and side effects**

Agent	Mechanism of action	Side effects
ATG	Fixes numerous antigens on lymphoid cells; depletion of circulating lymphocytes	Cytokine release syndrome Leukopenia, thrombopenia
OKT3	Fixes CD3 present on T-lymphocytes; depletion of circulating lymphocytes	Cytokine release syndrome Pro-coagulation effect Possible sensitization with loss of efficacy
Basiliximab	Binds the $\alpha$ -chain of IL-2 receptor; blocks the proliferation induced by IL-2	Unreported
Cyclosporin A	Binds cyclophilin; inhibits calcineurin; inhibits cytokine gene transcription	Nephrotoxicity Hypertension Hypercholesterolemia Hypertrichosis Gingival hypertrophy
Tacrolimus	Binds FKBP-12; inhibits calcineurin; inhibits cytokine gene transcription	Nephrotoxicity Hypertension Neurotoxicity Diabetes mellitus Alopecia
Azathioprine	Inhibits purine biosynthesis and lymphocyte proliferation	Leukopenia
Mycophenolate mofetil	Inhibits purine biosynthesis and lymphocyte proliferation	Diarrhea Leukopenia
Sirolimus/everolimus	Binds FKBP-12; inhibits the proliferative response to cytokines and growth factors	Hyperlipemia Thrombocytopenia Arthralgia

ATG: antithymocyte globulin; OKT3: monoclonal anti-CD3 antibody; IL: interleukin; FKBP: FK (tacrolimus)-binding protein.  
Adapted from Knoop, et al.<sup>6</sup> and Martinu, et al.<sup>11</sup>

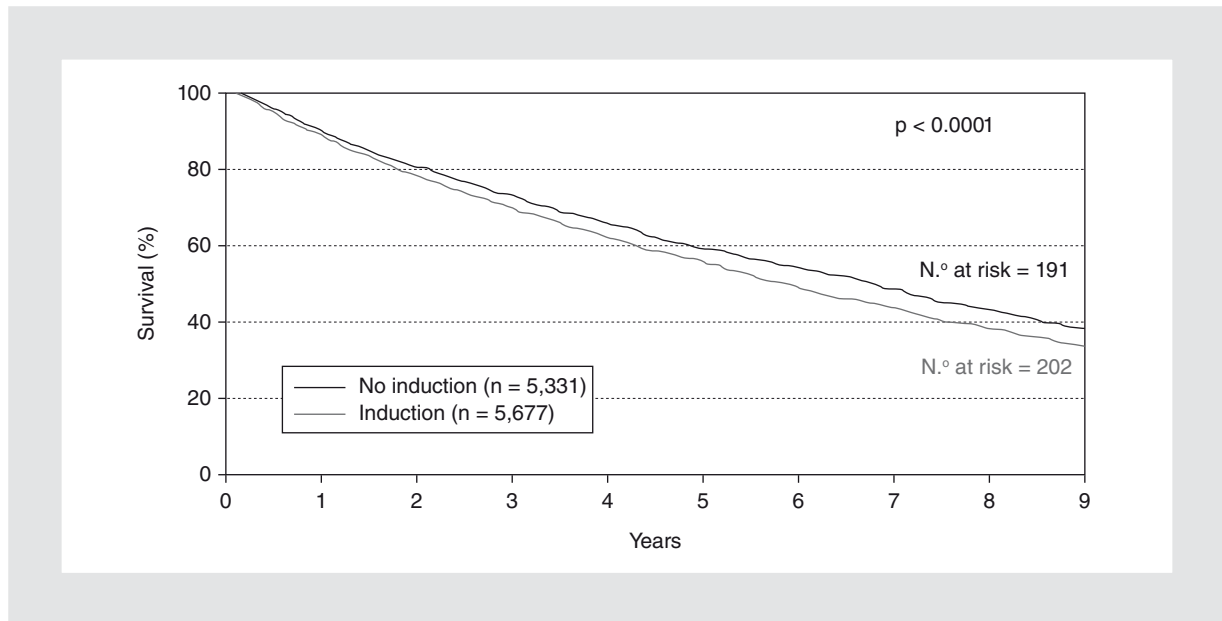
MMF (35%), followed by tacrolimus and azathioprine (20%), CsA and MMF (15%), and CsA and azathioprine (5%). Use of mammalian target of rapamycin (mTOR) inhibitors (everolimus and sirolimus) remains relatively low, less than 20% of lung transplant recipients receiving the drug at one and/or five years after transplantation<sup>5,19</sup>.

Induction therapy tries to modulate the response of T lymphocytes during antigen presentation in order to improve the effectiveness of immunosuppression. Its objective is to reduce the incidence of acute rejection during the first weeks after transplantation when the risk for rejection is higher and hence possibly to also reduce chronic rejection, without producing an increase in infections or cancer. Induction therapy also allows us to delay or decrease the CNI dose with consequent benefit for kidney function<sup>20</sup>. The ISHLT Registry

shows significant differences in survival for patients receiving induction treatment (Fig. 2).

According to the ISHLT registry report, between 2000 and 2009 it was shown that the use of any type of induction therapy increased by approximately 10% between 2006 and 2007, but has leveled off at about 60% of reported procedures in adult recipients during the past three years (Fig. 3). There appears to be no consensus regarding the use or choice of induction therapy according to the Registry data, despite an increase in the use of interleukin-2 receptor (IL-2R) antagonists and alemtuzumab during the past decade<sup>5</sup>.

Induction treatment is administered in the perioperative period and during the immediate posttransplant period. Induction drug infusion begins before allograft reperfusion.

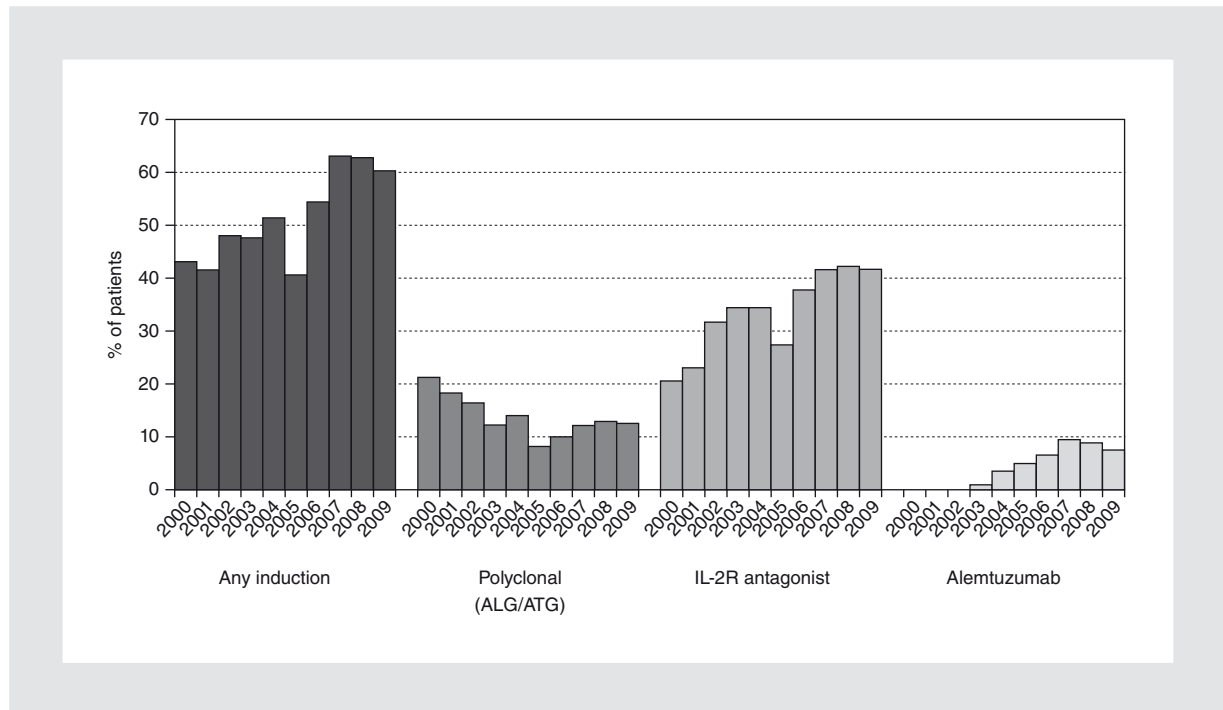


**Figure 2.** Kaplan-Meier survival after adult lung transplantation for transplants performed from January 2000 through June 2009, stratified by induction usage. Data presented are conditional on survival to 14 days. Source: ISHLT 2011 (adapted from Christie, et al.<sup>5</sup>).

There is little scientific evidence on induction therapy in lung transplantation and, moreover, results lack consistency. In general, studies reported in the literature are from single center experiences and compare retrospective cohorts, not always treated with the same immunosuppressant schemes. A review of the most relevant studies comparing the efficacy and safety of the different types of agents used for induction therapy in lung transplantation follows.

Initially, monoclonal anti-CD3 antibody (OKT3) was employed, and after hands-on experience with different induction agents, in 2001 a comparative study between OKT3, antithymocyte globulin (ATG) and daclizumab was conducted. The results showed a greater rate of bacterial infections in the OKT3 patients compared to the other two induction regimens. None of the induction agents delayed the development of chronic rejection or favored patient survival<sup>21</sup>. In contrast, a retrospective comparison (157 patients) of induction with basiliximab or ATG showed that induction with ATG was followed by a lower number and severity of acute rejection episodes. There was

no impact in BOS development or in infectious complications<sup>22</sup>. However, in the same year, Borro, et al. showed that induction with basiliximab has a trend to reduce the rate of acute and chronic rejection in lung transplant recipients, with no increased incidence of infections or malignancies. Also the two-year survival for patients treated with basiliximab was better than the control group<sup>23</sup>. In the same way, short-term beneficial effects with basiliximab had been communicated previously<sup>24,25</sup>. When the use of basiliximab versus ATG was compared<sup>26</sup>, survival in the basiliximab group was higher ( $p = 0.03$ ), but with a trend to CMV infection reactivation. Other studies comparing the efficacy of ATG vs. daclizumab (not available anymore) showed a wide range of results, from better results in favor of ATG<sup>27</sup>, to lack of differences between them<sup>28</sup>, or worse results with ATG<sup>29-31</sup>. None of these studies showed superiority of one drug over the other, either in chronic rejection rate or in survival. In a randomized, double-blind, placebo-controlled, multicenter study, 121 lung transplant recipients received either placebo or basiliximab; the results were not conclusive regarding BOS and patient survival<sup>32</sup>. Finally, regarding alemtuzumab in lung transplantation,



**Figure 3.** Use of induction immunosuppression by year of transplant in adult lung recipients. Analysis is limited to patients receiving prednisone and who were alive at the time of discharge. ALG: antilymphocyte globulin; ATG: antithymocyte globulin; IL-2R: interleukin-2 receptor. (adapted from Christie, et al.<sup>5</sup>).

McCurry, et al.<sup>33</sup> found less severe acute rejection episodes and decreased rates of CMV infection compared with induction with thymoglobulin. However, van Loenhout, et al.<sup>34</sup> found no difference in survival or acute rejection among patients treated with alemtuzumab induction and the no-induction control group. Recently, a retrospective analysis has been published<sup>35</sup> using prospectively collected data from a single-site clinical database of 336 lung recipients classified by induction type: alemtuzumab, thymoglobulin, daclizumab, and none. Survival analyses examined patient and graft survival, and freedom from acute cellular rejection, lymphocytic bronchiolitis, obliterative bronchiolitis, BOS, and posttransplant lymphoproliferative disorder (PTLD). Alemtuzumab recipients showed greater five-year freedom from each outcome than the other groups and the groups did not differ in PTLT rates.

In general, based on clinical experience and the scientific data available, we can conclude the following.

Basiliximab, the most used induction agent according to the ISHLT registry, has a good safety profile and is well tolerated. When used, the acute rejection rate is lower, but the efficacy of basiliximab in preventing chronic rejection has not yet been demonstrated. Its use also allows reducing the CNIs dose during the perioperative period.

Polyclonal antibodies have a greater immunosuppressive strength that leads to a lower rate of acute rejection episodes, but several publications suggest also an increased rate of adverse events.

Alemtuzumab, a more recently developed induction agent with a more limited use (single-center experience publications), seems promising in acute rejection prophylaxis, but not in the safety profile.

Nevertheless, one should be careful when interpreting the studies comparing induction agents as the great majority are

retrospective, with a limited number of patients and short follow-up. In conclusion, attempts to empirically establish the optimal immunosuppression regimen to minimize morbidity and maximize survival in lung transplantation remain limited. Induction therapies with reduced maintenance immunosuppression may provide additional strategies to improve patient care. Randomized controlled trials to rigorously establish the benefits and long-term safety profile of any induction agent are warranted.

## Recommendations

There are no current recommendations regarding induction therapy for lung transplantation and this remains a controversial area of postoperative treatment.

Considering the literature review, the experience in other solid organ transplantation, the results of the ISHLT Lung Transplant Report, and the clinical experience from some of the Spanish lung transplant teams, the use of induction is recommended in at least the following cases:

- CNI-sparing therapy in patients with or at high risk of acute renal dysfunction in the early posttransplant period;
- Patients with high immunological risk, PRA > 25%;
- Presence of multi-resistant organisms, in order to enable lower anti-calcineurin drug levels;
- Chronic renal dysfunction (creatinine clearance < 60 ml/min/1.73 m<sup>2</sup>);
- Age of recipients < 18 and > 60 years.

Our induction immunosuppressive regimen is described below.

## Perioperative protocol initial immunosuppression

1. Basiliximab (Simulect®): 20 mg within the first six hours after transplantation and 20 mg at day 4.
2. Start with cyclosporine 24-hour infusion at 1 mg/kg/day at 2-3 day in intensive care unit and perform a CsA steady state level at 12-24 hours.
  - In patients with high immunological risk: adjust upwards to 2 mg/kg/day, targeting cyclosporine levels around 300 µg/l within 36 hours.
  - For a CNI-sparing therapy in patients with or at high risk of renal dysfunction or with multi-resistant organisms: adjust downwards, targeting cyclosporine levels < 300 µg/l.
  - Convert to oral dosing regimen as soon as possible (nasogastric tube).
3. Or start with tacrolimus 24-hour infusion commencing at 0.1 mg/kg/day at 2-3 day in intensive care unit and measure tacrolimus steady state levels at 12-24 hours.
  - In patients with high immunological risk: adjust upwards to 0.15 mg/kg/day, targeting steady state tacrolimus levels between 10 and 15 ng/ml within 36 hours.
  - For a CNI-sparing therapy in patients with or at high risk of renal dysfunction or with multi-resistant organisms: adjust downwards, targeting tacrolimus levels < 10 ng/ml.
  - Convert to oral dosing regimen as soon as possible (nasogastric tube).
4. Mycophenolic acid/azathioprine: as per center practice.
5. Corticosteroids: as per center practice.



## References

- Moffatt-Bruce SD, Milliken JC, Talavera F, Karwande SV, Mancini MC. Lung Transplantation. Medscape Reference. 2011. <http://emedicine.medscape.com/article/429499-overview>.
- Barr ML, Schenkel FA, Bowdish ME, Starnes VA. Living donor lobar lung transplantation: current status and future directions. *Transplant Proc.* 2005;37:3983-6.
- Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant.* 2006;25:745-55.
- Román A, Ussetti P, Solé A, et al. Guidelines for the selection of lung transplantation candidates. *Arch Bronconeumol.* 2011;47:303-9.
- 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;30:1104-22.
- Knoop C, Haverich A, Fischer S. Immunosuppressive therapy after human lung transplantation. *Eur Respir J.* 2004;23:159-71.
- Hopkins PM, McNeil K. Evidence for immunosuppression in lung transplantation. *Curr Opin Organ Transplant.* 2008;13:477-83.
- Sato M, Waddell TK, Wagnetz U, et al. Restrictive allograft syndrome (RAS): A novel form of chronic lung allograft dysfunction. *J Heart Lung Transplant.* 2011;30:735-42.
- Saldanha IJ, Mckoy NA, Robinson KA. Immunosuppressive drug therapy for preventing rejection following lung transplantation in cystic fibrosis. *Cochrane Database Sys Rev.* 2011;11:CD009421.
- Fishman JA. Infection in solid-organ transplant recipients. *N Engl J Med.* 2007;357:2601-14.
- Martín T, Chen DF, Palmer SM. Acute rejection and humoral sensitization in lung transplant recipients. *Proc Am Thorac Soc.* 2009;6:54-65.
- Remund KF, Best M, Egan J. Infections relevant to lung transplantation. *Proc Am Thorac Soc.* 2009;6:94-100.
- Schilz R. Complications of Lung Transplantation. University Hospitals Lung Transplantation Patient Handbook. Adapted for use on NetWellness with permission, 2007.
- Solé A, Salavert M. Fungal infections after lung transplants. *Curr Opin Pulm Med.* 2009;15:243-53.
- Opelz G, Döhler B. Lymphomas after solid organ transplantation: A Collaborative Transplant Study Report. *Am J Transplant.* 2004;4:222-30.
- González Castro A, Llorca J, Suberviola Cañas B, Fernández-Miret B, Zurbano F, Miñambres E. Acute renal failure in lung transplantation: incidence, correlation with subsequent kidney disease, and prognostic value. *Arch Bronconeumol.* 2008;44:353-9.
- Paradela de la Morena M, De La Torre Bravos M, Prado RF, et al. Chronic kidney disease after lung transplantation: incidence, risk factors, and treatment. *Transplant Proc.* 2010;42:3217-19.
- Iceberg Study. Novartis data on file.
- Bhorade SM, Stern E. Immunosuppression for lung Transplantation. *Proc Am Thorac Soc.* 2009;6:47-53.
- Lyu DM, Zamora MR. Medical complications of lung transplantation. *Proc Am Thorac Soc.* 2009;6:101-7.
- 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;20:1282-90.
- Hachem RR, Chakinala MM, Yusef RD, et al. A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. *J Heart Lung Transplant.* 2005;24:1320-6.
- Borro JM, De la Torre M, Míguez C, Fernández R, González D, Lemos C. Comparative study of basiliximab treatment in lung transplantation. *Transplant Proc.* 2005;37:3996-8.
- Fischer S, Strueber M, Niedermeyer J, Simon AR, Anssar M, Haverich A. Anti-CD25 antibody (Basiliximab) therapy decreases early graft rejection and improves the outcome following pulmonary transplantation. *J Heart Lung Transplant.* 2005;24:1284-88.
- Steward KC, Guthrie TJ, Richardson G, et al. A comparative analysis of Basiliximab (Simulex) and antithymocyte globulin(ATGAM) for induction immunosuppression in clinical lung transplantation. *J Heart Lung Transplant.* 2002;21:66.
- Clinckart F, Bulpa P, Jamart J, Eucher P, Delaunois L, Evrard P. Basiliximab as an alternative to antithymocyte globulin for early immunosuppression in lung transplantation. *Transplant Proc.* 2009;41:607-9.
- 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;25:638-47.
- 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;26:504-10.
- Lischke R, Simonek J, Davidová R, et al. Induction therapy in lung transplantation: initial single-center experience comparing daclizumab and antithymocyte globulin. *Transplant Proc.* 2007;39:205-12.
- 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;135:594-602.
- Hartwig MG, Snyder LD, Appel JZ, et al. Rabbit anti-thymocyte globulin induction therapy does not prolong survival after lung transplantation. *J Heart Lung Transplant.* 2008;27:547-53.
- Wadell TK, Borro JM, Roman A, et al. A double-blind randomized trial comparing basiliximab to placebo in lung transplantation. *J Heart Lung Transplant.* 2006;25:114.
- McCurry KR, Iacono A, Zeevi A, et al. Early outcomes in human lung transplantation with Thymoglobulin or Campath-1H for recipient pretreatment followed by posttransplant tacrolimus near-monotherapy. *J Thorac Cardiovasc Surg.* 2005;130:528-37.
- Van Loenhout KCJ, Groves SC, Galazka M, et al. Early outcomes using alemtuzumab induction in lung transplantation. *Interact Cardiovasc Thorac Surg.* 2010;10:190-4.
- Shyu S, Dew MA, Pilewski JM, et al. Five-year outcomes with alemtuzumab induction after lung transplantation. *J Heart Lung Transplant.* 2011;30:743-54.