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Immunosuppression for Lung Transplantation: Current and Future

Satish Chandrashekaran, MBBS[1], **Stacy A. Crow Pharm, D**[2,3], **Sadia Z. Shah, MD**[4], **Chris J. Arendt Pharm, D**[2,3], and **Cassie C. Kennedy, MD**[3,5]

[1]Division of Pulmonary, Critical Care and Sleep Medicine, Lung Transplantation Program, University of Florida Gainesville, FL

[2]Pharmacy Services, Mayo Clinic, Rochester, MN

[3]William J. von Liebig Center for Transplantation and Clinical Regeneration, Mayo Clinic, Rochester, MN

[4]Division of Pulmonary and Critical Care Medicine, Mayo Arizona

[5]Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN

Abstract

Purpose of the review—The number of lung transplantations performed worldwide continues to increase. There is a growing need in these patients for more effective immunosuppressive medications with less toxicity.

Recent findings—This review article summarizes the recent studies and developments in lung transplant immunosuppression. Novel immunosuppressive medications and strategies used in other solid organ transplantations are being trialed in lung transplantation. This includes the use of co-stimulation blockers like belatacept and mTOR inhibitors like everolimus. Calcineurin sparing regimens have been described in an attempt to minimize nephrotoxicity. Assays to measure the bioactivity of immunosuppressive medications to determine the global immune competence, such as Immuknow assay and Gamma interferon response are gaining traction.

Summary—Immunosuppression in lung transplant is evolving with the development of newer drugs and promising strategies to optimize immunosuppression. Further studies with multicenter randomized trials are required to increase the strength of the evidence.

Keywords

Lung transplantation; immunosuppression; calcineurin-sparing regimens; global immune competence

Corresponding author: Cassie C. Kennedy MD, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Gonda 18S, 200 1st St. SW, Rochester, MN 55905, Phone: 507-284-2447 Fax: 507-266-4372 kennedy.cassie@mayo.edu.

Compliance with Ethical Standards

Conflict of Interest

Satish Chandrashekaran, Stacy A. Crow, Sadia Z. Shah, Chris J. Arendt, and Cassie Kennedy declare no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Therapeutic approaches to immunosuppression were limited at the time of first lung transplant in 1963.[1] Growth in drug development for other solid organ transplants has provided the foundation for immunosuppression approaches in lung transplant. In fact, none of the below medications are approved in the United States for use in lung transplantation by the Food and Drug Administration. Growth in lung transplant volume has paralleled drug development innovations over the past 50 years. Recent innovations center on new formulations, new medications, new regimens and new ways of choosing medications to mitigate the risks of immunosuppression and rejection.

Conventional Immunosuppression:

Induction Therapy

Perioperative administration of potent agents to suppress the T-cell immune response (i.e. induction agents) can be used for a finite period of time to mitigate the risk of acute cellular rejection (ACR) at the time of transplant. Induction agents can be divided into two groups: T-cell depleting (lymphocyte immune globulin, anti-thymocyte globulin, and alemtuzumab), and non T cell depleting Interleukin-2 receptor (IL-2R) antagonists (basiliximab). Even though there is no consensus regarding use of induction agents, roughly 70% of lung transplant centers utilize induction therapy, representing a roughly 20% increase in utilization over the past decade.[2] This increase is supported by a large retrospective registry study of 3,970 patients, in which the use of induction agent showed superior four-year survival following transplant compared to no induction agent.[3] IL-2R antagonists are the most common induction agents in adult lung transplantation and work by inhibiting T-cell proliferation and differentiation.[2] Unfortunately, comparative effectiveness research is insufficient to recommend one induction agent over another at this time.[4]

Maintenance Immunosuppression

Lifelong maintenance immunosuppressive regimens are utilized to reduce the rate of rejection. A conventional approach to maintenance therapy is commonly comprised of triple-drug therapy with calcineurin inhibitor (cyclosporine or tacrolimus), antimetabolite (azathioprine or mycophenolate), and corticosteroids (CS).

Calcineurin Inhibitors (CNI)—Cyclosporine (CSA) was the first CNI to market, approved in the US in 1983 with tacrolimus (TAC) following in 1997. Both work by preventing IL-2 transcription, therefore decreasing T cell proliferation and activation. In a 2013 Cochrane Review of available randomized controlled trials (N=413 patients) of TAC versus CSA in lung transplant, TAC was superior to CSA regarding incidence of bronchiolitis obliterans syndrome (BOS) (RR 0.46; 95% CI 0.29 0.74).[5] However, no differences in the outcomes of survival or incidence of ACR were observed. It was noted that the number of studies, patients, and events comparing TAC and CSA were limited and the included underlying studies were at high risk for bias.

Anti-metabolites—Azathioprine (AZA), a pro-drug of 6-mercaptopurine (6MP), was first developed in 1950s. By blocking both *de novo* and salvage pathways syntheses of purine, AZA prevents T- and B-cell proliferation.[6] As a derivative of 6-MP, AZA has numerous mechanisms of action, including inhibition of DNA synthesis, purine metabolism, nucleotide synthesis, and blocking the CD28 co-stimulation pathway; the net result is suppression of all hematopoietic cell lines.

Mycophenolate mofetil (MMF), a pro-drug of mycophenolic acid (MPA), was approved in 2000. Unlike AZA that targets both *de novo* and salvage pathway purine syntheses, MPA selectively affects the *de novo* pathway via inhibition of inosine monophosphate dehydrogenase, the rate- limiting enzyme in *de novo* synthesis of guanosine nucleotides. In randomized, placebo- controlled trials in kidney, liver, and heart transplantation, MMF was associated with a significant reduction in the incidence of ACR.[7, 6, 8, 9] Surprisingly, in a multi-national, landmark trial in lung transplant recipients by McNeil *et al.*, no differences were seen in ACR or BOS in patients treated with MMF or AZA in combination with CSA, corticosteroids, and ATG.[10] A prospective, MMF versus AZA combined with TAC trial has not been published in the lung transplant population.

mTOR Inhibitors: The mammalian target of rapamycin (mTOR) inhibitors (sirolimus [SRL] and everolimus) were introduced as a non-nephrotoxic CNI replacement. Everolimus has a shorter half-life compared to SRL (30 versus 62 hours) and improved bioavailability. mTOR inhibitors bind to FK506 binding protein 12 (FKBP12) with resulting complex inhibiting mTOR and ultimately leading to the inhibition of IL-2 induced T, NK, and B cell proliferation.[11] In addition, mTOR inhibitors inhibit the proliferation of human lung fibroblasts.[12, 13] Care must be taken therefore not to introduce mTOR inhibitors too early post-transplant as it could lead to anastomotic dehiscence.[14] There is limited data available on the performance of mTOR inhibitors following lung transplantation. There may be a benefit in decreased ACR rates of everolimus (but not SRL) compared to azathioprine, with a higher rate of adverse effects and medication withdrawals for the mTOR inhibitors.[15, 16] Adverse effects include hypertension, dyslipidemia, anemia, edema, venous thromboembolism, stomatitis, and aphthous ulcers. In addition, the majority of patients develop a mild increase in proteinuria (<0.3 g/24 hour) with improvement in renal function. However, patients with preexisting proteinuria and renal insufficiency can develop proteinuria in the nephrotic range with worsening renal function.[13]

Belatacept: Belatacept (BELA) is a selective co-stimulation blocker that binds to surface costimulatory ligands (CD80 and CD86) of antigen-presenting cells. The interaction of CD80 and CD86 with the surface costimulatory receptor CD28 of T-cells (signal 2) is required for full activation of T cells. Blockade of signal 2 inhibits T-cell activation, promoting anergy and apoptosis. BELA is derived from abatacept, a human fusion protein combining the extracellular portion of cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) with the constant-region fragment (Fc) of human IgG1 (CTLA4Ig).[17] BELA is approved for use in kidney transplantation and showed promising results in the BENEFIT study with higher mean glomerular filtration rate, kidney graft and patient survival, and improved metabolic and cardiovascular profiles at 3 years compared to CSA.[18] [19]

Given the scant amount of data available, the role of BELA in lung transplantation remains unclear. The data is restricted to few case reports and series. Iasella *et al.* described the use of BELA in a single-center case series in eleven recipients who could not tolerate CNI and underwent conversion to BELA. Of these eleven patients, four were changed from CNI to BELA for thrombotic thrombocytopenic purpura (TTP), three others were changed to BELA for posterior reversible encephalopathy syndrome (PRES). Additional maintenance immunosuppression included MMF and prednisone. Patients received either high or low intensity BELA regimen. The incidence of ACR and infection in their eleven patients was the same when compared to patients treated with the traditional immunosuppression that included CNI. Mean estimated GFR was higher in the BELA group. Two instances of severe invasive Aspergillus infection were observed after starting BELA in this cohort. One of these two patients had an Aspergillus infection prior to BELA conversion.[20]

In another case series reported by Timofte *et al.*, eight lung transplant recipients received BELA for acute or chronic renal insufficiency that persisted or worsened despite reduction in CNI dosing or SRL initiation. FEV_1 was stable and there was no increase in ACR episodes. The renal function was stable in two patients and improved in five patients. Two of three patients on hemodialysis prior to BELA initiation were no longer dialysis-dependent on BELA and reduced- exposure CNI dosing. There was no increase in infections in this cohort. Unlike the study by Iasella *et al.,* patients on BELA in this study were continued on lower CNI or mTOR trough level.[21, 20] Larger, multicenter prospective studies are required to evaluate the safety and efficacy of this drug as a renal-sparing immunosuppressing agent.

Changing formulations

Calcineurin Inhibitors (CNI)

Cyclosporine (CSA)—The original formulation of CSA was composed in a non-aqueous form. A modified version of CSA optimized to form microemulsions when in contact with water was released a few years later with a more desirable pharmacokinetic profile having a more consistent bioavailability and exposure.[22] Aerosolized CSA was the next formulation of the drug in 1999. In a single center, randomized, double-blind, placebo-controlled trial of inhaled CSA there was no improvement in the rate of ACR, but survival and chronic rejection–free survival did improve.[23] In another single-center trial, inhaled CSA appeared to slow the rate of decline of important pulmonary function parameters in lung transplant recipients compared to aerosol placebo and historical control patients.[24] Purev *et al.* revealed substantial delivery of CIS could be achieved in the airways with only minimal systemic absorption.[25]

Tacrolimus (TAC)—Attempts to reduce the complications of TAC have yielded newer formulations that reduce peak exposure, narrow peak trough differences, improve adherence. In addition, protocols have been introduced that reduce exposure to CNI by conversion to mTOR-based regimens.[26] A once daily extended-release (ER) TAC improves on the pharmacokinetics of conventional twice daily TAC, optimizing time-in-therapeutic range, and adherence and compliance.[27] Increasing TAC's time-in-therapeutic-range (TTR) is

associated with significantly decreasing the incidence of chronic lung allograft disease (CLAD), ACR, and AKI within the first year after lung transplant.[28] Thus finding the formulations that improve time-in-therapeutic range, adherence and compliance and reduce adverse effect exposure is meaningful. While none of the once-daily formulations are approved in the US for lung transplantation, their use in clinical practice is growing.

Pharmacokinetic studies have demonstrated 1:1 dose conversion between twice-daily to once daily ER TAC, resulting in a comparable area under the curve from 0–24 hours ($AUC_{0–24}$) except in the case of cystic fibrosis where higher doses were required. There is limited data available regarding important outcomes in lung transplant recipients when using ER TAC.[26] [29, 30]

New Combinations:

Basiliximab as renal-sparing agent:

Basiliximab is used for induction therapy during lung transplantation. However, there are some case series describing its use in maintenance immunosuppression in lung transplant recipients with renal failure from CNI. In one such case series, Ross *et al.* describe nine lung transplant recipients with renal failure who had TAC trough levels lowered and received monthly Basiliximab for six months or more, as a renal-sparing regimen. The regimen was well-tolerated and there was improvement in GFR in this small case series. The graft function was stable.[31] Hogerle *et al.* reported a case series of nine lung transplant recipients with renal failure for >14 days requiring continuous veno-venous hemofiltration in the first two months following lung transplantation. These patients had normal GFR before transplantation.

Basiliximab was administered on days 0, 4 and 20. TAC was either stopped or the target trough level was reduced to 2–4 ng/ml. Seven of these patients completely recovered from renal failure and were switched back to TAC. The remaining two patients did not demonstrate any renal function recovery and died from sepsis.[32]

Combination of Tacrolimus and mTOR inhibitor

In preclinical studies, subclinical doses of TAC used in combination with an mTOR inhibitor demonstrated significant inhibition of lymphocyte proliferation and expression of IL-2, induction of transformation growth factor β, compared to clinical doses of either agent alone. Hence there appears to be a synergistic effect that allows for the use of lower dose of TAC without compromising immunosuppression and allowing for preservation of renal function. Peddi *et al.* reviewed the safety and efficacy of immunosuppressive regimens containing mTOR inhibitor with TAC minimization therapy in solid organ transplantation. The review included 21 studies total (2 randomized controlled trials in lung transplant recipients, N=108). Results indicate that combination immunosuppressive regimens of mTOR inhibitors and minimized TAC have good overall efficacy and preserve renal function better than standard TAC dose without significant changes in patient survival or graft rejection rates. Rates of CMV infection and malignancy were low. However, adverse effects

that include dyslipidemia, hypertension, proteinuria, new onset diabetes, and wound complications were higher in the mTOR groups.[33]

Everolimus in lieu of Mycophenolate mofetil (MMF)

Strueber *et al.* compared early initiation of everolimus to MMF in a single-center study. One hundred and ninety lung transplant patients were randomized to everolimus versus MMF on day 28 post transplantation. Both groups received CSA and steroids. The CSA dose was reduced by 20–28% in the everolimus group. The rate of biopsy-proven ACR, BOS, CMV viremia, leukopenia, and lower respiratory tract infection were lower in everolimus group. As the study protocol was completed by only 51% of enrolled patients, the study was underpowered to determine BOS-free survival (the primary end point). The secondary endpoints indicate potential advantage of everolimus. However, the drug-related serious adverse effects were also higher in this group (included thrombotic microangiopathy in 5 patients).[34] One also worries about use of mTOR inhibitor that early following lung transplantation given the risk of anastomotic dehiscence.

A three-year multicenter, randomized, open-label, prospective study compared enteric coated Mycophenolate sodium (MPS) to delayed initiation of Everolimus in combination with CSA and steroids in 165 lung transplant recipients. The dose of CSA was reduced in the everolimus group to decrease cumulative nephrotoxicity. Everolimus was started between 1- and 3- months post- transplantation after documentation of anastomotic healing. The three-year freedom to BOS was the same both groups. However, the rate of biopsy-proven ACR, leukopenia, diarrhea, and CMV infection was higher in MPS group. On the other hand, thromboembolism was higher in everolimus group. Renal failure was not different in the two groups.[12]

Antibody Mediated Rejection Salvage Regimens

The ISHLT recently published a consensus document on the diagnostic criteria for antibody mediated rejection (AMR) in lung transplant recipients, a cause of graft dysfunction related to the presence of recipient antibodies towards donor-specific anti–human leukocyte antigens.[35] There is no current consensus regarding treatment of AMR in lung transplant. In general, treatment strategies involve disrupting the production of or depleting the amount of circulating recipient antibodies. Intravenous methylprednisolone, immune globulin (IVIG), plasmapheresis, and rituximab are all strategies reported in literature[36]. If clinical response remains inadequate despite these therapies, additional approaches have been attempted.

Proteosome inhibitors

Bortezomib (BTZ) is pro-apoptotic proteasome inhibitor that attacks plasma cells, the source of antibody production. Use in lung transplantation for both desensitization and treatment of AMR has been reported with mixed results [37, 38]. For example, when used for persistent AMR despite IVIG and rituximab, pediatric lung transplants demonstrated reduction in the median fluorescence intensity of donor specific antibodies (DSA) with complete resolution

of C3d and C4d deposits on lung biopsy.[39] Adverse reactions include dose-limiting thrombocytopenia, intractable nausea, nephrotoxicity, CMV disease, and lung infections.

Carfilzomib (CFZ), a second-generation proteasome inhibitor, inhibits both constitutive and immunoproteasomes similar to BTZ. Differing characteristics from BTZ include irreversible binding activity, longer half-life, and greater proteasome selectivity. An observational, proof-of- concept study by Ensor *et al.* looking at CFZ use in lung transplant examined the loss of DSA fixing ability *in vitro* after CFZ therapy with plasmapheresis and IVIG.[40] They report removal of C1q-fixing DSA and depletion of circulating immunodominant DSA as being associated with the return of graft function.

Eculizumab

The anti-C5 antibody eculizumab (ECU) carries a novel mechanism of action. *Dawson et al.* reported its use in a lung transplant with hyperacute AMR due to multiple class II DR and DQ DSAs in combination with BTZ, rituximab, IVIG and plasmapheresis.[41] Liberation from ECMO and improvement in CXR temporally correlated with the addition of ECU to the aggressive regimen.

New ways of choosing medications

Pharmacogenetics and Pharmacogenomics

Pharmacogenetics and pharmacogenomics together are emerging as potential clinical tools for management of lung transplant patients. Pharmacogenetics involves studying the relationship between immunosuppressive drug and gene polymorphism which may predict disposition of drug in transplant patient. Pharmacogenomics studies the reliability of critical biomarkers to predict clinical outcomes and thereby help develop patient-specific drug regimens for transplant patients[42] For example, Yousem *et al.* noted high percentage of P-gp positive cells on lung biopsy and its association with steroid resistance during treatment of ACR or OB.[43] In addition, the LARGO study showed that airway inflammation leads to upregulation of membrane metalloendopeptidase in lung transplant patients. A similar trend is seen for TNFSF6 (FasL), XCR3, and S100A, suggesting potential roles for matrix degradation, apoptosis, and cell trafficking in bronchiolar remodeling. The LARGO study also supported the hypothesis that peripheral blood gene expression profiles could be developed for the adverse drug effects that plague lung transplant patients. Different gene signatures would be expected for infectious diseases, renal toxicity from CSA or TAC, and tissue damage from metabolic diseases such as hyperlipidemia or post-transplant diabetes mellitus.[44]

Assays to guide immunosuppression

The ImmuKnow immune cell function assay (Cylex, Inc., Columbia, MD, USA) measures the bioactivity of immunosuppressing medications by measuring their net effect on immune cells (the activity of CD4+ T cells), ultimately determining the global immune competence by detecting the cell-mediated immunity (CMI) in immunosuppressed host. Three immune response stratifications were defined after comparing responses of healthy individuals and transplant recipients. Low response is ATP < 225 ng/ml, moderate between 226 to 524 and a

strong response is > 525 ng/ml. Infections in solid organ transplant recipients has correlated with very low ATP values compared to values obtained during clinical stability.[45]

Kowalski *et al.* described a meta-analysis of 504 solid organ transplant recipients (heart, kidney, liver, kidney-pancreas and small bowel) who had Cylex ImmuKnow assay analysis performed in 10 centers across US during clinically stable state, infection and during rejection.[46] Solid organ transplant recipients with an ATP level of 25 ng/ml were 12 times more likely to develop infection compared to recipients with a stronger immune response and a recipient with ATP level of 700 ng/ml was 30 times more likely to develop ACR.[46]

Husain *et al.* prospectively analyzed ImmuKnow ATP values in 175 lung transplant recipients during 129 infectious episodes.[47] The median ATP values were significantly lower during CMV disease (49.3 ng/ml), viral infection (70 ng/ml), bacterial pneumonias (92 ng/ml), fungal disease (85 ng/ml) compared to stable state (174.8 ng/ml). ImmuKnow values less than 100 ng/ml ATP was an independent predictor of infection, odds ratio (OR) 2.81. Values < 50 ng/ml had an OR of 9 for predicting infection. In patients with fungal colonization, the values were lower in patients who subsequently developed fungal disease when compared to those who did not (22.5 vs 183.5 ng/ml). Patients with fungal colonization whose Cylex ImmuKnow vales were < 50 ng/ml were the ones who progressed to invasive disease. Thus, Cylex ImmuKnow cell function assay may help in identifying a subset of patients who would need prophylaxis and possible decrease in immunosuppression.[47]

Piloni *et al.* measured ImmuKnow assay levels in 61 lung transplant recipients.[48] Over immunosuppression was associated with lower ATP levels (mean ATP levels 112.92 ng/ml vs 406.14 ng/ml). There were significant episodes of infections in the group with lower ATP levels compared to the group with higher ATP levels.[48]

Shino *et al.* analyzed ImmuKnow assay results in 175 lung transplant recipients during clinical stability and during episodes ACR and infection.[49] There were 66 episodes of ACR and 91 episodes of infection. A lung transplant recipient with ATP levels > 525 ng/ml was 2.1 times more likely to have ACR. Similarly, a recipient with ATP < 225 ng/ml was 1.9 times more likely to have respiratory infection. However, the sensitivity and specificity in this study to diagnose ACR or infection was rather low.[49]

Hence, several of the above studies seem to indicate that in lung transplant recipients ATP level < 100 ng/ml is a very strong predictor of infection. Single ImmuKnow assay values in a patient may not be useful as a diagnostic tool, but serial values in the same patient during clinical stability, ACR, or infection might be a helpful tool to make adjustment to the immunosuppression.

Plasma interferon-gamma (IFN - ɣ)

Mian *et al.* used a novel global cell-mediated immunity (CMI) assay (QuantiFERON Monitor [QFM], Qiagen) to measure plasma interferon-gamma (IFN-ɣ) after stimulation of whole blood with a combination of antigens designed to stimulate both innate and adaptive immunity in 137 solid organ transplant recipients (that included kidney, liver and lung). IFN-

ɣ levels were significantly lower in those who developed infection and opportunistic infections compared to patients without infection. A value of IFN-ɣ < 10 IU/ml was predictive of subsequent infection with an OR of 2–3. Lung transplant recipient had lower IFN-ɣ levels at all time points compared to kidney and liver transplant recipients, which could be related to the amount of immunosuppressive medications used in each organ group post-transplant. ATP levels and IF-ɣ provide potential strategies to measure global immunity. This would enable better risk stratification and better adjustment of immunosuppression and antimicrobial prophylaxis.[50]

Conclusion:

Lung transplant lags other solid organ transplantations in the study and adoption of novel immunesuppressants. Typically drugs used in lung transplantation are not FDA approved in the US. The introduction of CNI in 1980s transformed the field of lung transplantation. The one year survival improved while the incidence of ACR dropped.[51] CNI continue to remain the most important drug in chronic maintenance immunosuppressive regimen in lung transplantation. But CNI use is associated with development of adverse effects like CNI associated nephrotoxicity, TTP, renal failure, and PRES.

Lung transplant recipients who have renal insufficiency prior to transplantation have poor early and late outcomes.[52] About 20% and 43% of lung transplant recipients develop renal dysfunction at 1 and 5 years, respectively [2] The need for “kidney friendly” or “renal sparing” immunosuppression regimen is ever increasing due to aging and increasingly sicker recipients.[53, 51, 54] mTOR inhibitors and belatacept seem to hold some promise but these agents are better used with lower dose of CNI to prevent early onset rejection. There does not appear to be any new molecules in development that could displace the pivotal role occupied by CNI as of yet.

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Abbreviations:

mTOR	mammalian target of rapamycin
ACR	acute cellular rejection
Il-2R	Interleukin-2 receptor
CNI	calcineurin Inhibitors
TAC	tacrolimus
BOS	bronchiolitis obliterans syndrome
AZA	azathioprine

6MP	6-mercaptopurine
MMF	mycophenolate mofetil
MPA	mycophenolic acid
SRL	sirolimus
FKBP12	FK506 binding protein 12
BELA	belatacept
CTLA4	cytotoxic T-lymphocyte–associated antigen 4 (CTLA4)
TTP	thrombotic thrombocytopenic purpura
PRES	posterior reversible encephalopathy syndrome
ER	extended-release
TTR	time-in-therapeutic-range
CLAD	chronic lung allograft disease
AKI	acute kidney injury
GFR	glomerular filtration rate
CMV	cytomegalovirus
AMR	antibody mediated rejection
BTZ	bortezomib
DSA	donor specific antibodies
CFZ	carfilzomib
IVIG	intravenous immunoglobulin
ECU	eculizumab
IFN – ɣ	plasma interferon-gamma

References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

••Of major importance

1. HARDY JD, WEBB WR, DALTON ML, WALKER GR. LUNG HOMOTRANSPLANTATION IN MAN. JAMA 1963;186:1065–74. [PubMed: 14061414]
2. Chambers DC, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khusch K et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Lung

And Heart-Lung Transplantation Report-2017; Focus Theme: Allograft ischemic time. J Heart Lung Transplant 2017;36(10):1047–59. doi:10.1016/j.healun.2017.07.016. [PubMed: 28784324]

3. Hachem RR, Edwards LB, Yusen RD, Chakinala MM, Alexander Patterson G, 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(5):603–8. doi:10.1111/j.1399-0012.2008.00831.x. [PubMed: 18435784]
4. Penninga L, Møller CH, Penninga EI, Iversen M, Gluud C, Steinbrüchel DA. Antibody induction therapy for lung transplant recipients. Cochrane Database Syst Rev 2013(11):CD008927. doi:10.1002/14651858.CD008927.pub2. [PubMed: 24282128]
5. Penninga L, Penninga EI, Møller CH, Iversen M, Steinbrüchel DA, Gluud C. Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients. Cochrane Database Syst Rev 2013(5):CD008817. doi:10.1002/14651858.CD008817.pub2. [PubMed: 23728681]
6. Wiesner R, Rabkin J, Klintmalm G, McDiarmid S, Langnas A, Punch J et al. A randomized double-blind comparative study of mycophenolate mofetil and azathioprine in combination with cyclosporine and corticosteroids in primary liver transplant recipients. Liver Transpl 2001;7(5):442–50. doi:10.1053/jlts.2001.23356. [PubMed: 11349266]
7. Kobashigawa J, Miller L, Renlund D, Mentzer R, Alderman E, Bourge R et al. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. Mycophenolate Mofetil Investigators. Transplantation 1998;66(4):507–15. [PubMed: 9734496]
8. Zuckermann A, Klepetko W, Birsan T, Taghavi S, Artemiou O, Wisser W et al. Comparison between mycophenolate mofetil- and azathioprine-based immunosuppressions in clinical lung transplantation. J Heart Lung Transplant 1999;18(5):432–40. [PubMed: 10363687]
9. Wiesel M, Carl S. A placebo controlled study of mycophenolate mofetil used in combination with cyclosporine and corticosteroids for the prevention of acute rejection in renal allograft recipients: 1-year results. The European Mycophenolate Mofetil Cooperative Study Group. J Urol 1998;159(1):28–33. [PubMed: 9400430]
10. McNeil K, Glanville AR, Wahlers T, Knoop C, Speich R, Mamelok RD et al. Comparison of mycophenolate mofetil and azathioprine for prevention of bronchiolitis obliterans syndrome in de novo lung transplant recipients. Transplantation 2006;81(7):998–1003. doi:10.1097/01.tp.0000202755.33883.61. [PubMed: 16612275]
11. Schwarz S, Jaksch P, Klepetko W, Hoetzenecker K. Immunosuppression after lung transplantation: the search for the holy grail continues. J Thorac Dis 2017;9(6):1412–4. doi:10.21037/jtd.2017.04.66. [PubMed: 28740645]
12. Glanville AR, Aboyoun C, Klepetko W, Reichenspurner H, Treede H, Verschuuren EA et al. Three-year results of an investigator-driven multicenter, international, randomized open label de novo trial to prevent BOS after lung transplantation. J Heart Lung Transplant 2015;34(1):16–25. doi:10.1016/j.healun.2014.06.001. [PubMed: 25049068]
13. Fine NM, Kushwaha SS. Recent Advances in Mammalian Target of Rapamycin Inhibitor Use in Heart and Lung Transplantation. Transplantation 2016;100(12):2558–68. doi:10.1097/TP.0000000000001432. [PubMed: 27495747]
14. King-Biggs MB, Dunitz JM, Park SJ, Kay Savik S, Hertz MI. Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. Transplantation 2003;75(9):1437–43. doi:10.1097/01.TP.0000064083.02120.2C. [PubMed: 12792493]
15. Snell GI, Valentine VG, Vitulo P, Glanville AR, McGiffin DC, Loyd JE et al. Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. Am J Transplant 2006;6(1):169–77. doi:10.1111/j.1600-6143.2005.01134.x. [PubMed: 16433771]
16. Bhorade S, Ahya VN, Baz MA, Valentine VG, Arcasoy SM, Love RB et al. Comparison of sirolimus with azathioprine in a tacrolimus-based immunosuppressive regimen in lung transplantation. Am J Respir Crit Care Med 2011;183(3):379–87. doi:10.1164/rccm.201005-0775OC. [PubMed: 20833822]
17. Vincenti F, Larsen C, Durrbach A, Wekerle T, Nashan B, Blancho G et al. Costimulation blockade with belatacept in renal transplantation. N Engl J Med 2005;353(8):770–81. doi:10.1056/NEJMoa050085. [PubMed: 16120857]

18. Vincenti F, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant 2010;10(3):535–46. doi:10.1111/j.1600-6143.2009.03005.x. [PubMed: 20415897]

19. Vincenti F, Larsen CP, Alberu J, Bresnahan B, Garcia VD, Kothari 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(1):210–7. doi:10.1111/j.1600-6143.2011.03785.x. [PubMed: 21992533]

••20. Iasella CJ, Winstead RJ, Moore CA, Johnson BA, Feinberg AT, Morrell MR et al. Maintenance Belatacept-Based Immunosuppression in Lung Transplantation Recipients Who Failed Calcineurin Inhibitors. Transplantation 2018;102(1):171–7. doi:10.1097/TP.0000000000001873. This case series of 11 lung transplant recipients who were changed to be latacept based immunosuppression. This study demonstrated resonable results in this cohort of patients who did not tolerate CNI or who failed CNI. [PubMed: 28691954]

21. Timofte I, Terrin M, Barr E, Sanchez P, Kim J, Reed R et al. Belatacept for renal rescue in lung transplant patients. Transpl Int 2016;29(4):453–63. doi:10.1111/tri.12731. [PubMed: 26678245]

22. Kovarik JM, Mueller EA, van Bree JB, Tetzloff W, Kutz K. Reduced inter- and intraindividual variability in cyclosporine pharmacokinetics from a microemulsion formulation. J Pharm Sci 1994;83(3):444–6. [PubMed: 8207699]

23. Iacono AT, Johnson BA, Grgurich WF, Youssef JG, Corcoran TE, Seiler DA et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. N Engl J Med 2006;354(2):141–50. doi:10.1056/NEJMoa043204. [PubMed: 16407509]

24. Groves S, Galazka M, Johnson B, Corcoran T, Verceles A, Britt E et al. Inhaled cyclosporine and pulmonary function in lung transplant recipients. J Aerosol Med Pulm Drug Deliv 2010;23(1):31–9. doi:10.1089/jamp.2009.0748. [PubMed: 19580368]

25. Purev E, Gormley N, Ramos C, Reger R, Tian X, Cho E et al. Inhaled cyclosporine solution for the treatment of bronchiolitis obliterans following hematopoietic stem cell transplantation (HSCT) or lung transplantation. Biology of Blood and Marrow TransplantationFebruary, 2015 p. S347–S8.

26. Patel Neha ea. Overview of extended release tacolimus in solid organ transplantation. World Journal of Transplantation 2016:144–54. [PubMed: 27011912]

27. Ho E, et al. Once-daily extended release versus twice-daily standard release tacrolimus in kidney transplant recipients: a systematic review. Transplantation 2013;95((9)):1120–8. [PubMed: 23542469]

28. Cea Moore. Increasing Tacrolimus Time-in-Therapeutic Range Is Associated with Reduced Chronic Lung Allograft Dysfunction. The Journal of Heart and Lung Transplantation 2017:S411.

29. Méndez A, Berastegui C, López-Meseguer M, Monforte V, Bravo C, Blanco A et al. Pharmacokinetic study of conversion from tacrolimus twice-daily to tacrolimus once-daily in stable lung transplantation. Transplantation 2014;97(3):358–62. doi:10.1097/01.TP.0000435699.69266.66. [PubMed: 24492423]

30. Soto GAC, Ruiz-Antorán B, Laporta R, Sancho A, Lázaro MT, Herrera CP et al. Dose increase needed in most cystic fibrosis lung transplantation patients when changing from twice- to once-daily tacrolimus oral administration. Eur J Clin Pharmacol 2015;71(6):715–22. doi:10.1007/s00228-015-1859-2. [PubMed: 25953736]

31. Monthly DJR basiliximab treatment improves chronic renal dysfunction with allograft stability after lung transplantation. Journal of Heart Lung Transplantation; 2017 p. S411.

32. Högerle BA, Kohli N, Habibi-Parker K, Lyster H, Reed A, Carby M et al. Challenging immunosuppression treatment in lung transplant recipients with kidney failure. Transpl Immunol 2016;35:18–22. doi:10.1016/j.trim.2016.02.002. [PubMed: 26892232]

33. Peddi VR, Wiseman A, Chavin K, Slakey D. Review of combination therapy with mTOR inhibitors and tacrolimus minimization after transplantation. Transplant Rev (Orlando) 2013;27(4):97–107. doi:10.1016/j.trre.2013.06.001. [PubMed: 23932018]

••34. Strueber M, Warnecke G, Fuge J, Simon AR, Zhang R, Welte T et al. Everolimus Versus Mycophenolate Mofetil De Novo After Lung Transplantation: A Prospective, Randomized, Open-Label Trial. Am J Transplant 2016;16(11):3171–80. doi:10.1111/ajt.13835. This single

center, prospective, randomized study in lung tranplant recipients demonstrated potential benefit of early initiation of everolimus based immunosuppression regimens. [PubMed: 27104933]

35. Levine DJ, Glanville AR, Aboyoun C, Belperio J, Benden C, Berry GJ et al. Antibody mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2016;35(4):397–406. doi:10.1016/j.healun.2016.01.1223. [PubMed: 27044531]
36. Kulkarni HS, Bemiss BC, Hachem RR. Antibody-mediated Rejection in Lung Transplantation. Curr Transplant Rep 2015;2(4):316–23. doi:10.1007/s40472-015-0074-5. [PubMed: 27896040]
37. Witt CA, Gaut JP, Yusen RD, Byers DE, Iuppa JA, Bennett Bain K et al. Acute antibody- mediated rejection after lung transplantation. J Heart Lung Transplant 2013;32(10):1034–40. doi:10.1016/j.healun.2013.07.004. [PubMed: 23953920]
38. Snyder LD, Gray AL, Reynolds JM, Arepally GM, Bedoya A, Hartwig MG et al. Antibody desensitization therapy in highly sensitized lung transplant candidates. Am J Transplant 2014;14(4):849–56. doi:10.1111/ajt.12636. [PubMed: 24666831]
39. Hayes D, Nicholson KL, Baker PB. Bortezomib for antibody-mediated rejection in a young lung transplant recipient. Pediatr Transplant 2016;20(1):178–9. doi:10.1111/petr.12651. [PubMed: 26667373]
40. Ensor CR, Yousem SA, Marrari M, Morrell MR, Mangiola M, Pilewski JM et al. Proteasome Inhibitor Carfilzomib-Based Therapy for Antibody-Mediated Rejection of the Pulmonary Allograft: Use and Short-Term Findings. Am J Transplant 2017;17(5):1380–8. doi:10.1111/ajt.14222. [PubMed: 28173620]
41. Dawson KL, Parulekar A, Seethamraju H. Treatment of hyperacute antibody-mediated lung allograft rejection with eculizumab. J Heart Lung Transplant 2012;31(12):1325–6. doi:10.1016/j.healun.2012.09.016. [PubMed: 23063321]
42. Burckart GJ, Hutchinson IV, Zeevi A. Pharmacogenomics and lung transplantation: clinical implications. Pharmacogenomics J 2006;6(5):301–10. doi:10.1038/sj.tpj.6500376. [PubMed: 16520825]
43. Yousem SA, Sartori D, Sonmez-Alpan E. Multidrug resistance in lung allograft recipients: possible correlation with the development of acute and chronic rejection. J Heart Lung Transplant 1993;12(1 Pt 1):20–6. [PubMed: 8095160]
44. Keshavjee S, Trulock E, Doyle R, Davis R, Golden J, McCurry K et al. Immunoregulatory influences on peripheral blood gene expression in lung transplant patients:The lung allograft rejection gene expression observational (Largo) study. The Journal of Heart and Lung TransplantationFebruary 2006 p. S78.
45. Zeevi A, Lunz J. Cylex ImmuKnow Cell Function Assay. Methods Mol Biol 2013;1034:343–51. doi:10.1007/978-1-62703-493-7_21. [PubMed: 23775749]
46. Kowalski RJ, Post DR, Mannon RB, Sebastian A, Wright HI, Sigle G et al. Assessing relative risks of infection and rejection: a meta-analysis using an immune function assay. Transplantation 2006;82(5):663–8. doi:10.1097/01.tp.0000234837.02126.70. [PubMed: 16969290]
47. Husain S, Raza K, Pilewski JM, Zaldonis D, Crespo M, Toyoda Y et al. Experience with immune monitoring in lung transplant recipients: correlation of low immune function with infection. Transplantation 2009;87(12):1852–7. doi:10.1097/TP.0b013e3181a75ad2. [PubMed: 19543064]
48. Piloni D, Magni S, Oggionni T, Benazzo A, Stella G, Scudeller L et al. Clinical utility of CD4+ function assessment (ViraCor-IBT ImmuKnow test) in lung recipients. Transpl Immunol 2016;37:35–9. doi:10.1016/j.trim.2016.04.001. [PubMed: 27095000]
49. Shino MY, Weigt SS, Saggar R, Elashoff D, Derhovanessian A, Gregson AL et al. Usefulness of immune monitoring in lung transplantation using adenosine triphosphate production in activated lymphocytes. J Heart Lung Transplant 2012;31(9):996–1002. doi:10.1016/j.healun.2012.05.012. [PubMed: 22884386]

••50. Mian M, Natori Y, Ferreira V, Selzner N, Husain S, Singer L et al. Evaluation of a Novel Global Immunity Assay to Predict Infection in Organ Transplant Recipients. Clin Infect Dis 2017. doi: 10.1093/cid/cix1008. This article describes a novel assay of plasma gamma interferon in immunosuppressed lung transplant recipients. A low level of gamma interfoeron was very predicitve of infection.

51. Webber AB, Vincenti F. An Update on Calcineurin Inhibitor-Free Regimens: The Need Persists, but the Landscape has Changed. Transplantation 2016;100(4):836–43. doi:10.1097/TP.0000000000000872. [PubMed: 27003097]

52. Banga A, Mohanka M, Mullins J, Bollineni S, Kaza V, Torres F et al. Association of pretransplant kidney function with outcomes after lung transplantation. Clin Transplant 2017;31(5). doi: 10.1111/ctr.12932.

53. Wigfield CH, Buie V, Onsager D. “Age” in lung transplantation: factors related to outcomes and other considerations. Curr Pulmonol Rep 2016;5:152–8. doi:10.1007/s13665-016-0151-y. [PubMed: 27610336]

54. Grimm JC, Lui C, Kilic A, Valero V, Sciortino CM, Whitman GJ et al. A risk score to predict acute renal failure in adult patients after lung transplantation. Ann Thorac Surg 2015;99(1):251–7. doi: 10.1016/j.athoracsur.2014.07.073. [PubMed: 25440281]