Immunosuppressive strategies in lung transplantation

Paul A. Chung, Daniel F. Dilling

Division of Pulmonary and Critical Care, Loyola University Chicago, Stritch School of Medicine, Maywood, IL, USA

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Correspondence to: Daniel F. Dilling, MD. Division of Pulmonary and Critical Care, Loyola University Chicago, Stritch School of Medicine, 2160 S 1st Ave, Maywood, IL 60153, USA. Email: ddillin@lumc.edu.

Abstract: Lung transplantation is a viable option for those with end-stage lung disease which is evidenced by the continued increase in the number of lung transplantations worldwide. However, patients and clinicians are constantly faced with acute and chronic rejection, infectious complications, drug toxicities, and malignancies throughout the lifetime of the lung transplant recipient. Conventional maintenance immunosuppression therapy consisting of a calcineurin inhibitor (CNI), anti-metabolite, and corticosteroids have become the standard regimen but newer agents and modalities continue to be developed. Here we will review induction agents, maintenance immunosuppressives, adjunctive therapies and other strategies to improve long-term outcomes.

Keywords: Lung transplantation; induction; maintenance; review

Introduction

Since the first human lung transplant in 1963 (1), nearly 65,000 lung transplantations have been reported worldwide (2). Unfortunately, median survival remains the lowest of the solid organ transplants at 6.5 years (2). The main challenges to long-term survival are acute and chronic rejection, infectious complications, drug toxicities, and malignancies. Although conventional maintenance immunosuppression therapy consisting of a calcineurin inhibitor (CNI), anti-metabolite, and corticosteroids remains the dominant drug regimen for lung transplantation, immunosuppressive strategies continue to evolve to address these challenges. We will review the current available immunosuppressive medications, the data behind their use, and some of the adjunctive therapies and clinical tools that are being developed to improve long-term outcomes. In this review, the term chronic lung allograft dysfunction (CLAD) as described by a consensus definition from the pulmonary council of the International Society of Heart and Lung Transplantation (ISHLT) (3) including its subtypes, bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS), has been used in place of the historical term BOS unless specified by the study.

Induction immunosuppression

Induction therapy utilizes intensive immunosuppression in the perioperative and/or the immediate post-operative period to reduce the risk of T-cell mediated early rejection. Induction agents primarily target T-cells and cause depletion and/or interruption of their activation and proliferation. According to the most recent International Society for Heart and Lung Transplantation (ISHLT) registry data, the proportion of patients receiving induction immunosuppression has increased over the last decade with 76% of adult lung transplant recipients receiving any induction agent in 2016 (2). The three commonly used induction agents are basiliximab, anti-thymocyte globulin (ATG) and alemtuzumab (*Table 1*). Two other induction agents that had previously been used are now no longer available due to manufacturers voluntary withdrawal

Table 1 Induction agents for lung transplantation

Induction agent	Mechanism	Adverse effects	Additional notes
Basiliximab [Simulect® (4)]	Chimeric (murine/human), monoclonal antibody that binds and blocks interleukin-2 receptor α-chain (IL-2Rα; CD25 antigen) on the surface of activated T lymphocytes; does not cause depletion of T lymphocytes	Hypersensitivity reaction including anaphylaxis (onset within 24 hours)	
Anti-thymocyte globulin: rabbit [Thymoglobulin® (5)]; Horse [Atgam® (6)]	Polyclonal antibody to multiple antigens on T lymphocytes that causes depletion and modulation of T-cell activation, homing, and cytotoxic activities	Cytokine release syndrome/ infusion reaction, serum sickness, thrombocytopenia, neutropenia, lymphopenia, hyperkalemia, fever, chills, shortness of breath, headache	Also utilized for treatment of acute and chronic rejection
Alemtuzumab [Campath® (7)]	Monoclonal antibody that binds to the CD52 antigen causing antibody-dependent cellular-mediated lysis and profound depletion of T lymphocytes; other cells affected to a lesser extent include B lymphocytes, a majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes	Cytokine release syndrome/ infusion reaction, thrombocytopenia, neutropenia, autoimmune cytopenias, insomnia, anxiety; rare cause of diffuse alveolar hemorrhage	Newly marketed for multiple sclerosis in 2012 [Lemtrada® (8)]

(daclizumab and muromonab-CD3).

Basiliximab (Simulect®) is a monoclonal antibody that is selectively directed against the interleukin-2 (IL-2) receptor alpha-chain, specifically binding to the CD25 antigen on activated T-lymphocytes thereby preventing binding of IL-2, a signal for T-cell proliferation, which results in a decrease in circulating T-cells without depletion (4). Rabbit ATG (rATG, Thymoglobulin®) is a purified, pasteurized, immunoglobulin G obtained by immunization of rabbits with human thymocytes whereas equine or horse ATG (eATG, Atgam®) is a purified, concentrated, and sterile gamma globulin, primarily monomeric IgG, from hyperimmune serum of horses immunized with human thymus lymphocytes. ATG depletes T-cells from circulation and modulates T-cell activation, homing, and cytotoxic activities (5,6). Alemtuzumab (Campth®) is a recombinant DNA-derived humanized monoclonal antibody that is directed against CD52, a surface glycoprotein expressed on T- and B-lymphocytes, NK cells, monocytes, and macrophages causing antibody-dependent lysis of cells (7), leading to prolonged T- and B-cell depletion. Consistent with previous registry data, the use of IL-2 receptor antagonists continues to increase as the use of anti-lymphocyte/ATG declines; the use of alemtuzumab has been variable throughout the last decade

with a modest decline since 2014 (2) (*Figure 1*).

The rationale for induction immunosuppression in lung transplantation is based on outcomes from previous studies in other solid organ transplantation. To date, studies of induction immunosuppression in lung transplantation have been either small or retrospective in nature and although there are conflicting results, there are trends suggesting that induction agents decrease the incidence of acute rejection and provide improvements in long-term outcomes without a significant increase in infectious complications or adverse side effects (9-23). The most convincing data showing benefits of induction immunosuppression come from two large, retrospective studies using the ISHLT and United Network for Organ Sharing (UNOS) registry databases. Hachem *et al.* (10) found that among 3,970 adult single and bilateral lung transplant recipients, the use of an IL-2 receptor antagonist was associated with lower incidence of acute rejection (15% *vs.* 22%, P<0.0005) and a higher graft survival rate at 4 years (64% *vs.* 57%, log rank P=0.0067) compared to no induction immunosuppression. Importantly, there was a 4-year survival advantage in both single and bilateral lung transplant recipients receiving an IL-2 receptor antagonist versus no induction [relative risk (RR) =0.82; 95% confidence interval (CI): 0.71–0.95, P=0.007] independent of other risk factors. Induction with ATG
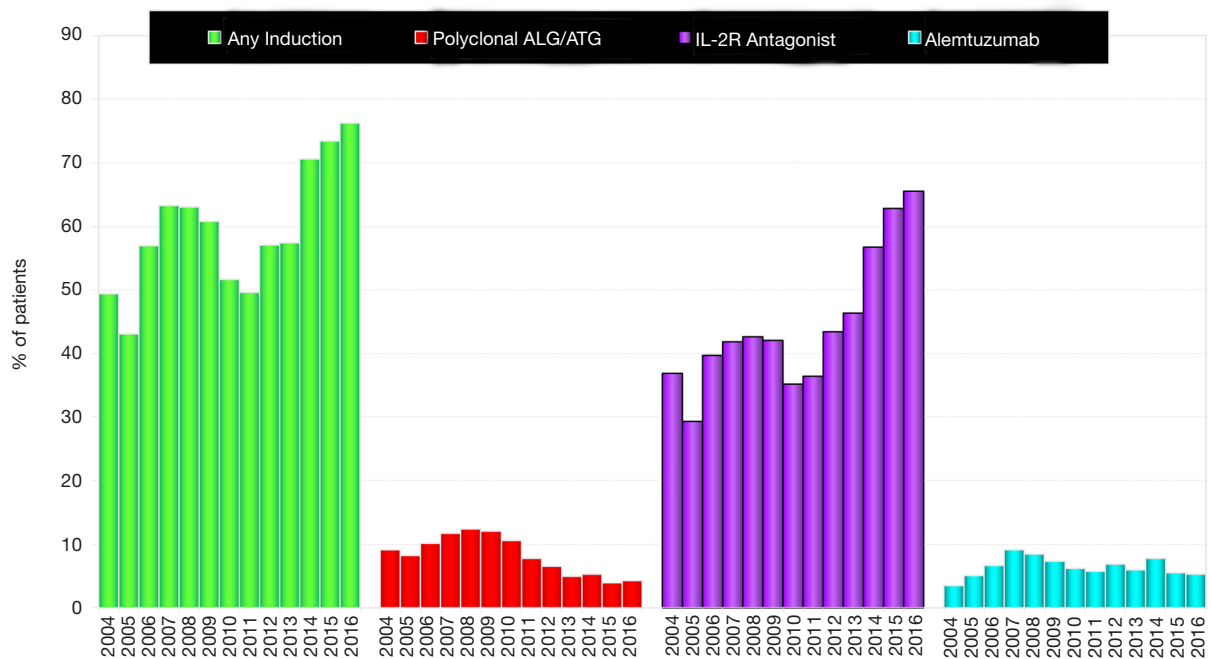
Figure 1 Use of induction immunosuppression as a percentage of all adult lung transplantation reported to the International Society of Heart and Lung Transplantation registry database from January 2004 to December 2016. Included patients were those who were on prednisone and alive at discharge post-lung transplantation. ALG/ATG, anti-lymphocyte globulin/anti-thymocyte globulin; IL-2R, interleukin-2 receptor. Reproduced from (2).

led to improvements in outcomes only in bilateral lung transplant patients when compared to no induction; there were no significant differences in outcomes in single lung transplant recipients receiving ATG versus no induction. More recently, Furuya *et al.* (17) reviewed 6,117 bilateral lung transplant recipients and found that either the use of alemtuzumab or basiliximab led to longer median survival compared to no induction immunosuppression (2,321 *vs.* 2,152 *vs.* 1,967 days, P<0.001). Moreover, the development of CLAD at 5 years was significantly lower in patients who received alemtuzumab (22.7%) versus basiliximab (55.4%) versus no induction (55.9%) (P<0.001).

The superiority of using one induction agent over another has not been proven, although most (but not all) studies tend to favor basiliximab and alemtuzumab over ATG (22,24-28). A 2013 Cochrane review found no clear benefits or harms when comparing the different induction agents (22). However, this review was based on only six randomized control trials (RCTs) that were at high risk of methodological bias and included a total of 278 patients. Therefore, the authors concluded that future RCTs were needed. Given the equivocal differences in outcomes, the

use of basiliximab has increased likely due to the favorable side effect profile that is generally well tolerated by most patients and the possibility, given the above data, that an induction agent could improve long-term outcomes.

ATG and alemtuzumab can cause profound myelosuppression and infusion-related reactions due to cytokine release, which tends to be more severe with ATG. There is also concern that both agents might increase the risk of malignancy based on studies from kidney transplantation, although the data are conflicting (29,30). The allure of alemtuzumab is based on study protocols that have used decreased doses of maintenance immunosuppression (12,18,20). This is especially appealing as it would allow the use of decreased doses of CNI, which are known to be nephrotoxic. However, since 2012, alemtuzumab has been newly marketed for use in multiple sclerosis (Lemtrada®) (8) and is otherwise available on a limited basis, which may be a reason for its recent decline in use. Although the use of induction agents in lung transplantation has increased, large randomized controlled trials will need to be performed to clearly assess the benefits and harms before induction agents become universal.
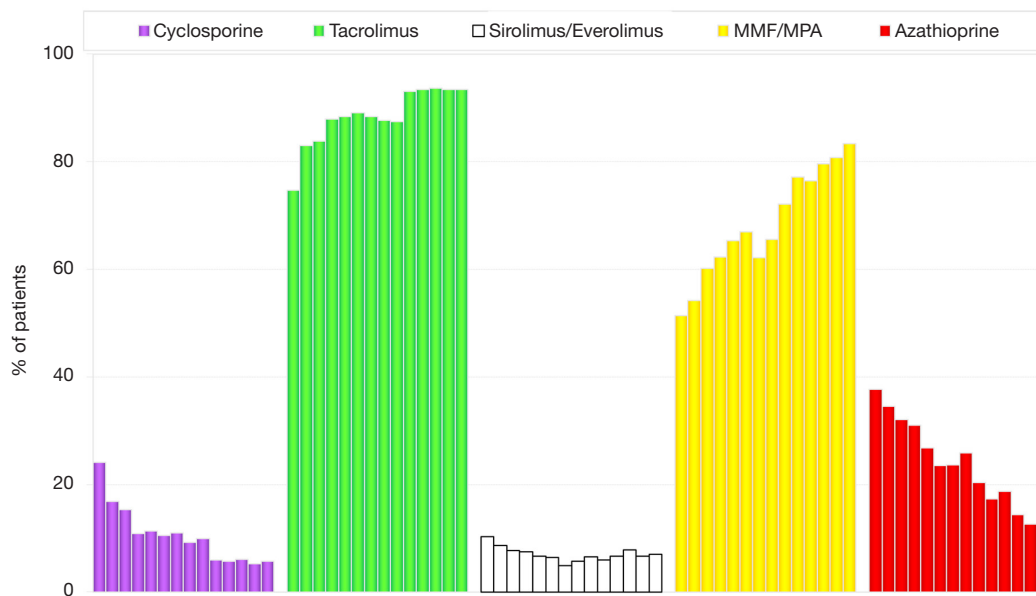
Figure 2 Maintenance immunosuppression as a percentage for all adult lung transplantation at 1-year follow-up reported to the International Society of Heart and Lung Transplantation registry database. Each bar represents the one-year follow up from 2004 to 2017. Included patients were those who were on prednisone and were alive at 1-year follow-up. MMF/MPA, mycophenolate mofetil/mycophenolic acid. Reproduced from (2).

At Loyola, our preference is to use basiliximab for induction immunosuppression. This is based on (I) experience with the agent, (II) tolerability of the medication, (III) evidence of its benefits in reducing acute lung rejection which has been linked to early onset of CLAD (31), and (IV) improved long-term survival as evidenced using the ISHLT registry database (2). The main contraindication to induction therapy is high risk for infection, including cytomegalovirus (CMV) in cases with CMV antibody primary mismatch (positive CMV donor, negative CMV recipient). The first dose of basiliximab is given perioperatively and a second dose is given on post-operative day 4. Overall, until large RCTs are able to clearly assess benefits versus harms of the induction agents and delineate an immunosuppressive regimen, transplant physicians should weight the risk of rejection with the risk of the complications and toxicities associated with the inducting agent in order to improve the long-term outcomes of lung transplantation.

Maintenance immunosuppression

The purpose of maintenance immunosuppression after lung transplantation is to prevent acute and chronic rejection.

This is delicately balanced by the need to prevent adverse side effects, infectious complications, and the risk of malignancy from the immunosuppressives. Conventional maintenance immunosuppression has been triple drug therapy and most commonly includes a CNI (tacrolimus or cyclosporine), an antiproliferative agent (mycophenolate or azathioprine), and corticosteroids. According to the 2018 International Society for Heart and Lung Transplantation (ISHLT) registry database report, the most commonly used combination at 1-year follow-up is one including tacrolimus, mycophenolate, and corticosteroids (2). The use of cyclosporine and azathioprine has seen a steady decline in the last decade while the introduction of mammalian target of rapamycin (mTOR) inhibitors and a co-simulation blocker have emerged to aid in maintenance immunosuppression for those who do not tolerate a conventional regimen (*Figure 2*; see also *Table 2* for available maintenance immunosuppression agents).

CNIs

Since FDA approval of cyclosporine in 1983 and then tacrolimus in 1997, CNIs have become the backbone of conventional maintenance immunosuppression although

Table 2 Maintenance immunosuppression in lung transplantation

Agent	Mechanism	Adverse effects	Additional notes
Calcineurin inhibitors			
Tacrolimus [Prograf® (32), Envarsus XR®, Astagraf XL®]	Forms a complex that inhibits the phosphatase activity of calcineurin, preventing transcription of cytokines; leads to decreased activation and proliferation of T lymphocytes	Nephrotoxicity, neurotoxicity including posterior reversible encephalopathy syndrome, hyperglycemia, hypertension, hyperlipidemia, hyperkalemia, tremor	Possible association with hyperammonemia; see text regarding aerosolized forms
Cyclosporine [Neoral® (33), Gengraf®, Sandimmune®]			
Anti-metabolites			
Mycophenolate mofetil [MMF, Cellcept® (34)]; Enteric-coated Mycophenolate sodium [EC-MPS, Myfortic® (35)]	Noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase which inhibits the *de novo* pathway of guanosine nucleotide synthesis	Gastrointestinal symptoms including abdominal pain, nausea, vomiting, diarrhea; neutropenia, anemia, thrombocytopenia	Cellcept® doses and Myfortic® doses are not interchangeable
Azathioprine [Imuran® (36)]	Metabolized to 6-mercaptourine which is then incorporated into DNA and blocks the *de novo* and salvage pathways of purine syntheses	Neutropenia, anemia, thrombocytopenia, pancreatitis, hepatotoxicity	Consider genotyping and phenotyping for TPMT and NUDT15 as low levels increase risk for severe myelosuppression
mTOR inhibitors			
Everolimus [Zortress® (37)]	Binds to and forms a complex with immunophilin FK506-BP12 that binds mTOR and inhibits progression of the cell cycle from G1 to S phase; decreases activation and proliferation of T lymphocytes.	Delayed wound healing, neutropenia, anemia, peripheral edema, dyslipidemia, TMA/TTP/HUS, hyperglycemia, stomatitis/mouth ulcer, interstitial lung disease, pneumonitis, venous thromboembolism	Increased risk for anastomotic dehiscence if given early post-transplant
Sirolimus [Rapamune® (38)]			
Co-stimulation blocker			
Belatacept [Nulojix® (39)]	Blocks CD28 mediated co-stimulation of T lymphocytes by binding to CD80 and CD86 on antigen-presenting cells; inhibits T cell proliferation and cytokine production	Anemia, diarrhea, peripheral edema, hypertension, fever, hypokalemia, hyperkalemia, neutropenia, PTLD, PML	Use in EBV seropositive transplant recipients only; contraindicated in EBV seronegative or unknown EBV serostatus due to increased risk for PTLD

Brand names are those available in the USA. EBV, Epstein-Barr virus; HUS, hemolytic uremic syndrome; NUDT15, nucleotide diphosphatase; PML, progressive multifocal leukoencephalopathy; PTLD, post-transplant lymphoproliferative disease; TMA, thrombotic microangiopathy; TPMT, thiopurine S-methyltransferase; TTP, thrombotic thrombocytopenic purpura.

neither medication is currently FDA approved specifically for lung transplantation. Cyclosporine binds to intracellular cyclophilin in T lymphocytes and tacrolimus binds to intracellular FKBP-12, both of which form a complex that inhibit the phosphatase activity of calcineurin, preventing transcription of cytokines such as IL-2, leading to decreased activation and proliferation of T lymphocytes (32,33). Tacrolimus is more often used in maintenance immunosuppression, as most studies have shown an improvement in incidence of acute rejection and long-term outcomes including a reduced risk for CLAD as compared to cyclosporine (40-44). In one of the largest RCTs comparing tacrolimus to cyclosporine in addition to mycophenolate and corticosteroids, Treede *et al.* showed that the use of tacrolimus resulted in a lower 3-year cumulative incidence of CLAD compared to cyclosporine

(11.6% vs. 21.3%, P=0.037) (45). However, survival between the two groups at 1- and 3-year was not significantly different. Similarly, a 2013 Cochrane Review which included three RCTs of 413 patients showed that tacrolimus was superior to cyclosporine in incidence of CLAD and lymphocytic bronchitis score but there was no difference in mortality or incidence of acute rejection (46).

While acute and chronic rejection may be improved with tacrolimus, there may be other factors that affect survival including drug-related side effects such as nephrotoxicity. In this regard, new formulations including aerosolized CNIs, mixed formulation regimens including an initial intravenous bolus plus oral CNIs, and extended release CNIs have been reported (47-50). Although these formulations and regimens show promise, larger RCTs will need to clearly show benefit before they are uniformly adopted. Interestingly, the most recent ISHLT registry data set shows both improved 1-year survival and 1-year rejection rate for patients receiving tacrolimus versus cyclosporine (2). Moreover, within several of the studies previously cited, patients were transitioned to tacrolimus from cyclosporine to treat ongoing rejection. For these reasons, tacrolimus is the first-line CNI for maintenance immunosuppression at Loyola. Cyclosporine is mainly used if patients are not able to tolerate tacrolimus.

Anti-metabolites

Mycophenolate is metabolized to mycophenolic acid, which inhibits inosine-5'-monophosphate dehydrogenase preferentially in T and B lymphocytes. This prevents *de novo* guanosine nucleotide synthesis through depletion of guanosine and deoxyguanosine nucleotides, inhibiting proliferation and activation (51). Azathioprine is a pro-drug of 6-mercaptopurine (6-MP), which is converted into several compounds that block both the *de novo* and salvage pathway syntheses of purine, preventing T- and B-cell proliferation (52). Caution must be used in patients on xanthine oxidase inhibitors such as allopurinol as xanthine oxidase is responsible for the conversion of 6-MP into its metabolites, possibly leading to profound bone marrow suppression. In addition, patients with low or absent thiopurine or methyltransferase activity are at increased risk of azathioprine associated myelosuppression (53).

Early reports favored mycophenolate over azathioprine in regards to acute rejection (54,55) but subsequent studies have been conflicting, showing similar incidence in acute rejection, survival and CLAD (56-58). Mycophenolate is used more often as it is likely more tolerable to patients.

McNeil *et al.* found that although acute rejection, CLAD, and survival at 3 years was similar between patients on mycophenolate and azathioprine, more patients discontinued azathioprine (59.6% vs. 46.5%, P=0.02) (57). Moreover, there is evidence that mycophenolate offers benefit in patients with existing CLAD (59) and switching from azathioprine to mycophenolate has been associated with a reduced incidence of cutaneous squamous cell carcinoma (60). There have not been any prospective, randomized trials comparing mycophenolate to azathioprine in patients on tacrolimus. At Loyola, mycophenolate is first-line therapy while azathioprine is used only in patients who do not tolerate mycophenolate.

Corticosteroids

Corticosteroids suppress multiple inflammatory genes leading to a decrease in T cell proliferation, decrease in macrophage activation, inhibition of cytokine production and altered lymphocyte migration (61). Corticosteroids are a foundation of maintenance immunosuppression. Although there have been a few reports of successful steroid withdrawal in patients with stable pulmonary function tests after a mean duration of more than 2 years post lung transplantation (62,63), it is currently not recommended to discontinue steroid therapy, and at Loyola we do not completely stop steroid therapy, instead reducing the prednisone dose after 1 year down to 5 mg daily in men and 2.5 mg daily in women.

mTOR inhibitors

Sirolimus and everolimus bind to intracellular immunophilin FK506-BP12 forming a complex that binds to mTOR, a signaling pathway necessary to promote progression of the cell cycle from G1 to S phase, thus decreasing activation and proliferation of T lymphocytes (52). The role of mTOR inhibitors continues to be defined and, both sirolimus and everolimus have been used as an alternative to anti-metabolites (64,65), to decrease CNI doses and therefore, their nephrotoxic effects (66-72), prevention of cancers in those at high-risk, and for the prevention (73,74) and treatment (75-77) of CLAD. However, data on improvement of renal function is equivocal as the early benefits provided by mTOR inhibitors may be lost long-term in lung transplantation (68,71). Moreover, the timing of initiation still needs to be clarified as most studies converted to an mTOR based immunosuppressive

strategy 3 months to 1 year post transplantation given the catastrophic side effect of decreased wound healing and anastomotic dehiscence (78,79). In addition, mTOR inhibitors have many other adverse effects including increased risk of interstitial lung disease (71,80,81) and venous thromboembolism (82) as well as increased risk for infections and metabolic disorders reported in previous studies, often times leading to discontinuation. Currently, mTOR inhibitors are used in a small percentage of lung transplant patients (2), and at Loyola, are considered months or years after the transplant as a renal-sparing strategy, if skin cancers become prolific or problematic, or if patients are not able to tolerate either of the CNIs or either of the anti-metabolites.

Co-stimulation blocker

Belatacept inhibits T cell proliferation and cytokine production by blocking CD28 mediated co-stimulation of T lymphocytes (39). Belatacept has improved graft survival when replacing CNIs in adult kidney transplantation (83,84). However, evidence for its use in lung transplantation is sparse and its role may be as a replacement of CNIs in patients who are intolerant of either tacrolimus or cyclosporine or as a renal-sparing agent (85,86). As with most of the immunosuppressive regimens in lung transplantation, carefully done clinical trials are needed to identify the benefits and timing before its use becomes common. Belatacept is contraindicated in Epstein-Barr virus seronegative patients or in those with unknown status due to the 9-fold increase in post-transplant lymphoproliferative disease found in kidney transplant trials (39).

Adjunctive therapies

Although not considered immunosuppressive therapy, azithromycin and statins can be used as adjunctive therapy on a case by case basis to improve long term outcomes including as prophylactics against CLAD. Azithromycin is a macrolide antibiotic with anti-inflammatory, immunomodulatory, and pleiotropic effects (87) in addition to its antibacterial activity, and it has been used successfully as a part of maintenance therapy in lung transplant patients with CLAD, providing stabilization or improvement in lung function (88-98). Responders to azithromycin therapy were those with higher bronchoalveolar lavage neutrophil count and interleukin-8 protein levels (91,92,94). Given

these results, a study by Vos et al. demonstrated a decrease in CLAD with azithromycin therapy compared to placebo (12.5% vs. 44.2%, P=0.0017) and increased CLAD-free survival (HR 0.27; 95% CI, 0.092–0.816; P=0.020), both 2 years after lung transplantation (99). The beneficial effects of azithromycin were sustained even after reevaluation through post-hoc analysis of the same study after the classification system for CLAD had been updated (100). Azithromycin should be considered in patients with high BAL neutrophilia and/or IL-8 protein levels. Since it is quite well tolerated, some programs initiate azithromycin soon after transplant, even in the absence of such indicators.

Statins are hydroxy-3-methylglutaryl coenzyme A reductase inhibitors used for lowering lipid levels. However, they have other immunomodulatory effects that may improve long-term outcomes after lung transplantation. Johnson et al. compared 39 patients on statins for treatment of hyperlipidemia to 161 control patients not on statin therapy (101). The incidence of biopsy proven acute rejection grade 2 or higher was less in the statin group (15.1% vs. 25.6%, P<0.01). Fifteen patients started on a statin within the post-transplant year one did not develop CLAD whereas 37% in the control group did (P<0.01). Finally, the 6-year survival was greater in the statin group (91% vs. 54%, P<0.01). Similarly, Li et al. used a propensity score analysis comparing 75 lung transplant patients on pravastatin to 340 control patients not on statin therapy (102). Their findings included improvement in survival, maintenance of graft function, and a delay of the onset of CLAD in the pravastatin group. These findings will need to be confirmed with large RCTs, but these studies show promise.

Other considerations

Throughout the first year post lung transplantation, patients require a plethora of medications in addition to immunosuppressives, especially if there were other preoperative comorbid conditions. That said, the pharmacokinetic and pharmacodynamic properties must be reviewed carefully for each patient, as many of the immunosuppressives (including tacrolimus, cyclosporine, sirolimus, and everolimus) have narrow therapeutic indices that are affected by medications that modulate enzymes of drug metabolism. Frequent therapeutic drug monitoring and a knowledge of the effects of commonly used medications in lung transplantation is necessary to

help tailor immunosuppressive regimens. This is especially apparent in patients with cystic fibrosis who have increased volumes of distribution, decreased plasma concentration, and enhanced renal and nonrenal elimination of drugs as well as variable gastrointestinal absorption of medications (103). Given these factors and the complexity of drug-drug interactions, the transplant pharmacist plays a vital role as part of the multidisciplinary team and is a key to improving patient outcomes (104).

Closely related to the pharmacokinetics and pharmacodynamics of medications is the field of pharmacogenetics and pharmacogenomics. Simply, pharmacogenetics refers to how single genes and their polymorphisms altar the effect of a drug and pharmacogenomics refers to how the individual's whole genome affects the action of a drug (105), both of which contribute to the interindividual variable response to drug regimens. Within lung transplantation, Burckart *et al.* has provided an excellent review of specific gene polymorphisms such as CYP3A5 and ABCB1 as well as biomarkers that have had clinical implications (106). As an example, Zheng *et al.* studied polymorphisms in cytochrome P4503A and found that lung transplant recipients who were CYP3A5*1 expressors had an increased tacrolimus dose requirement compared to CYP3A5*3 nonexpressor genotypes (107). As additional gene polymorphisms and biomarkers are discovered, pharmacogenetics and pharmacogenomics hold the promise of drug individualization that is tailored to each specific patient with the hopes of improving their long-term outcomes.

Infection is common in lung transplantation and remains a significant cause of death throughout the lifetime of the recipient (2). Two assays, the ImmuKnow® immune cell function assay and an assay that measures plasma IFN-γ have been developed to assess the global immune competence of the immunosuppressed host. Neither test correlates well with immunosuppression drug levels, but there was a correlation between low levels of global immune function and increased infectious risk and high levels correlated with rejection (108-112). However, the data is conflicting regarding the sensitivity of identifying infectious risk and the ImmuKnow® assay has poor specificity. No prospective, randomized trials have been performed utilizing these assays to modify immunosuppression doses. Clinical utility of these assays may be best used to serially monitor patients who have had recurrent infections.

Conclusions

The number of lung transplants performed continues to increase with improved median survival since the advent of successful lung transplantation in 1983. However, overall survival is impeded by acute rejection, CLAD, infections, and comorbidities, as a result of the adverse effects of immunosuppressive therapy. Transplantation physicians optimize current available therapy to each individual patient but challenges and questions regarding the optimal immunosuppressive strategy remain. Although large randomized trials may help to identify the ideal immunosuppressive regimen for the adult lung transplant population, further research is needed to grow the immunosuppressive armamentarium and develop clinical tools to individualize therapy. Thus, the future direction of immunosuppressive strategies should consider the interindividual variability in response to drug regimens to improve the long-term success of lung transplantation.

Footnote

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