Immunosuppression in lung transplantation: a narrative review

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Background and Objective: Lung transplantation has grown as a treatment option for patients with end stage lung disease. Unfortunately, median survival for lung transplant recipients remains low at 6.7 years. Acute rejection and chronic lung allograft dysfunction (CLAD) are among the main challenges to graft function and overall survival. Immunosuppression is utilized to reduce the rate of rejection, and can be utilized as a treatment for acute rejection and CLAD. The purpose of this review is to describe the immunosuppressive agents used in lung transplantation for induction therapy, maintenance therapy, and prevention of both acute and chronic allograft rejection.

Methods: PubMed was searched using keywords including "lung transplantation, immunosuppression, induction, maintenance" from January 1985 to June 2022. Systematic reviews, randomized clinical trials, retrospective and cross-sectional studies, case series, and some animal studies were considered for inclusion in this review, with no language restrictions.

Key Content and Findings: Immunosuppressive strategies may begin with induction therapy, which typically includes agents such as basiliximab, anti-thymocyte globulin (ATG), or alemtuzumab, in addition to high dose corticosteroids. Maintenance immunosuppression typically consists of a calcineurin inhibitor (CNI), antiproliferative agent, and corticosteroids. Numerous adjunctive agents have been evaluated for prevention and treatment of rejection, particularly CLAD, though robust data supporting use of these agents is limited.

Conclusions: Immunosuppression in lung transplantation remains crucial for prevention and treatment of acute and chronic rejection, which continue to represent significant sources of morbidity and mortality in this population. Induction and maintenance immunosuppression strategies vary across lung transplantation centers. Additional research is needed to better define the optimal strategies and choices of agents for immune suppression following lung transplantation.

Keywords: Lung transplantation; immunosuppression; narrative review

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Introduction

Lung transplantation has grown as a treatment option for patients with end stage lung disease. Unfortunately, in spite of improvement in survival rates over the last three decades, median survival for lung transplant recipients remains low at 6.7 years (1-3). Acute and chronic rejection are among the main challenges to graft function and overall survival in this population. Roughly 27% of patients experience an episode of treated acute rejection within the first post-transplant year, and bronchiolitis obliterans syndrome (BOS), one form of chronic lung allograft dysfunction (CLAD) continues to affect approximately 10% of patients each year (1). Restrictive allograft syndrome (RAS), the restrictive form of CLAD, is also being increasingly recognized (4). Immunosuppression is utilized to reduce

Table 1 The search terms used

("Lung Transplantation" [MeSH Terms) AND ("Immunosuppression" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Induction")
("Lung Transplantation" [MeSH Terms]) AND ("Basiliximab" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Anti-thymocyte globulin" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Alemtuzumab" [Mesh])
("Lung Transplantation" [MeSH Terms]) AND ("Alemtuzumab" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Alemtuzumab" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Maintenance")
("Lung Transplantation" [MeSH Terms]) AND ("Cylcosporine" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Tacrolimus" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Mycophenolate Mofetil" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Azathioprine" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Sirolimus" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Everolimus" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Belatacept" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Azithromycin" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Montelukast")
("Lung Transplantation" [MeSH Terms]) AND ("Statins" [MeSH Terms])
("Lung Transplantation" [MeSH Terms]) AND ("Pirfenidone")

rates of rejection, and can consist of induction therapy, in addition to maintenance therapy that typically includes a calcineurin inhibitor (CNI), antiproliferative agent, and corticosteroids. The need for induction therapy, the optimal choice of agents for induction and maintenance therapy, and the utility of adjunctive agents for preventing acute rejection or CLAD remains unclear. Consequently, practice patterns surrounding immunosuppression vary at different lung transplant centers. We will review current immunosuppressive medications that are available, the data behind their use in lung transplantation, and discuss adjunctive or novel therapies being used to improve lung transplant outcomes. We present the following article in accordance with the Narrative Review reporting checklist (available at https://ccts.amegroups.com/article/view/10.21037/ccts-21-42/rc).

Methods

Several PubMed searches were performed, using combinations of the keywords "lung transplantation, immunosuppression, induction, maintenance, basiliximab, anti-thymocyte globulin, alemtuzumab, belatacept, tacrolimus, cyclosporine, mycophenolate, azathioprine, sirolimus, everolimus, azithromycin, statins, and pirfenidone" from January 1985 to June 2022 (*Table 1*). Systematic reviews, randomized clinical trials, retrospective and cross sectional studies, case series, and some animal studies were considered for inclusion in this review. Papers were selected based on their relevance to the topic, and there were no language restrictions (*Table 2*).

Induction immunosuppression

Induction therapy utilizes intense immunosuppression in the perioperative period to reduce the risk of acute rejection that is mediated by a robust native T-cell response to the transplanted organ. Induction therapy may also aid with the reduction of doses of maintenance immunosuppression. Agents used target T-cells by causing T-cell depletion and/or disruption of T-cell activation and subsequent proliferation. The most commonly

Table 2 The search strategy summary

Items	Specification
Date of search	1/15/2021 to 6/15/2022
Databases and other sources searched	PubMed
Search terms used	See *Table 1* for details
Timeframe	1/1/1985–6/15/2022
Inclusion and exclusion criteria	Inclusion criteria: systematic reviews, randomized clinical trials, retrospective and cross-sectional studies, case series, and some animal studies. No language restrictions
	Exclusion criteria: some papers excluded due to poor quality or limited association with the review's topic
Selection process	Benjamin J. Atkinson conducted the selection, and Nirmal S. Sharma reviewed selected papers and added additional references that may have been missed.
Any additional considerations, if applicable	Some papers were identified by reviewing reference lists of relevant publications

Table 3 Agents for induction immunosuppression

Agent	Mechanism of action	Dosing	Adverse effects	Notes on use
Basiliximab	Monoclonal antibody that binds to the IL-2 receptor, preventing T-cell proliferation and differentiation	Intravenous. 20 mg at the time of implantation and on post-operative day 4	Rare hypersensitivity reactions	Most commonly used induction agent. 1st line at many centers due to side effect profile
ATG	Polyclonal immunoglobulin preparation containing antibodies to human T-cells that act through Fc receptors to deplete cytotoxic T-cells	Intravenous. Weight based dosing on day one, with 2–4 additional doses every 24 hours. Single dose regiments also described	Chills, anxiety, abdominal pain, nausea, hyperkalemia, pancytopenia, infusion reactions, immune complex mediated glomerulonephritis, serum sickness, and cytokine release syndrome	Not commonly used as 1st line therapy in lung transplantation
Alemtuzumab	Monoclonal antibody to the CD52 antigen present on all B- and T-lymphocytes. Binding causes antibody-dependent cell lysis resulting in B- and T-cell depletion	Intravenous or subcutaneous. One 30 mg dose at the time of allograft reperfusion or immediately following transplantation	Pancytopenia, insomnia, anxiety, infusion reaction, cytokine release syndrome, secondary autoimmunity	Used as 1st line therapy at some centers. Use limited by concern for prolonged immunosuppression (B-cell depletion for months, T-cell depletion for up to 3 years)

ATG, anti-thymocyte globulin; IL-2, interleukin-2.

used induction agents are basiliximab, anti-thymocyte globulin (ATG), and alemtuzumab (*Table 3*) (1). High dose corticosteroids are often used intraoperatively, just before perfusion of the lung allograft, in order to reduce the risk of reperfusion injury. While the use of corticosteroids is not generally thought to be a part of induction therapy, there is likely some contribution to initial immunosuppression. Not all centers utilize induction therapy. However, most recent registry data from the International Society for Heart and Lung Transplantation (ISHLT) indicates that the proportion of patients receiving induction immunosuppression has steadily risen, with 80% of patients who underwent transplantation in 2017 receiving any form of induction (1). Slightly over 70% of

patients who received induction therapy received an IL-2 receptor antagonist (IL-2RA) such as basiliximab, with other patients receiving ATG or alemtuzumab.

Basiliximab and daclizumab are chimeric murine/human monoclonal antibodies to the alpha subunit of the interleukin-2 (IL-2) receptor alpha chain, specifically binding to the CD25 antigen on activated T-lymphocytes (5,6). This prevents IL-2 mediated T-cell proliferation and differentiation, however, does not result in T-cell depletion. Daclizumab was removed from the US market in 2009 due to the development of several cases of severe, often fatal, inflammatory brain diseases, so basiliximab remains the only IL-2RA available for clinical use at this time. Basiliximab is administered intraoperatively or within two hours after transplantation, with a second dose typically given on post-operative day four. It is generally well tolerated, with no increase in adverse advents compared to placebo in clinical trials (3).

ATG is a polyclonal immunoglobulin preparation created from horses (equine ATG, ATGAM©) or rabbits (rATG, Thymoglobulin©) that contains antibodies against human T-cells (7,8). These antibodies act through Fc receptors and additional proteins on T-cell surfaces to deplete cytotoxic T-cells. ATG has also been shown induce B-cell apoptosis, modulate molecules that impact interaction of leukocytes and the endothelium, impact dendritic cell function, and induce regulatory T-cells and NK cells (9). ATG is administered using weight-based dosing starting on day one, often intraoperatively. Two to four additional doses are typically given every 24 hours, though single dose regimens have been described. Premedication with glucocorticoids, antihistamines and antipyretics is frequently used to prevent or reduce infusion related symptoms. Common adverse effects of ATG include chills, anxiety, abdominal pain, nausea, hyperkalemia, leukopenia, and thrombocytopenia. More serious adverse reactions, including infusion reactions, immune complex mediated glomerulonephritis, serum sickness, and cytokine release syndrome have also been reported (7,8).

Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody directed against the CD52 antigen present on all B- and T-lymphocytes (10). The use of this agent results in antibody-dependent cell lysis, and can cause sustained T-cell depletion for up to 3 years, and B-cell depletion for up to several months (11). Alemtuzumab also results in the depletion of monocytes, macrophages, and some subsets of dendritic cells, all of which express CD52, and impacts additional immune cell maturation resulting in a tolerogenic immune environment (12). Alemtuzumab is given as a single intravenous or subcutaneous injection at the time of organ reperfusion or immediately following transplantation. Common adverse reactions include infusion reactions, lymphopenia, infection, and secondary autoimmune disease, most notably thyroid disease. Less common, but more serious adverse reactions include cytokine release syndrome and prolonged pancytopenia (10).

Overall, an increasing proportion of patients undergoing lung transplantation receive induction therapy, with most patients using an IL2RA compared to ATG or alemtuzumab. For example, slightly over 70% of patients received an IL2RA for induction in 2017 (1). While data for induction therapy in lung transplantation consists largely of retrospective studies or small prospective trials, there is suggestion that induction reduces rates of acute rejection, and may improve long term survival (13-24). The most robust data in favor of induction can be found in retrospective trials of large transplant registries. Whitson *et al.* evaluated 12,858 patients from the United Network for Organ Sharing (UNOS) Registry, and found that induction therapy with basiliximab, alemtuzumab, or ATG improved overall survival when compared to no induction (median survival 71.3 *vs.* 63.2 months, P<0.001) (20). Additionally, a composite end point of treatment for rejection or death within the first year was significantly lower in the induction cohort compared to no induction (37% *vs.* 42%, P<0.001). Hachem *et al.* performed a retrospective cohort study of 3,970 patients from the ISHLT Registry and found that four year graft survival rates were better in patients who received induction with an IL-2RA or ATG compared to those who received no induction (64% and 60% *vs.* 57%, P=0.0067) (16). Rates of rejection were also decreased with IL-2RA and ATG therapy. There is some data suggesting that induction therapy may also have an impact on crucial long-term outcomes, such as CLAD. Furuya *et al.* reviewed 6,117 patients from the UNOS Registry, and found that induction therapy with basiliximab or alemtuzumab improved survival compared to no induction, and patients receiving alemtuzumab had a lower incidence of BOS at 5 years compared to no induction (22.7% *vs.* 55.4%, P<0.001) (19).

Prospective data regarding the use of induction therapy has been more mixed (13,25-29). Palmer *et al.* randomized 44 patients undergoing lung transplant to induction therapy with ATG or no induction, and found that grade II or greater acute rejection was less common in the ATG group (23% *vs.* 55%, P=0.03) (13). On the

other hand, in a double blind, placebo-controlled trial of induction with ATG compared to no induction, Snell *et al.* found no difference in rates of death, graft loss, or acute rejection at one year. It is worth noting, however, that the protocol used in this study featured a single dose of ATG instead of a more traditional protocol utilizing additional doses of ATG on post-operative days 2–4 (29). Penninga *et al.* conducted a systematic review of six randomized controlled trials representing 278 patients who received either ATG, IL-2RA or muromonab-CD3, a monoclonal antibody to CD3 found on T-cells, and found no difference in mortality, acute rejection, or BOS with induction compared to no induction (28).

A major concern surrounding the use of induction therapy is the risk of complications, most notably post-transplant infection and malignancy. Some of the larger retrospective studies available did not evaluate these complications with induction, however, when reviewing the ISHLT Registry, Hachem *et al.* noted an increased incidence of early treated infection with IL-2RA and ATG when compared with no induction (45% and 43% *vs.* 38%, P<0.005) (16). In Furuya *et al.*'s UNOS registry review, a non-cytomegalovirus (CMV) infectious cause of death was more common in patients receiving alemtuzumab induction compared to basiliximab induction or no induction (29.9% *vs.* 20.8% *vs.* 22.3%, P<0.001). Alemtuzumab recipients were also more likely to have post-transplant lymphoproliferative disorder (PTLD) (4.5% *vs.* 0.4% basiliximab *vs.* 1.5% no induction, P<0.001) and other malignancies (9.0% *vs.* 6.2% basiliximab *vs.* 5.1% no induction, P<0.001) as a cause of death (19). However, the majority of retrospective studies have failed to demonstrate an increased risk of infection or malignancy with either IL-2RA, ATG, or alemtuzumab induction (14,15,18,22,30). Prospective studies have also failed to show an increased risk of these adverse outcomes with induction (13,26-29). Snell *et al.* noted a higher adverse event rate in patients treated with ATG, particularly high dose ATG, when compared to placebo, however, there was no significant difference in rates of infection or malignancy (29). In Penninga *et al.*'s systematic review, induction therapy was not associated with any increased risk of infection, pneumonia, CMV infection, PTLD or cancer when compared to no induction (28).

Data comparing induction agents is limited and primarily retrospective, but several studies seem to favor IL-2RAs compared to ATG (31-33). Ailawadi *et al.* reviewed 163 consecutive lung transplant patients at the University of Virginia who received either ATG or daclizumab, and found that patients that received daclizumab experienced significantly less acute rejection, BOS, and death compared to ATG (31). In a small study of 37 patients receiving ATG or basiliximab for induction, acute rejection rates were similar, however, survival was 20% higher in the basiliximab group (32). However, conflicting data does exist. In a review of 157 patients from Hachem *et al.*, when comparing basiliximab to ATG, basiliximab patients were more likely to develop acute rejection of grade A2 or more, and were more likely to develop BOS at 2 years (36% *vs.* 26%, P=0.036) (34). Though alemtuzumab is not commonly used for induction therapy at this time, there is some data that suggests alemtuzumab may lead to reduced rates of acute rejection and potentially BOS (30,35-38). Shyu *et al.* reviewed 336 patients from a single center and found that five year patient and graft survival was significantly better in patients receiving induction with alemtuzumab (59%/59%) compared to ATG induction (60%/44%), daclizumab induction (44%/41%), and no induction (47%/46%) (30). Alemtuzumab patients also demonstrated improved 5-year freedom from acute cellular rejection (ACR), obliterative bronchiolitis, and BOS. Furukawa *et al.* retrospectively reviewed 807 lung transplants performed at a single center, of which 453 underwent alemtuzumab induction and 354 underwent basiliximab induction (38). Compared to basiliximab induction, alemtuzumab induction was associated with decreased rates of grade 3 primary graft dysfunction within 72 hours (19.9% *vs.* 29.9%, P=0.002), ACR in the first year (39.1% *vs.* 53.4%, P<0.001), and improved rates of survival at 5 years (64.1% *vs.* 52.3%, P<0.001). However, the basiliximab group had notably higher risk patients, with a significantly higher number of patients with a history of pulmonary fibrosis, HIV, hepatitis C, cancer, CMV positivity and CMV mismatch. In a prospective, open label, randomized controlled trial, Jaksch *et al.* randomized 60 patients to induction therapy with alemtuzumab or ATG, and found that alemtuzumab was associated with fewer episodes of ≥ A2 ACR within the first year compared to ATG (0 *vs.* 5, P=0.019) (36). There was no difference in survival, lymphocytic bronchiolitis, infection or BOS between the two groups. A meta-analysis by of six studies including 595 patients by Li *et al.* showed that alemtuzumab was associated with lower odds of ACR compared to ATG, and lower rates of acute rejection and infection when compared to basiliximab (39).

Overall, given the lack of prospective data available, it is clear that large randomized controlled trials will be needed to better clarify the utility of induction therapy, the risks associated with induction, and the optimal agent to be used

Table 4 Agents for maintenance immunosuppression

Agent	Mechanism of action	Dosing	Adverse effects	Notes on use
Calcineurin inhibitors				
Tacrolimus	Macrolide antibiotic that binds to intracellular FK-binding proteins. Drug-receptor complex inhibits calcineurin, which decreases cytokine production, and subsequent activation and proliferation of T-lymphocytes	Oral, sublingual, or intravenous. Dosed by drug level, with goal trough concentrations of 5–15 ng/mL	Tremor, headache, neuropathy, seizures, hypertension, hyperlipidemia, nephrotoxicity, hyperkalemia, hypomagnesemia, diabetes, PRES, TMA	1st line therapy at most centers. 10–100 times more potent than cyclosporine. Higher rates of neurotoxicity and diabetes compared to cyclosporine
Cyclosporine	Lipophilic peptide that binds to intracellular FK-binding proteins. Drug-receptor complex inhibits calcineurin, which decreases cytokine production, and subsequent activation and proliferation of T-lymphocytes	Oral (modified and non-modified), intravenous. Dosed by drug level: goal trough 100–450 ng/mL, goal 2-hour post-dose 800–1,400 ng/mL	Tremor, headache, neuropathy, seizures, hypertension, hyperlipidemia, nephrotoxicity, hyperkalemia, hypomagnesemia, diabetes, PRES, TMA	2nd line therapy at most centers. Used for patients unable to tolerate tacrolimus
Antiproliferatives				
Mycophenolate	Reversible inhibitor of inosine monophosphate dehydrogenase, decreasing purine synthesis and their B- and T-lymphocyte proliferation	MMF: Oral, intravenous. 1,000–1,500 mg twice daily. MPS: Oral. 720–1,080 mg twice daily (oral formulation only)	Pancytopenia, nausea, abdominal pain, diarrhea	1st line therapy at most centers
Azathioprine	Metabolized to 6-MP, which produces compounds that interfere with purine synthesis resulting in a decrease in production of B- and T-lymphocytes	Oral, intravenous. 2 mg/kg daily (50–150 mg/day)	Pancytopenia, hepatotoxicity, pancreatitis	2nd line therapy. Excess toxicity can occur when used with xanthine oxidase inhibitors (i.e., Allopurinol), or in patients with low or absent TPMT activity
mTOR inhibitors				
Sirolimus and everolimus	Bind to FK binding protein, inhibiting mTOR, causing arrest of the cell cycle in the G1-S phase and preventing cell cycle progression and lymphocyte proliferation	Sirolimus: Oral. Dosed by drug level, goal trough 5–13 ng/mL. Everolimus: Oral. Dosed by drug level.	Pancytopenia, hyperlipidemia, hyperglycemia, impaired wound healing, pneumonitis, venous thromboembolism.	Can be used as adjunct to conventional immunosuppression to limit toxicity of those agents. Due to complications of airway dehiscence, initiation must be delayed until 3 months after transplantation

PRES, posterior reversible encephalopathy syndrome; TMA, thrombotic microangiopathy; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; mTOR, mammalian target of rapamycin; TPMT, thiopurine-S-methyltransferase.

for induction.

Maintenance

Maintenance immunosuppression is lifelong therapy after lung transplantation that is used to prevent acute and chronic rejection. There is additional focus on preventing side effects, which can include nephrotoxicity, cytopenias, infection and malignancy. Typically, maintenance immunosuppression regimens consist of a CNI, antiproliferative agent, and corticosteroids (*Table 4*). Previously, cyclosporine and azathioprine were used along

with prednisone, however, the use of these two agents has decreased over the last several years. According to 2019 ISHLT registry data, the most commonly used maintenance regimen was tacrolimus, mycophenolate mofetil/mycophenolic acid (MMF/MPA), and prednisone (1). Mammalian target of rapamycin (mTOR) inhibitors have also emerged, and have been used as adjunctive agents for maintenance immunosuppression.

CNIs

CNIs have served as the backbone for conventional immunosuppression in solid organ transplant for over 25 years. The primary agents available are cyclosporine and tacrolimus. Cyclosporine is a lipophilic peptide that binds to cytoplasmic proteins called cyclophilins, while tacrolimus is a macrolide antibiotic that binds intracellular FK-binding proteins. In both cases, the drug-receptor complex that is formed in T-lymphocytes subsequently binds and inhibits calcineurin, a phosphatase needed to activate transcription factors for cytokines such as IL-2 and TNF-alpha. By inhibiting this cytokine production, cyclosporine and tacrolimus decrease activation and proliferation of T-lymphocytes (40-42).

Cyclosporine is available in intravenous formulation and two oral formulations, non-modified (Sandimmune©) and modified (Neoral©) (41,42). Absorption of non-modified cyclosporine is dependent on bile, so can exhibit variable gastrointestinal absorption patterns and therefore bioavailability. Modified cyclosporine is a microemulsion formula that does not depend upon bile salts for absorption and therefore exhibits more consistent absorption and increased bioavailability. Both oral formulations can be used but should not be considered to be interchangeable (43). Dosing of cyclosporine varies between centers but is typically done using trough or 2-hour post-dose drug levels. Generally, target trough levels range from 100–450 ng/mL, while target 2-hour post-dose levels range from 800–1,400 ng/mL. Target levels may be influenced by time from transplantation, with centers often targeting higher levels in the first 12 months after transplantation. The major side effects of cyclosporine include neurotoxicity (tremor, headache, neuropathy, seizures), hypertension, hyperlipidemia, nephrotoxicity (acute and chronic), electrolyte derangements (hyperkalemia, hypomagnesemia), diabetes, and hirsutism. Rare but serious side effects include posterior reversible encephalopathy syndrome (PRES) and thrombotic microangiopathies (41,42).

Tacrolimus is 10–100 times more potent than cyclosporine, and is available in intravenous and oral formulations (40). Tacrolimus is not currently available as an oral suspension, however, sublingual administration can be utilized at reduced doses. Extended release formulations of tacrolimus also exist, and are currently approved for immunosuppression following kidney transplantation (44). There is limited data for use of extended release tacrolimus in lung transplant patients, however, safety data has been promising, and there are several trials evaluating its efficacy compared to immediate release tacrolimus currently ongoing (45,46). Tacrolimus dosing is dosed based on drug level, with most centers targeting trough concentrations from 5–15 ng/mL. Many centers adjust target trough levels based on time from transplantation, with higher targets utilized during the first 12 months. Tacrolimus has similar adverse effects to cyclosporine, with some data suggesting increased rates of neurotoxicity and diabetes with tacrolimus (40).

Data evaluating tacrolimus and cyclosporine in the lung transplant population is limited to small prospective trials and retrospective studies (47-56). Overall, data suggests that tacrolimus is more efficacious than cyclosporine, with lower rates of acute and chronic rejection in several studies, though limited data suggesting differences in mortality when using these two agents. In a systematic review including 413 lung transplant patients from 3 prospective trials, Penninga *et al.* found that tacrolimus use was associated with lower rates of BOS, lymphocytic bronchitis and hypertension when compared to cyclosporine. There were no differences in survival, acute rejection, infection or malignancy (54). A meta-analysis of 297 patients from 3 randomized controlled trials by Fan *et al.* also showed no difference in mortality at 1 year, however, noted lower rates of acute rejection and a trend toward decreased BOS in patients treated with tacrolimus compared to cyclosporine (52). In an open label trial of 249 lung transplant recipients, Treede *et al.* found that tacrolimus use was associated with decreased incidence of BOS at 3 years when compared with cyclosporine, though rates of mortality and acute rejection were similar in both groups (53). Erdman *et al.* retrospectively analyzed 25,355 lung transplant recipients from the Scientific Registry of Transplant Recipients and found that a backbone immunosuppression regimen of tacrolimus and MMF resulted in a significantly lower risk of death or graft failure at 1 year compared to cyclosporine plus MMF and cyclosporine plus azathioprine (56). There is additional data supporting the use of tacrolimus over cyclosporine in

other solid organ transplant recipients, with some studies demonstrating lower rates of 1 year mortality, graft loss and acute rejection with tacrolimus when compared to cyclosporine (57-61).

Due to the systemic toxicity associated with the use of enteral CNIs, there has been interest in the use of inhaled CNIs for prevention of acute and chronic rejection. In animal models of lung transplantation, inhaled tacrolimus has been shown to reduce histologic rejection and serum drug levels, though compelling human data has been limited to one case report (62-64). Inhaled cyclosporine has been more thoroughly evaluated in human subjects, and has shown some promise for treatment and prevention of CLAD (65-67). In a single-center, randomized, double-blind, placebo-controlled trial, Iacono *et al.* randomized 58 patients to inhaled cyclosporine plus usual care and placebo plus usual care (65). Though rates of acute rejection were similar in the two groups, survival at 3 years was improved in the cyclosporine group (3/28 patients died in the cyclosporine group *vs.* 14/30 in the control group, P=0.005). The inhaled cyclosporine group also demonstrated improved chronic rejection-free survival based on spirometric and histologic evaluation. There is no current FDA approved formulation of inhaled cyclosporine, and further studies will be needed to confirm its safety and efficacy.

Antiproliferative agents

The primary antiproliferative agents available for use in lung transplantation include azathioprine and MMF/MPA. Azathioprine is metabolized to 6-mercaptopurine (6-MP), which is further metabolized intracellularly to produce compounds that interfere with the production of adenine and guanine ribonucleotides. Reduced purine synthesis results in a decrease in production of circulating B- and T-lymphocytes, reduced immunoglobulin synthesis and decreased IL-2 secretion (68). MMF and mycophenolate sodium (MPS) are metabolized into MPA, a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase, which is required for the *de novo* synthesis of guanosine nucleotides. By decreasing purine synthesis, MMF/MPA decreases B- and T-lymphocyte proliferation and antibody production (69-71). MMF/MPA may also contribute to immunosuppression via induction of apoptosis in activated T-lymphocytes, and by suppression of adhesion molecules that aid in lymphocyte recruitment.

Azathioprine is available in intravenous and oral formulations, and target dosing is typically 2 mg/kg daily (50–150 mg/day) (68). Major side effects include significant leukopenia, anemia, thrombocytopenia, hepatotoxicity, and pancreatitis. Azathioprine must be used with caution when used along with xanthine oxidase (XO) inhibitors, most notably allopurinol. XO is responsible in part for the metabolism of 6-MP to inactive metabolites, so XO inhibitors can potentiate the activity of azathioprine and 6-MP, resulting in an increased risk of significant bone marrow suppression. 6-MP is also metabolized by the enzyme thiopurine-S-methyltransferase (TPMT), which may exhibit decreased or absent activity in certain patients with genetic polymorphisms of the TPMT gene. These patients are also at risk for significant bone marrow suppression or additional side effects with typical doses of azathioprine.

Mycophenolate is the most commonly used antiproliferative agent in lung transplantation and is available in intravenous and two different oral formulations. MMF (CellCept©) is available in intravenous and oral formulations, with target dosing of 1–1.5 g twice daily (69). MPS (Myfortic©) is only available in oral formulation, with target dosing of 720 mg twice daily (70). Doses of MMF and MPS are not interchangeable, and require adjustment when switching between formulations. Common side effects of mycophenolate include leukopenia, anemia, thrombocytopenia, and gastrointestinal symptoms, most notably abdominal pain, nausea and diarrhea.

Data on the use of antiproliferative agents in lung transplantation is limited to retrospective studies and small prospective trials (72-77). This data has been largely mixed, however, there is some suggestion of improved outcomes and tolerability profile with mycophenolate compared to azathioprine. In a prospective cohort study of 156 lung transplant recipients, Speich *et al.* found that compared to azathioprine, the use of MMF was associated with decreased incidence, severity, and recurrence of acute rejection, in addition to reduced graft loss due to BOS (76). In a prospective, open-label, randomized controlled trial of 320 patients, McNeil *et al.* found no differences in the incidence of acute rejection, BOS, and survival in patients treated with MMF or azathioprine (75). However, more patients discontinued azathioprine than MMF (59.6% *vs.* 46.5%, P=0.02), with most patients withdrawing from the azathioprine group due to a lack of therapeutic response. Earlier data also suggests that MMF may be beneficial in stabilization and lung function and prevention of BOS progression (72).

mTOR inhibitors

Due to the systemic toxicities of CNIs, most notably renal dysfunction, interest in the use of mTOR inhibitors as adjunctive immunosuppressive agents has risen over the last several years. Sirolimus and everolimus bind to the FK binding protein, forming a complex that modulates mTOR, a kinase that participates in IL-2 mediated signal transduction and lymphocyte activation. Through the inhibition of mTOR, the cell cycle is arrested in the G1-S phase, thereby blocking cell cycle progression and proliferation in lymphocytes (78,79). mTOR inhibitors are available in oral tablets and oral solutions, and notable side effects include leukopenia, anemia, thrombocytopenia, dyslipidemia, hyperglycemia, impaired wound healing, pneumonitis, and venous thromboembolism.

Sirolimus and everolimus have been evaluated in the lung transplant population with primarily retrospective reviews and small prospective studies. Some data suggests that mTOR inhibitors may be added to backbone immunosuppression in order to reduce CNI doses and therefore preserve renal function (80-83). In a prospective, open-label, randomized controlled trial, Gottlieb *et al.* randomized 130 patients to conventional immunosuppression with CNI, antiproliferative agent, and steroids and an everolimus-based quadruple low CNI regimen, with lower target tacrolimus and cyclosporine troughs. The low CNI regimen demonstrated better eGFR at 12 months compared to conventional therapy, and there were no differences between the two groups in acute rejection, CLAD, or death (83). A retrospective review of 12 randomized controlled trials evaluating the use of sirolimus and everolimus to minimize tacrolimus dosage in solid organ transplants found that including an mTOR inhibitor plus tacrolimus minimization better preserves renal function with no changes in patient survival or graft rejection rates (84). A current prospective, randomized trial is evaluating the use of alemtuzumab induction followed by low-dose everolimus and low-dose tacrolimus compared to traditional immunosuppression with typical doses of tacrolimus (24).

mTOR inhibitors are potent inhibitors of fibroblast proliferation, so there has also been interest in the use of these agents for the treatment and prevention of CLAD in lung transplant recipients. While some small studies have suggested potential benefit to mTOR inhibitors in preserving post-transplant lung function, larger studies and prospective trials have largely failed to show consistent benefit (85-94). In a randomized, double-blind clinical trial, Snell *et al.* randomized 213 BOS-free patients to everolimus or azathioprine in combination with cyclosporine and steroids, and found that change in FEV1 >15%, change in FEV1 >15% with BOS, and acute rejection were less common in everolimus group at 12 months (89). However, at 24 months, only incidence of acute rejection remained significantly lower in the everolimus group. An open label trial of 180 patients comparing use of sirolimus to azathioprine found no differences in acute rejection, chronic rejection, and graft failure at one year, with a higher rate of adverse events leading to discontinuation of sirolimus compared to azathioprine (90).

One of the major concerns regarding the widespread use of mTOR inhibitors is the development of severe, and sometimes catastrophic side effects with these agents. The use of sirolimus in the immediate post-operative period has been associated with severe wound healing complications, notably anastomotic airway dehiscence. In a prospective study of 15 lung transplant recipients receiving an immunosuppressive regimen with sirolimus, tacrolimus and prednisone, 4 patients developed significant airway complications, 3 of whom died. Similarly, in a pilot study evaluating a sirolimus-based immunosuppression regimen, 3/4 patients developed severe wound healing complications, including 2 patients developing bronchial airway dehiscence, resulting in 1 death (95,96). Consequently, the use of mTOR inhibitors has largely been limited to 3 months after initial transplantation. Sirolimus and everolimus have been associated with additional adverse reactions, notably interstitial pneumonitis and lung disease, and venous thromboembolism (97-99). Further data will be needed to clarify the safety of mTOR inhibitors, and to better delineate their role in lung transplant immunosuppression.

Belatacept

Belatacept is a costimulatory antagonist that serves to prevent binding of CD28 on T-cells, and thereby limit T-cell activation and replication in response to antigen presenting cells (100). Belatacept has been shown to be associated with improved renal function, reduced incidence of *de novo* donor specific antibodies (DSA), and favorable impacts on graft survival when compared to CNIs in patients undergoing kidney transplantation. Experience with belatacept in lung transplant has been limited, with prior data limited to small, retrospective case series (101-104). However, in a recent pilot randomized controlled trial, Huang *et al.* randomized 27 patients to *de novo* immunosuppression with belatacept

or traditional immunosuppression with tacrolimus, MMF, and prednisone. The trial was stopped early after 3 patients in the belatacept group died, compared to none in the control group. Following cessation of randomization, there were 2 additional deaths in belatacept group, yielding a total of 5 deaths in the belatacept group and none in the control group (P=0.016) (105). Additionally, there have been case reports of severe, fulminant ACR in patients who underwent transition to belatacept from CNI-based immunosuppression (106,107). In light of these results, belatacept does not currently have a role in maintenance immunosuppression for lung transplant patients.

Corticosteroids

Corticosteroids have been used in both induction and maintenance immunosuppression throughout the history of solid organ transplants. Corticosteroids affect the immune system in myriad ways, but primarily lead to immunosuppression through sequestration of T-lymphocytes in the reticuloendothelial system, prevention of T-cell proliferation, inhibition of inflammatory cytokine production, and alteration of lymphocyte recruitment and migration (108-110). The most commonly used agents in lung transplantation are prednisone and methylprednisolone. Dosing of corticosteroids varies by center, but generally, initial doses range from 500–1,000 mg daily in the immediate perioperative period, with a subsequent taper over weeks to a target maintenance dose of 2.5–5 mg daily. The side effects of corticosteroids are well known, and include hypertension, hyperlipidemia, weight gain, hyperglycemia and diabetes mellitus, osteopenia and increased fracture risk, poor wound healing, neuropsychiatric changes, and increased risk of infection. In light of the long-term sequelae of chronic steroid therapy, there has been some interest in steroid withdrawal in the lung transplant population. There is some data suggesting that in carefully selected patients with stable lung function, steroids may be successfully withdrawn, with subsequent improvement in cholesterol profiles, blood pressure control, and hyperglycemia (111,112). However, these data are collected from small, observational studies, so further research will be required to determine if steroid withdrawal in lung transplantation can be more broadly applied. Corticosteroids are also a first line treatment for ACR. Initial episodes of ACR are typically treated with a short course of high-dose methylprednisolone (10–15 mg/kg daily for 3 days), followed by a taper of prednisone to the maintenance dose. There are no studies evaluating alternative steroid dosing strategies or treatment paradigms in the lung transplant population.

The role of inhaled corticosteroids in the lung transplantation population remains unclear. Inhaled steroids may lead to improvements in symptoms and FEV1 in patients who develop BOS following allogeneic stem cell transplantation (113-115). However, data for the use of steroids in the treatment of either acute or chronic rejection in lung transplantation is largely limited to small case series (116,117). In a randomized controlled trial of 30 lung transplant patients, Whitford *et al.* evaluated the use of inhaled fluticasone *vs.* placebo added to routine maintenance immunosuppression, and found no differences in rates of treated acute rejection, development of stage 1 BOS, incidence of fungal infection or survival at 3 months and 2 years (118).

Adjunctive therapies

Given the limitations of conventional immunosuppression, there is considerable interest in the development of additional therapies for the treatment and prevention of both ACR and CLAD. Research has demonstrated the potential utility of numerous agents, including azithromycin, montelukast, statins, and pirfenidone (*Table 5*).

Azithromycin is a macrolide antibiotic with anti-inflammatory properties that has been utilized in the lung transplantation population primarily for its potential benefit in stabilization of lung function and prevention of CLAD. Data evaluating azithromycin consists of retrospective studies and small prospective trials. Overall, this data suggests that azithromycin may contribute to stabilization of lung function and improvement in FEV1, with some studies demonstrating a reduction in the incidence of CLAD (119-132). In a randomized, double-blind, placebo-controlled trial, Vos *et al.* randomized 83 patients to azithromycin or placebo and found that those treated with azithromycin had lower rates of BOS (12.5% *vs.* 44.2%, P=0.0017), improved FEV1, and lower airway neutrophilia. Overall survival, acute rejection, pneumonitis, and colonization were similar between the intervention and control groups (127). There is also some data supporting the use of azithromycin to prevent progression of CLAD. In a meta-analysis of 10 studies, including 140 patients with known BOS, treatment with azithromycin was associated with an increase in FEV1 and a lower likelihood of death from BOS.

Montelukast is a leukotriene receptor antagonist that has been evaluated as a potential adjunct therapy for patients with

Table 5 Adjunctive agents for use in lung transplantation

Agent	Mechanism of action	Potential uses
Azithromycin	Macrolide antibiotic with anti-inflammatory properties	May stabilize lung function and delay rate of decline in FEV1 in patients with CLAD. May be helpful for prevention of CLAD
Montelukast	Leukotriene receptor antagonist	May attenuate rate of decline in FEV1 in patients with known BOS
Statins	HMG-CoA reductase inhibitors	Prevents BOS in animal models. Use has been associated with decreased rates of acute rejection, improved graft function, slower onset of BOS, and improved survival
Pirfenidone	Antifibrotic agent that downregulates production of growth factors and procollagens	Decreases graft obliteration in animal models. Limited use in human subjects

HMG-CoA, hydroxy-3-methylglutaryl coenzyme A; FEV1, forced expiratory volume at 1 second; CLAD, chronic lung allograft dysfunction; BOS, bronchiolitis obliterans syndrome.

known CLAD. Data is limited, however, one retrospective study demonstrated attenuation in the decline of FEV1 in patients with BOS treated with montelukast (133). However, randomized trial data has shown no difference in rates of lung function decline, graft loss, or rejection in patients treated with montelukast compared to placebo (134).

Statins are hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, and are used broadly as lipid lowering therapy and for cardiovascular disease. Statins are widely accepted to exhibit anti-inflammatory properties, and are thought to play a significant role in reducing inflammation associated with atherogenesis (135). In the field of lung transplantation, statins have been shown to prevent the development of BOS in rats (136). In retrospective studies, statin use has also been associated with lower rates of acute rejection, improved graft function, slower onset of BOS, and improved survival (137,138). Though widely used for other indications, further study is needed to clarify the role of statins in the lung transplantation population.

Pirfenidone is an antifibrotic agent that downregulates the production of growth factors and procollagens. It has been used in pulmonary fibrosis, and has been shown to reduce disease progression and decline in lung function in patients with that disease (139). Pirfenidone has been shown to decrease graft obliteration in animal models of BOS, so interest has arisen in its use for fibroproliferative BOS (140). However, data for the use of pirfenidone in human subjects is largely limited to case reports and small cohort studies (141,142). A recent multicenter, randomized, double-blind placebo controlled trial in patients with BOS did not show a significant benefit of pirfenidone on pulmonary function decline, though complete data from this trial is not currently available (143,144). There is a small trial ongoing evaluating the use of pirfenidone in RAS, the restrictive variant of CLAD (NCT03359863), and a large trial evaluating the use of nintedanib, another antifibrotic agent, in patients with BOS (NCT03283007).

Rejection

An in-depth discussion of ACR, antibody mediated rejection (AMR), and CLAD is beyond the scope of this review. However, many of the agents used for induction and maintenance immunosuppression can be used in the treatment of different forms of rejection. Regarding ACR, as above, first line treatment at most centers is high dose corticosteroids. For persistent or recurrent ACR, other options include ATG, which has not been studied in lung transplant patients, and alemtuzumab, which has shown some promise in small case series (145). Additional management strategies include adjusting maintenance immunosuppression, adding an mTOR inhibitor to backbone immunosuppression, and the use of extracorporeal photopheresis (ECP), and total lymphoid irradiation (TLI) (146-150). AMR is challenging to treat, and there is limited data supporting therapeutic options. Therapies used generally focus on antibody reduction, and include plasmapheresis, intravenous immunoglobulin (IVIG), rituximab, proteasome inhibitors, and complement inhibitors (151-167). CLAD is also challenging to treat (168). As above, azithromycin and montelukast may help stabilize lung function, and pirfenidone is currently being evaluated for both BOS and restrictive CLAD (96-111). Alemtuzumab has been used for CLAD, with retrospective data demonstrating promise for stabilization of lung function, and ATG has been shown to demonstrate

improved lung function in 40% of patients in one retrospective review, albeit with a high rate of serious adverse effects, including serum sickness, cytokine release syndrome, and infection (145,169-171). ECP, TLI and re-transplantation can also be considered for these patients (169,172-180).

Conclusions

Lung transplantation continues to rise in prominence as a treatment for patients with advanced lung disease. However, long-term survival and transplant success continue to be limited by acute rejection, CLAD, infection, and the deleterious side effects associated with immunosuppression. Current strategies for induction and maintenance immunosuppression, along with treatment paradigms for acute rejection and CLAD have evolved over the last several decades. Still, randomized clinical trials are needed in order to identify the optimal strategies for immune suppression following transplant. Furthermore, additional research is needed to identify additional options for immune suppressive agents, along with adjunctive therapies that may help address the drivers of morbidity and mortality in the lung transplant population.

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