Review Article on Lung Transplantation: Past, Present, and Future

Review: immunosuppression for the lung transplant patient

Sakhee Kotecha, Steven Ivulich, Gregory Snell

Lung Transplant Service, Alfred Hospital and Monash University, Melbourne, Australia

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Correspondence to: Dr. Sakhee Kotecha. Lung Transplant Service, Alfred Hospital, Commercial Rd, Melbourne, 3004, Australia.
Email: s.kotecha@alfred.org.au.

Abstract: Lung transplantation (LTx) has evolved significantly since its inception and the improvement in LTx outcomes over the last three decades has predominantly been driven by advances in immunosuppression management. Despite the lack of new classes of immunosuppression medications, immunosuppressive strategies have evolved significantly from a universal method to a more targeted approach, reflecting a greater understanding of the need for individualized therapy and careful consideration of all factors that are influenced by immunosuppression choice. This has become increasingly important as the demographics of lung transplant recipients have changed over time, with older and more medically complex candidates being accepted and undergoing LTx. Furthermore, improved survival post lung transplant has translated into more immunosuppression related comorbidities long-term, predominantly chronic kidney disease (CKD) and malignancy, which has required further nuanced management approaches. This review provides an update on current traditional lung transplant immunosuppression strategies, with modifications based on pre-existing recipient factors and comorbidities, peri-operative challenges and long term complications, balanced against the perpetual challenge of chronic lung allograft dysfunction (CLAD). As we continue to explore and understand the complexity of LTx immunology and the interplay of different factors, immunosuppression strategies will require ongoing critical evaluation and personalization in order to continue to improve lung transplant outcomes.

Keywords: Immunosuppression; lung transplant

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Introduction

While lung transplantation (LTx) starts with extensive surgery in a patient with end-stage lung disease, it is actually the balance of intrinsic host immunity and extrinsic added immunosuppressive strategies that will most likely ultimately determine the long-term success of this therapy. The general management of immune deficient patients and the use of immunosuppressive agents has some commonality across different types of solid organ transplantation (SOT)—but the transplanted lung has some unique properties that require extra consideration. Particular issues for the lung allograft include: exposure to the external environment, the absence of lymphatic, bronchial arterial reconnection or cilial innervation, being the primary site of several infections problematic in all immune deficient patients [e.g., cytomegalovirus (CMV), pneumocystis] and being co-transplanted with whole lymph nodes of donor immune cells (1). Starting with the recipient, and moving through common early post-LTx scenarios and onto longer-term immunosuppression maintenance issues, the current review will consider the clinician and pharmacist's challenges and options.

Modification of early immunosuppression

In decades past, LTx immunosuppression strategies followed

Table 1 The Alfred Hospital's current LTx 'Induction and initiation of Immunosuppression' protocol (1,2)

Induction

- ❖ Tacrolimus: 5 mg orally if weight >50 kg, and 3 mg po if weight <50 kg

  Tacrolimus should not be given to patients on bosentan, azoles, orkambi or age >55 with borderline renal function

- ❖ Azathioprine: 2 mg/kg orally on acceptance of organs

  Mycophenolate mofetil 500 mg^{-1}·gm may be preferred in select patients (i.e., those who are (sensitized or have low TPMT level i.e., <0.50) as discussed with transplant physician

Intra-operative

- ❖ Methylprednisolone 500 mg intravenously on reperfusion of each lung

Early post-operative

- ❖ Methylprednisolone:
  - 75 mg (50 mg if weight <50 kg) intravenously every 8 hours for three doses followed by
  - 1 mg/kg at 10.00 am daily, weaning by 5–10 mg every day until 20 mg/day (Intravenous or oral as tolerated)
- ❖ Tacrolimus:
  - Aim to commence within 12 hours of arrival in ICU (assuming adequate urine output and renal function). Initial dose should be delayed or lowered in patients:
    - Taking bosentan, azoles or orkambi
    - Renal impairment
  - Day 0–1: >50 kg 0.5 mg intravenously twice daily; (<50 kg 0.3 mg) as a 4-hour infusion
  - Day 2–4: Convert to oral administration; 10:1 conversion (i.e., 0.5 mg IV tacrolimus is equivalent to 5 mg oral tacrolimus)
  - Daily through levels and adjust, targeting a trough level of 10–12 mcg/L
- ❖ Azathioprine:
  - 1.5 mg/kg/day intravenously or orally daily
  - If TPMT activity <0.5 then consider mycophenolate
  - Sensitized patients to commence mycophenolate mofetil with target dose 1gm twice daily if >50 kg; 15 mg/kg if <50 kg
- ❖ Basiliximab:
  - 20 mg given intravenously days 0 and 4 in selected patients

  Indications for use:
    - Baseline renal impairment
    - Complicated surgical procedure, shock state or poor urine output in ICU where renal injury is anticipated
    - Pediatric patients (dose of 10 mg to be used where <35 kg)

LTx, lung transplantation.

the pathway of other more numerous SOT (particularly kidney transplantation), but given the above features there has been definite evolution to modify practice to enhance outcomes (1,2). So in 2020, while LTx immunosuppression typically starts with a combination of the calcineurin inhibitor (CNI) tacrolimus, an anti-proliferative agent (azathioprine or mycophenolate), corticosteroids and an IL-2 blocker (basiliximab) (*Table 1*), clinical situations or infection or rejection events very commonly require individualization and revision of the initial protocol

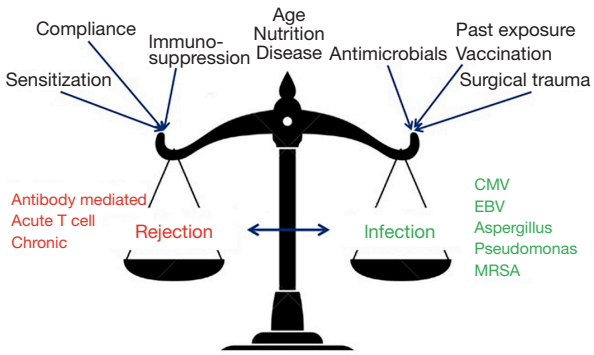

Figure 1 The concept of the net balance of immunosuppression in LTx. LTx, lung transplantation.

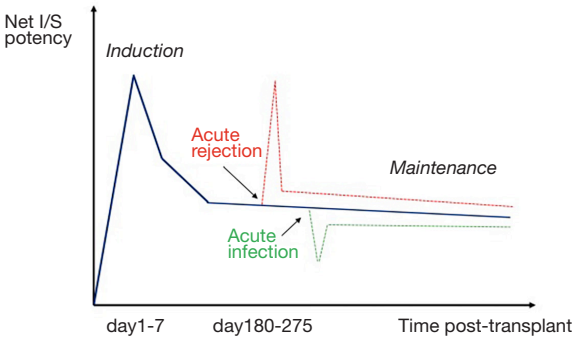

Figure 2 Current targeting strategies for LTx immunosuppression. LTx, lung transplantation.

(*Figures 1,2*) (1-4).

Recipient host factors and immunosuppression

Intrinsic immune deficiency, advancing age

A small cohort of patients receiving a transplant may be intrinsically immunosuppressed from the pre-existing indication for transplant. The risk of acute rejection in these patients may be lower and immunosuppression with induction agents may not be required. Following a "one size fits all approach" would put the patient at higher risk of sepsis in the perioperative period if the immunosuppression is not tailored to the specific infection risk of the patient.

Lung transplant recipients transplanted for bronchiectasis have a higher infection burden due to being intrinsically immunosuppressed. A more cautious approach with immunosuppression in the perioperative period may be required as bronchiectasis transplant recipients are predicted to suffer from higher rates of infection (5). Common variable immune-deficiency (CVID) is not a common indication for lung transplant with variable outcomes reported (6). CVID can predispose patients to recurrent infections, leading to the development of bronchiectasis, irreversible lung damage and eventual need for LTx (7). Immunoglobulin (IVIG) plays an important role in the management of immunosuppression post LTx. IVIG has immune-modulatory effects as well as an anti-infective role and can be utilized to minimise the higher risks of infection (8). Mycophenolate is known to have effects on IgG production and is associated with lower IgG levels after transplant due to its strong anti-proliferative effects on B-lymphocyte function (7,9).

Immunosenescence may predispose elderly patients to the risks of over-immunosuppression and theoretically less immunosuppression may be needed compared to younger patients. Elderly patients have lower rates of acute rejection and higher rates of bacterial infections and malignancies (10). In the perioperative period, the use of induction agents in older patients (>65 years) may not be appropriate in recipients who are at higher risk of infection, such as those with CMV mismatch or at higher risk of sepsis.

Longer life expectancies and modern antiretroviral therapies have ensured that HIV-positive recipients are now considered for LTx with favourable outcomes reported. Data suggests that HIV recipients should receive induction immunosuppression due to concerns with viral suppression and increased infection risk. However, the acute rejection rate is higher for HIV infected transplants in other SOTs suggesting an excessively cautious use of immunosuppression. Ongoing larger studies are investigating the higher rejection rates in other SOTs and the optimum approach to immunosuppression in the HIV-positive recipients (11).

Acquired immune deficiency

Many potential LTx recipients come to transplant already affected by immunosuppressant medications. This could be a modest dose of prednisolone for refractory airways disease, pirfenidone for pulmonary fibrosis, a mammalian target of rapamaycin (mTOR) inhibitor (e.g., sirolimus) for lymphangioleiomyomatosis—right through to complex multidrug regimens or monoclonal antibodies that have been indicated for a prior transplant or autoimmune lung diseases. These agents often require modification of LTx induction therapy to avoid impacting early transplant

Table 2 Immunosuppressive or immunomodulatory therapies used in potential LTx recipients that require consideration of modifying immunosuppression

Medication/therapy	Indication	Specific effect on allograft/recipient	Induction immunosuppression modification
Corticosteroids	• Obstructive airways disease	Poor wound healing	Decrease induction steroid dose
	• ILD		
Tacrolimus, Cyclosporine	Prior transplant	Poor renal function	Delay re-start of drug
Anti-proliferative agents	• ILD	• Low white cell count	Decrease induction
	• Prior transplant	• Non-specific	Anti-proliferative or steroid dose
Pirfenidone, Nintedanib	ILD	Poor wound healing	Decrease induction steroid dose
Rituximab	Autoimmune ILD	• Interferes with donor/recipient cross match	No change
		• Lasts 9 months	
Sirolimus, Everolimus	• LAM	• Poor wound healing	Decrease induction steroid
	• Prior transplant	• Low white cell count	Dose
Intravenous gamma globulin	• Prior immune deficiency	• Interferes with serology testing	Lost with haemorrhage- so replace early
	• Highly sensitized	• Anti-rejection/anti infective	

LTx, lung transplantation; ILD, interstitial lung disease.

outcomes (2), see *Table 2*.

Specific challenging recipient infective or commensal organisms

There are several scenarios where the risk of uncontrolled peri-LTx infection is known or suspected to be very challenging. Clear-cut examples include the isolation of *Burkholderia Cepacia Complex* (12) or *Mycobacterium Abscessus* (13). The potential for complications mandates a specific reduced immunosuppression plan that dovetails existing co-morbidities (e.g., gastro-intestinal symptoms, renal impairment), anti-infective agent side-effects and anti-rejection immunosuppressant mode of action and side-effects. Delayed introduction of the CNI, the routine use of basiliximab and a reduced dose of anti-proliferative agents and steroids is a good starting point (2). Avoidance of potent or long-acting agents such as high-dose pulsed steroids, anti-thymocyte globulin or rituximab is critical. Photophoresis, although an expensive and uncommon therapy, may provide an efficacious and safe alternative mode of immunomodulation (14).

Specific recipient co-morbidities

Neurological

Patients with pre-existing neurological conditions may require special consideration leading into LTx. Elderly patients at risk of stroke are likely to require additional pre-transplantation workup. The incidence of stroke, although lower than other solid organ transplants, is 2% to 3% after lung transplant (15).

Patients with epilepsy need special consideration in the perioperative period. Seizures with CNIs are often generalized and can occur even when serum levels are therapeutic. Many treatments for seizures also have the potential to interact with immunosuppressant regimens due to their hepatic metabolism and cytochrome interactions. Levetiracetam is the drug of choice for post-transplant due to the minimal drug interactions (15).

Gastrointestinal

A small cohort of lung transplants recipients may be prescribed immunosuppressants for a range of autoimmune and inflammatory diseases such as rheumatoid arthritis, ulcerative colitis and Crohn's disease and may be significantly immunosuppressed leading into LTx. Treatments may vary from mild immunosuppression such as azathioprine to more potent cytokine modulators such as infliximab or adalimumab. Azathioprine, utilized in many regimes for inflammatory bowel disease, is also incorporated into standard immunosuppressant regimens. However, other disease modifying agents such as sulfasalazine or

mercaptopurine are usually ceased post-LTx.

Hematological

Lung transplant is a feasible option for patients with severe pulmonary chronic graft versus host disease (GVHD). Patients with GVHD are likely to have had a complicated course coming into LTx with IVIG replacement complicating serological testing, risk of opportunistic infections post allogeneic hematopoietic stem cell transplant (HSCT) and deficiencies in bone marrow reserve after many years of receiving immunosuppression (16). Patients with GVHD are likely to benefit from less intense immunosuppressive regimens post LTx. A retrospective Japanese study demonstrated that postoperative complications within the first year after LTx can be minimized by using a lower dose of prednisolone (17).

Induction agents such as the T-cell depleting agents (anti-thymocyte globulin, alemtuzumab, basiliximab) or anti-metabolites can all cause varying degrees of leukopenia (18). Testing for thiopurine methyltransferase (TPMT) activity is required to ensure LTx recipients can adequately metabolize that 6-mercaptopurine. Those without adequate TPMT activity are at risk of leukopenia from azathioprine, the pro-drug of 6-mercatopurine. Reduced activity is seen in 10% of Caucasians with a smaller cohort completely absent of activity. In patients with low TPMT activity, an alternative antimetabolite such as mycophenolate would be given (19).

Specific recipient drug interactions

Patients receiving a lung transplant may be taking a medication that has the potential to destabilize immunosuppressant regimens if continued in the peri-operative period. Many of these medications, such as the gene modifiers for cystic fibrosis (CF) and endothelin receptor antagonists for pulmonary hypertension are usually ceased once the transplant has taken place. However, their impact may linger for a few days and this may necessitate the delay of immunosuppression. Others, such as azole antifungals may need to be reinitiated immediately post-LTx and significant modifications may be required. *Table 3* gives an overview of significant interactions to consider in the peri-operative period.

Traditional antiviral treatments for HIV or hepatitis C contributed to complex drug-drug interactions with immunosuppressant regimens. Modern anti-retroviral and hepatitis therapies can now be safely administered post-LTx utilizing a standard immunosuppressant regimen without problematic interactions.

Perioperative issues and immunosuppression

LTx is commonly surgically challenging and unpredictable. A seemingly perfectly fine pre-LTx immunosuppression protocol may therefore need immediate modification in the early post-LTx period.

Extensive intra-operative hemorrhage

Effectively such patients will lose their pre-LTx induction immunosuppression with the replacement of lost blood volume. Almost universally an acute kidney injury (AKI) is associated, and in extreme cases hemofiltration via an extra-corporeal membrane oxygenation (ECMO) circuit is required. In the short term, corticosteroids, a reduced dose of the anti-proliferative agent and basiliximab are appropriate, while avoiding nephrotoxic agents such as CNI (2). However, if the AKI appears to be well established then implementing a reduced steroid dose and starting up the CNI may actually be a superior combination in providing anti-rejection cover while improving wound healing responses and decreasing the broad infection association of systemic steroids.

Perioperative sepsis and septic shock

Immunosuppression is required for rejection prophylaxis, but it needs to be recognized that in the setting of a serious septic event, anti-infective therapy and circulatory stabilization are the first priorities. Immunosuppression can be rationalized to a hydrocortisone infusion and IVIG as appropriate, or even a basiliximab 'holiday' (if not previously given) (2,20). In the vast majority of cases the patient survives and the allograft will be relatively easily salvaged days to weeks subsequently.

Altered conscious state and neurotoxicity

Lung transplant recipients are particularly vulnerable to neurological complications post-surgery for several reasons (21). Chronic hypoxemia is common in those with end-stage lung diseases, hemodynamic instability from cardiopulmonary bypass devices and neurotoxicity from immunosuppression can all contribute to neurotoxicity (22). Encephalopathy is the most common neurological complication post- LTx with an incidence of 30% (15,21). Neurotoxicity from CNIs can manifest as headache, confusion or tremor to more serious consequences such as altered mental status, seizures or posterior reversible encephalopathy syndrome (PRES). Corticosteroids can exacerbate delirium in the peri-operative period and minimization of corticosteroid dose may also be necessary (15).

Patients with pre-existing neurological conditions leading into LTx who are at risk of complications are likely to benefit from delayed introduction of CNIs. Our

Table 3 Specific recipient Drug Interactions used in potential LTx recipients that require modification of Maintenance Immunosuppression

Medication/therapy	Examples	Method of Interaction	Recommendation
Azole antifungals	Voriconazole	Strong CYP3A4 inhibitor	Avoid loading with CNI prior to surgery
	Posaconazole	Increases serum levels of CNIs	Consider use of induction agents e.g., basiliximab
	Itraconazole		Initiation of CNI at a lower dose within a few days
	Fluconazole (Moderate)		Not routinely continued post LTx. Brief washout period recommended prior to initiating CNI
	Isavuconazole (Moderate)		
Endothelin receptor antagonists	Bosentan	Bosentan – Moderate CYP3A4, 2C9 Inducer	As above
	Ambrisentan	Ambrisentan – Minimal CYP3A4, 2C9 inducer	Ceased post LTx
	Macitentan	Macitentan – Lower potential for interactions	
Gene Modifiers	Ivacaftor	Ivacaftor – Weak CYP3A4 inhibitor	As above
	Lumacaftor-Ivacaftor	Lumacaftor – Strong CYP3A4 induction – Net overall induction with the combination	Ceased post LTx
Antibiotics	Clarithromycin	Strong CYP3A4 inhibitors	As above
	Erythromycin	Increased serum levels of CNIs	Consider alternative agents post LTx
	Rifampicin	Strong CYP3A4 inducer	
		Decreased serum levels of CNIs	
Calcium channel blockers	Diltiazem	Moderate CYP3A4 inhibitors	Consider alternative agents post LTx
	Verapamil		
Xanthine oxidase	Allopurinol	Inhibits metabolism of xanthine oxidase – Increasing risk of myelosuppression	Use mycophenolate instead of azathioprine
HIV Protease inhibitors	Ritonavir	Strong CYP3A4 Inhibitors	Consider modifying regimen prior to LTx to a non-interacting regimen e.g., HIV-1 Integrase inhibitor based
	Cobicistat		
	Saquinavir		
	Nevirapine	Strong CYP3A4 Inducers	
	Efavirenz		
Anticonvulsants	Phenytoin	Strong CYP3A4 inducers	Consider modifying regimen prior to LTx to a non-interacting regimen e.g., levetiracetam
	Carbamazepine		
	Phenobarbitone		

LTx, lung transplantation. CNI, calcineurin inhibitor.

approach to patients with an altered conscious state in the peri-operative period has been to withhold the CNI. The substitution of tacrolimus for cyclosporine may provide benefit in some patients.

Hyperammonemia is a rare but potentially fatal complication of SOT. Immunosuppressive agents and hepatic enzyme deficiency may play a role, but recently an infective component has been identified (23). The association with *Ureaplasma* infection has changed the approach to this syndrome. Measurement of ammonia levels is recommended in patients developing neurological symptoms (24).

Absorption and gastrointestinal motility issues

Tacrolimus based immunosuppressant regimes form the cornerstone of immunosuppression post LTx. Managing tacrolimus post LTx can be challenging due to a number

of unique factors specific to LTx. Tacrolimus has a narrow therapeutic index, high intra-patient variability and TDM is essential for treatment individualization (25). Achieving therapeutic levels can be further complicated by a number of unique gastrointestinal factors specific to LTx. Patients with CF have unique pharmacokinetic profiles with delayed drug absorption as well as increased clearance of medications. Therefore, patients with CF require a higher mg/kg dose of tacrolimus compared to those without CF (26).

The motility of the gastrointestinal tract may be significantly altered in the perioperative phase. The duodenum, the primary site of tacrolimus absorption may be significantly impacted in hemodynamically unstable patients. The oral route is the preferred route of administration, but sublingual or intravenous may be useful for a limited period of time. However, sublingual absorption of tacrolimus is minimal, whilst intravenous administration may be limited by lack of available lumens and higher rates of neuro and nephrotoxicity (27).

Immunosuppressive drug metabolism and dosing on ECMO and dialysis

The most common reason for modification of induction immunosuppression regimens is pre-existing renal impairment. Renal failure in the acute setting after LTx increases the risk of early and late post-LTx morbidity and mortality (28). Indeed, in one study (29) the incidence of AKI post-LTx was 52.5%, with 9.3% of patients will requiring renal replacement therapy (RRT). Screening for high-risk patients at the time of LTx will minimize the risk of AKI as CNI minimization strategies can then be put in place. The use of induction agents such as basiliximab or alemtuzumab may delay the need for the early utilization of CNIs (30).

CNIs cause AKI through direct vasoconstriction of the afferent and efferent arterioles. High levels of unbound plasma concentrations of tacrolimus can contribute to toxicity, even when tacrolimus concentrations are in the therapeutic range. The potent vasoconstriction is likely caused by higher levels of endothelin and impaired production of nitric oxide (31).

In the LTx peri-operative phase, the pharmacokinetics of immunosuppressants can become markedly complex. Factors that may impact the pharmacokinetics of tacrolimus in the critically ill patient include inflammation, hypo-albuminemia, blood transfusions and hypotension.

ECMO can further impact drug pharmacokinetics by increasing the volume of distribution requiring more drug to achieve the same concentration as well as potential sequestration into the circuit (32). Additionally, absorption and sequestration of immunosuppressants (tacrolimus and mycophenolate) in the ECMO bypass circuit can be expected as they are highly lipophilic and protein bound drugs. However, at least in a heart transplant study, levels may rise and doses may need to be decreased (33).

Modification of maintenance immunosuppression

Host factors identified at baseline

Once the early post LTx period has passed and the acute challenges dealt with, a maintenance immunosuppression strategy must be considered. Immunosuppression is traditionally maintained with maintained with triple therapy consisting of a CNI (usually tacrolimus), anti-proliferative (mycophenolate or azathioprine) and corticosteroids. Dosing is adjusted over time to reflect the changes in immune tolerance to the allograft and is reduced in most cases over the first 12 months to a baseline prednisolone dose of 5–10 mg per day and a tacrolimus trough level target of 4–8 mcg/L (*Table 4*). There are various scenarios however which give rise to varying the standard regime.

Many transplant recipients have factors identified at baseline, which leads to alteration of the regime or target drug levels. These have been already been outlined above. Many of these modifications to the induction regime often persist for a long course post-LTx, if not indefinitely, reflecting the non-modifiable host factors that impact the net immunosuppression strategy in patients.

Drug interactions

The addition of interacting medications has the ability to destabilize immunosuppressant regimens. The most frequently encountered would be the addition of azole antifungals (posaconazole, voriconazole, itraconazole and fluconazole) for the treatment of Aspergillus. The extent of the interaction cannot always be predicted and despite pre-emptive dosage reduction when initiated, there is a large amount of inter-patient variability. Patients initiating or ceasing azoles are at greatest risk of variability.

The advent of novel oral anticoagulant (NOAC) agents for venous thromboembolism and atrial fibrillation has been variable for LTx recipients requiring anticoagulation. While there has been uptake of NOAC usage for LTx recipients, this can be problematic. While there are no significant changes in tacrolimus levels, the effects of NOACs have

Table 4 The Alfred's maintenance immunosuppression dosing guidelines

Months	0–3	3–6	6–12	>12
Tacrolimus trough level	10–12		8–10	4–8
Azathioprine	1.5 mg/kg/day			
Mycophenolate	0.5–1 g twice daily			
Prednisolone (mg/day, weight >50 kg)	20	15	12.5	5–10
Cyclosporine trough level	250–300		200–250	100–200
Cyclosporine 2-hour (C2) level	1,200–1,400		1,000–1,200	400–800
Sirolimus level	4–8			
Everolimus level	4–8			

only been studied in kidney transplant recipients (34). Furthermore there is a contraindication to using NOAC agents in patients already on azole antifungals, highlighting the ongoing complex nature of medication management post-LTx (2).

Allograft dysfunction

Lung allograft rejection remains the main barrier to achieving better long-term outcomes post-LTx. Acute cellular rejection (ACR) on transbronchial biopsies signals acute allograft failure, but is a risk factor for the development of chronic lung allograft dysfunction (CLAD) (35). Tacrolimus level variability increases the risk of ACR and CLAD, particularly if occurring after the first 6 months post-LTx (2). The mainstay of management in this scenario is pulsed corticosteroids (intravenous methylprednisolone, 500–1,000 mg daily for three days) in addition to reviewing medication compliance and dosing. Additional factors contributing to tacrolimus variability are reviewed including absorption and drug interactions as well as aiming for a higher target tacrolimus trough level. Those on azathioprine can be transitioned to mycophenolate as the preferred anti-proliferative agent with some trial evidence of potential for a reduction in subsequent ACR, CLAD and improved graft survival (36).

Antibody-mediated rejection (AMR) remains a challenging entity without a definitive histopathological pattern, but rather relies on a constellation of clinical, histopathological and immunological features to formulate a diagnosis (37). This challenge also translates to treating AMR given the difficulties in diagnosis and also ongoing assessment. Nevertheless, when treatment of AMR is undertaken, there are acute and longer term management strategies for immunosuppression. After a pulse of corticosteroids, further management of AMR includes a combination of IVIG, plasmapheresis and a proteasome inhibitor (e.g., bortezomib) or anti-CD20 monoclonal antibody (e.g., rituximab) (38). Concurrently baseline immunosuppression is reviewed and changes may be instituted to enhance baseline immunosuppressant levels: including increasing the corticosteroid dose (often to 10 mg per day or more), ensuring mycophenolate is the anti-proliferative agent used (or at a higher dose—750–1,000 mg twice daily), as well as targeting a higher tacrolimus trough level.

Where CLAD is suspected or established, azithromycin is added to the regime to improve allograft function (39). More recently while there is emerging evidence that montelukast may have a role in established CLAD to reduce the rate of lung function decline and improve outcomes, this is not currently standard practise (40).

Renal dysfunction

Renal impairment remains a common and challenging issue post-LTx. AKI can be due to peri-operative issues and maybe short term as discussed above. AKI is a risk factor for chronic kidney disease (CKD), however, the predominant etiology for CKD are nephrotoxins, namely CNIs (41). CNI have both short (renal vasoconstriction) and longer term (chronic arteriolar changes and interstitial fibrosis) effects (28). While the severity of CKD amongst LTx recipients is variable, 5–10% of recipients have severe CKD (creatinine >221 μmol/L or a need for dialysis or renal transplant) within 1 year post LTx, with 16% and 25% having CKD by 5 and 10 years respectively (3).

Management of CKD post-LTx includes reducing target tacrolimus levels (42) or switching to mTOR-based immunosuppression. Early transition to an mTOR inhibitor is not recommended due to the risk of delayed wound healing, but ideally LTx recipients should be switched prior to the onset of proteinuria so as to increase the likelihood of renal recovery (43). Management of other reno-vascular disease factors remains paramount, including aggressive management of hypertension and diabetes (both known complications of tacrolimus and steroid-based immunosuppression), to ensure all possible sources of renal injury are targeted appropriately.

Gastrointestinal issues

LTx immunosuppression plays a major role in the development of Gastrointestinal (GI) complications, due to the relatively high doses given. It can be difficult to differentiate whether the complication is due to infection due to the immunosuppressed nature or a direct action of the immunosuppression (44).

Nausea is the most common GI complaint post-LTx, attributed to side-effects of immunosuppressants such as mycophenolate, azathioprine or other commonly prescribed medications such as valganciclovir (44). Persistent nausea can be attributed to gastroparesis, an unfortunate surgical complication post-LTx can be caused by intra-operative vagal nerve damage or medications such as narcotic analgesics (45). Immunosuppressant levels may become sub-therapeutic secondary to gastric stasis. As doses are escalated to achieve a pre-determined protocolized target level, there is potential for supra-therapeutic levels once gut motility is restored, with an abrupt rise to toxic concentrations. Although symptoms usually resolve within 6 months post-LTx, there are concerns with the risk of aspiration from a poorly emptying stomach and the subsequent eventual development of CLAD (46).

CF may be associated with liver disease as well as motility-related issues due to mutations of the chloride channel resulting in gastroparesis, meconium ileus and more severe manifestations such as distal intestinal obstruction syndrome. Pancreatic insufficiency will impact the absorption of medications. Patients with CF have erratic gastrointestinal absorption impacting on achieving adequate levels potentially resulting in lower immunosuppression exposure (47).

Hepatotoxicity can also be problematic post-LTx. Many commonly prescribed medications post-LTx all contribute to hepatic dysfunction such as cell anti-proliferatives, azole antifungals and infrequently CNIs. Lung transplant recipients treated with voriconazole have a higher incidence of hepatotoxicity compared to other SOTs and the risk is greatest when initiated within 30 days post-LTx. Additional serious gastrointestinal complications that may occur including cholecystitis, intestinal perforation, pancreatitis and diverticulitis (48).

Situations with increased gastrointestinal motility, such as diarrhoeal illness can result in increased serum concentrations of immunosuppressants. CNIs and mTOR inhibitors are metabolized by CYP3A and p-glycoprotein in the gut wall and decreased transient times result in potential toxicity of tacrolimus. Patients with diarrhoeal illness are likely to have supra-therapeutic tacrolimus levels on admission with associated AKI. Our approach in this situation is to withhold the CNI or mTOR inhibitor until the AKI has resolved and reintroduce cautiously (49).

The incidence of gastro-esophageal reflux disease (GERD) is high post-LTx and has been linked to the development of CLAD (50). Steroid immunosuppression can contribute to the development of duodenal ulcers or poor wound healing (51). Dose reduction, temporary cessation, or discontinuation of certain immunosuppressive drugs is an important strategy to manage GI toxicities. However, the duration of these interventions can potentially increase the risk of graft rejection, if inadequate immunosuppression is not provided through routes or strategies.

Metabolic issues

Immunosuppressants can contribute to cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus (DM) and renal disease. DM is common post-LTx and can be associated with immunosuppressant regimens containing corticosteroids or CNIs, while 50% of CF patients being considered for LTx having pre-existing DM (52,53). Glucose intolerance is more likely in patients receiving tacrolimus than cyclosporine (25). The emergence of DM post-LTx is not an indication to switch CNIs or aim for lower therapeutic levels. Instead, close monitoring of glucose levels and the implementation of standard DM therapies is essential to prevent long-term morbidity associated with under-treated DM.

Hypertension, caused by renal vasoconstriction and sodium retention develops relatively early following CNI initiation and can lead to the development of CKD, stroke

and other cardiovascular complications post-LTx (54). Calcium channel blockers are the agents of choice for CNI-induced hypertension, as they reverse CNI-induced vasoconstriction. Hyper-cholesterolemia or hyper-triglyceridemia are more common with CsA than Tacrolimus (53). CNIs, predominantly cyclosporine, have the potential to significantly increase statin exposure and those metabolized via cytochrome P_{450} enzymes (atorvastatin and simvastatin) are at higher risk of potential rhabdomyolysis (55).

Given the long term cardiovascular and renal consequences of uncontrolled hypertension, hyper-cholesterolemia and DM, management of these predictable side-effects is essential to minimize long-term morbidity.

Hematological issues

Leukopenia of varying severities can be attributed to several immunosuppressants utilized in standard LTx regimens. Azathioprine, and to a lesser extent mycophenolate, are the most likely agents to cause leukopenia. Leukopenia associated with azathioprine is usually reversible with dose reduction or discontinuation (18). Trough levels of the active metabolite of mycophenolate (mycophenolic acid = MPA) is related to the risk of leukopenia associated with this drug. However, trough levels are not routinely performed at many institutions. Current practices include adjusting doses to maintain a white cell count of >4,000. Co-administration of the antimetabolites with other medications such as valganciclovir and co-trimoxazole are other frequently implicated as causative factors in the high incidence of leukopenia post-LTx (56).

Patients with mutations of the telomerase complex are at high risk of hematological complications following LTx. Thrombocytopenia is the most common hematological complication, followed by anemia and neutropenia. LTx recipients with this manifestation may have mycophenolate or azathioprine removed from the drug regimen after LTx without undue rejection consequences (57).

The incidence of anemia post-LTx has been reported at an incidence of 65% (31). The development of anemia is closely linked to post-LTx renal impairment. The use of erythropoietin has been administered to improve hemoglobin levels (31). The anti-metabolites (e.g., azathioprine and to a lesser extent mycophenolate) and mTOR inhibitors have all been implicated as causes of anemia. Although relatively rare, hemolytic anemia is not associated with immunosuppression, but more commonly with therapies for *Pneumocystis Jirovecii Pneumonia* prophylaxis (e.g., dapsone or primaquine).

Thrombotic thrombocytopenic purpure (TTP) is an infrequent, but serious, complication attributed to CNIs. CNIs can injure endothelial cells, cause vasoconstriction and increase platelet aggregation resulting in TTP (58). Neurological symptoms or a decline in renal function may be attributed to CNI-related neurotoxicity or nephrotoxicity confounding a TTP diagnosis (59). TTP can occur at any time post LTx and is independent of levels, with the highest risk when an mTOR inhibitor is used in conjunction with a CNI (58).

Advanced age and frailty strategies

The number of elderly patients receiving LTx has increased significantly in recent years (60). The elderly are impacted by immunosenescence that is characterized by a gradual deterioration of the immune system with impairment of adaptive or innate immune response (61). Immunosenescence is likely to increase the risk of DM, bacterial infections and malignancies, although may be associated with lower rates of acute rejection. Age-related changes can result in altered pharmacokinetics of immunosuppressants in the elderly resulting in increased medical comorbidities, including hypertension, renal dysfunction and hyperlipidemia (60-62). Despite these distinct changes, there are no specific recommendations for maintenance immunosuppression in the elderly. Clinicians may intuitively reduce the baseline immunosuppression in the elderly due to their susceptibility to side effects and infection. A reduced CNI target concentration and lower corticosteroid maintenance dose is appropriate with the aim of reducing the risk of nephrotoxicity and the risk of metabolic complications.

Frailty, generally defined as a functional decline with decreased reserve across multiple physiologic systems, is associated with poorer outcomes post-LTx (63). Symptoms of frailty may overlap with some of those seen in ageing, although it can also be seen in younger patients (64). There is a paucity of information regarding the correct approach to immunosuppression in the frail patient. However, frailty has a number of distinct characteristics including a chronic inflammatory, pro-coagulant and sarcopenic state that can all impact immunosuppressant pharmacokinetics (64).

Chronic infection issues

Chronic and recurrent infections post-LTx remains a challenge and significant contributor to CLAD, morbidity and mortality. Bacterial infections remain problematic, particularly in those who come into LTx with suppurative lung disease such as CF and other types of bronchiectasis, particularly with sinus and proximal airway pathogen colonization. In these patients, an active reduction in maintenance immunosuppression is appropriate, often via cessation of the anti-proliferative agent, potentially with the addition of IVIG.

This same strategy is applied in those with recurrent CMV infection. Epstein-Barr virus (EBV) reactivation remains a less common occurrence post LTx. EBV is predominantly seen in those who are an EBV mismatch (donor positive, recipient negative) and should be considered for life-long prophylactic antiviral therapy. The development of EBV-driven post-transplant lymphoproliferative disease (PTLD) is problematic in a significant portion of the mismatched LTx recipients, likely associated with the greater volume of lymphoid tissue in the transplanted lung (compared to other SOT) (65). This requires more aggressive reduction in immunosuppression with cessation of the anti-proliferative agent and a reduction in tacrolimus target levels to the lowest acceptable levels.

LTx for patients with concurrent blood borne viruses (BBV), namely hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV), is currently a rare occurrence. Similarly, the transmission of donor-acquired BBV via transplantation remains rare, even in those who are deemed high risk donors (66).

Historically, a BBV was a contraindication to SOT, but with the advent of newer therapies with more favorable side-effect profiles has the real prospect of viral cure in those with HCV and good disease control in those with HBV and HIV, LTx is now a therapeutic option in these patients. HBV treatment is limited to interferon-free regimes, due to the risk of allograft rejection with interferon therapy (67). HCV treatment has been revolutionized with direct-acting antiviral agents to a degree that HCV infected donors are now knowingly utilized and their organs transplanted to HCV negative recipients, expanding the donor pool significantly. These HCV therapies do not interact with conventional immunosuppression, are only required for a short duration if commenced early post-LTx and have demonstrated excellent virological response rates. Subsequent lung allograft function and survival are equivalent to those seen with conventional non-HCV donors (68).

While liver and renal transplantation has become standard practice for those patients with HIV and end-organ disease, LTx in this population remains relatively recent and limited (11). Evidence to date suggests increased rates of ACR but similar survival in LTx recipients with HIV compared to the standard cohort, which is in keeping with the outcomes seen in other SOT. This may in part be due to drug interactions between CNI and HIV anti-retroviral agents (ARV), namely protease inhibitors or non-nucleoside reverse transcriptase inhibitors, which affects CNI metabolism via cytochrome P450-3A (11). This issue has been successfully managed by switching patients with HIV from these interacting agents to an integrase inhibitor based ARV regime and ensuring stability of HIV control prior to LTx. This allows conventional immunosuppression to be commenced in these patients post-LTx without concern for complex drug interactions (2).

Malignancy strategies

The risk of malignancy post LTx is predominantly due to immunosuppression with a 2.5- to 3-fold increased risk compared to the general population (65). Skin cancers, in particular, are common post LTx. In the setting of recurrent non-melanoma skin cancers or any other malignancy, immunosuppression is aggressively reduced with cessation of the anti-proliferative agent. Tacrolimus target levels are reduced or LTx recipients are switched to an mTOR inhibitor given its potential to reduce the risk of malignancy via its action on anti-proliferation and cell metabolism (69).

Future strategies and direction of LTx immunosuppression

Nebulized LTx immunosuppression

The theoretical advantage of nebulized immunosuppression is that additional doses of conventional immunosuppression may be administered while encountering less systemic side effects such as renal or hepatic impairment (70-73). An initial randomized trial found that inhaled cyclosporine did not improve the rate of ACR, but did improve survival and periods of chronic rejection-free survival (74). However, a larger multi-center, randomized did not improve CLAD-free survival or overall mortality (75). A small study of inhaled tacrolimus has additionally been undertaken (76).

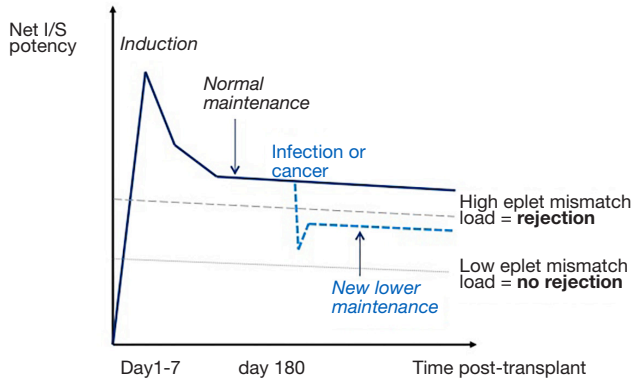

Figure 3 The potential of allo-immunity risk profiling versus immunosuppression.

A randomized trial of inhaled corticosteroids did not show significant benefit (77).

Allo-immunity risk profiling to understand absolute allograft risk

Wiebe and colleagues have recently shown that is possible to use a calculated score (HLA Matchmaker, Pittsburgh, PA, USA) of the extent of donor-recipient immunological mismatch to stratify the net requirement for post-renal transplant immunosuppression (78). *Figure 3* gives a schematic view of how this measure could be utilized clinically.

Novel markers to quantify the impact of immunosuppressive medication

Best characterized following liver transplantation, the ImmuKnow (Cylex, Columbia, MD, USA) assay is a potential tool to determine the net overall state of immunosuppression post-transplant (79). Bhorade and colleagues found that ImmunoKnow levels were lower in infected LTx recipients compared with non-infected recipients (80).

The QuantiFERON Monitor (QFM)(Qiagen, Hombrechtikon, Switzerland) provides assessment of an individual's cell-mediated response through dual innate (R848) and adaptive (anti-CD3) immune system stimulation, providing both qualitative and quantitative analysis of cell-mediated immunity. Studies in other SOT (81,82) populations have shown the QFM is able to quantify the net level of immunosuppression and predict the risk of subsequent infection episodes.

Other biomarkers may also potentially reflect the total degree of immunosuppression (83,84). Torque Teno virus (TTV) is a human DNA virus that causes persistent asymptomatic viremia in the general population. Replication of TTV is subject to immune control (85). Recently, it was found an association between high plasma TTV levels and the development of CLAD, suggesting that TTV monitoring may be useful in identifying those at highest risk (86).

Measuring the biological activity of immunosuppressants on intracellular target enzymes is an alternate approach to measuring whole blood levels. Measuring inosine monophosphate dehydrogenase levels correlates with mycophenolic acid activity (87) and measuring intracellular concentrations of CNIs correlates more tightly than blood levels with efficacy (88) and infection risk (89).

Detecting sub-clinical allograft dysfunction from any cause

Allograft function is historically assessed by the measurement of lung function, however early sub-clinical alloimmune activation may well go undetected in the absence of overt spirometric change. The detection of graft-derived cell free DNA in the blood is a recognized marker of early allograft dysfunction (90,91). It is a non-invasive measure that is specific for damage to the transplanted allograft. In the LTx setting it is also possible to measure directly from the allograft by utilizing bronchoalveolar lavage samples.

A number of other biomarkers that may also predict early graft changes have been described (92). These assessments are providing insights into the mechanisms of CLAD development and may identify potential immunosuppressive targets prior to the development of clinically evident disease. Notwithstanding, there are real challenges translating a promising research tool into a routine clinical practice measure (93).

Molecular assessment of rejection and injury

Extending work done in renal and cardiac transplantation, a microarray-based diagnostic system (Molecular Microscope® Diagnostic System, Edmonton, Canada) has recently emerged as an alternative to conventional histology (94). The system features a microarray-based central diagnostic system developed for real time assessment by defining rejection-associated transcripts that consist of 200 probe sets

associated with acute rejection (both T cell- and antibody-mediated), non-specific lung injury (infection) and normal allograft function (94). These analyses can be performed on transbronchial and endobronchial biopsies (94,95), as well as blood (96) and BAL (97).

Based on renal transplant work (98), it is now possible to go one step deeper and assess lung cell transcriptomics using single-cell RNA-sequencing (scRNAseq).

Conclusions

With increasingly complex LTx candidates being successfully transplanted and improved survival in these patients, immunosuppression regimes have evolved from a standard recipe to fit all types into a nuanced and tailored individualized approach to balance the risk of immunosuppression against the competing risk of rejection. This requires careful consideration of a single recipient's unique multiple inherent host factors, their perioperative course and immunosuppressant side-effects, all the while targeting the minimization of comorbidities and CLAD while aiming for overall excellent long-term LTx outcomes. As our understanding of the many complex factors involved in allograft dysfunction expands, coupled with novel emerging molecular and biomarker assessments, immunosuppression strategies will continue to require ongoing evolution and personalization.

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