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Lung transplant immunosuppression – time for a new approach?

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Summary

Outcomes after lung transplantation remain worse compared to other solid organ transplants, which is in large part due to high rates of graft rejection. Despite emerging data that immune responses to lungs differ from other organs, immunosuppression for lung transplant recipients is still based on strategies established for recipients of other grafts. There exists an urgent need to develop immunosuppressive strategies for lung transplant recipients that take the unique immunological features of this organ into account.

Keywords

lung transplantation; immunosuppression; graft rejection; innate immunity; adaptive immunity; chronic rejection

Lung transplantation remains the ultimate treatment option for patients with end-stage lung disease. The number of lung transplant procedures continues to increase, with 3640 lung transplants reported to the International Society of Heart and Lung Transplantation (ISHLT) in 2011.[1] The majority of lung transplant recipients experience at least one episode of acute rejection. The principal life-limiting factor for lung recipients after 1-year post-transplantation remains chronic rejection manifesting as chronic lung allograft dysfunction (CLAD).

Studies regarding the use of induction immunosuppression at the time of lung transplant are predominantly single-center, retrospective analyses or large registry studies resulting in significant variability among different centers, including approximately 50% of centers forgoing induction immunosuppression.[2] The largest multicenter, randomized controlled trial to date assessing antithymocyte globulin for induction immunosuppression in lung recipients found no difference in acute rejection, graft loss, or death in the treatment arm.[3]

The majority of lung transplant recipients are maintained on a three-drug immunosuppression regimen life-long, comprised of a calcineurin inhibitor (e.g

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cyclosporine or tacrolimus), an antimetabolite (e.g. azathioprine or mycophenolate mofetil), and corticosteroids. Tacolimus has been shown to be superior to cyclosporine with respect to acute rejection and chronic rejection in the form of bronchiolitis obliterans syndrome (BOS).[4,5] Mycophenoalte mofetil (MMF) has not clearly been shown to be superior to azathioprine in lung recipients, however many centers have converted to MMF as the first-line antimetabolite for lung recipients.

The role of mammalian target of rapamycin (mTOR) inhibitors (e.g. sirolimus and everolimus) in lung recipients is not clear and is an area of active investigation. Early use of mTOR inhibitors has been associated with catastrophic airway anastomotic complications and the use of these agents should be delayed until anastomotic healing is complete.[6] Although some studies have suggested the benefit of substituting an mTOR inhibitor in place of the antimetabolite, there is no consensus on the use of mTOR inhibitors in lung recipients.[7] The macrolide antibiotic azithromycin is known to have a myriad of antibacterial, antiviral, and immunomodulatory effects and has been shown to decrease the incidence of BOS in addition to improving or stabilizing lung function in lung recipients with BOS.[8,9] Lastly, extracorporeal photopheresis (ECP) has been used to treat CLAD/BOS in lung recipients with some success and may have some effect on donor specific antibodies and autoantibodies. There appear to be responders and nonresponders to ECP and hopefully prospective identification of responders will be possible in the future.[10] Of interest, ECP has been shown to be effective when started in the immediate post-operative period in heart transplant recipients and would be an intriguing strategy to investigate in lung recipients. [11]

The role of donor specific anti-HLA antibodies (DSA) and antibody-mediated rejection (AMR) is an emerging concern in lung recipients. DSA have been associated with CLAD, and although exactly how to deplete DSA in lung recipients is not known, it has been demonstrated that the clearance of DSA is associated with improved outcomes.[12] Our center described a case series of lung recipients with acute AMR, and in that series 6 of 21 patients died during their index hospitalization.[13] Additionally, one patient had CLAD prior to acute AMR and 14 of the 15 patients that survived the initial episode of AMR went on to develop CLAD. This underscores the importance of future studies on the treatment of DSA and the diagnosis and treatment of AMR in lung recipients.

Compared to other organs the outcomes after lung transplantation remain disappointing. The most recent data for adult lung recipients demonstrate a median survival of only 6.1 years.[1] Immunosuppressive regimens used in lung transplantation were historically derived from the experience with other solid organ transplants. However, such strategies may be flawed as data from our laboratory and others have clearly demonstrated that immune responses to lung grafts differ from those after transplantation of other organs.[14,15] Moreover, data have emerged that currently used immunosuppressants are associated with a higher incidence of certain malignancies in lung transplant recipients compared to kidney transplant patients.[16] Therefore, immunosuppressive protocols need to be developed that take unique immunological features of lungs into consideration.

Importantly, with the possible exception of small bowel grafts, lungs are the only commonly transplanted organs that are constantly exposed to the environment. This feature allows

innate immune stimuli access to the graft that can modulate and often potentiate adaptive immune responses. Such stimuli that have been shown to increase the risk of chronic rejection in the clinics include respiratory bacterial, viral, and fungal infections and gastroesophageal reflux. In addition, ischemia reperfusion injury, an innate immune insult that also predisposes to pulmonary graft rejection, can be particularly severe after lung transplantation. To this end, clinical data from Duke University have shown that lung transplant recipients, who are hyporesponsive to endotoxin due to polymorphisms in the innate immune receptor TLR4 experienced fewer episodes of acute rejection.[17] Our group has shown that ischemia reperfusion injury following lung transplantation enhances neutrophil production in the bone marrow and neutrophilic influx into the graft.[18] We identified that neutrophils, recruited to the transplanted lung due to either ischemia reperfusion injury or bacterial infection, interact directly with immune cells in the graft, which can result in T cell activation and rejection.[18,19] These observations build a case that partially depleting neutrophils during insults that result in their recruitment to the lung graft could ameliorate rejection responses. This may in part explain the finding that azithromycin may be more effective in cases of CLAD associated with bronchoalveolar lavage neutrophilia.[20] Furthermore, monocytes facilitate neutrophil entry into lung grafts during ischemia reperfusion injury and can also enhance $CD4^+$ T cell responses to donor antigens.[21,22] In addition, autoimmune responses triggered through an interaction between monocytes and T_h17 cells can contribute to the development of CLAD.[23] Therefore, future studies will have to investigate whether targeting this innate immune cell population can ameliorate lung rejection in the clinics.

It had been observed several decades ago in both experimental and clinical settings that rejection of lungs was initiated more rapidly than rejection of other organs. Work from our group has provided a potential mechanistic explanation for this observation. Unlike the case for other organ grafts where initiation of graft rejection depends on cell trafficking to graft-draining lymphoid organs, T lymphocytes can be primed within the lung graft itself.[14] In addition, we have shown that $CD8^+$ T cells can be activated within the graft airways.[24] To this end, some promising results have been reported with the use of inhaled immunosuppressants, which can achieve high levels within the lung.[25] Further development of such approaches could ameliorate rejection responses while limiting systemic toxicities.

Blockade of co-stimulatory pathways has been efficacious in preventing rejection and even inducing tolerance in several small animal transplant models. We have demonstrated in mouse lung transplant models that while blockade of the B7-CD28 co-stimulatory pathway alone was not sufficient to prevent rejection, peri-operative blockade of both B7-CD28 and CD40-CD40 Ligand pathways resulted in long-term graft survival and development of tolerance to donor antigen.[15,26] If such approaches could be translated to the clinics it would avoid the need for long-term maintenance immunosuppression with all its associated toxicities and complications. While blockade of the B7-CD28 pathway with belatacept is in clinical use for kidney transplantation, the experience with this agent is very limited in the case of lung transplantation at this point.[27] A recent study from our group has challenged the notion of indiscriminately depleting T cell populations as part of induction regimens and has further highlighted that principles established in other organ transplants may be deleterious for lungs. We have shown that a population of $CD8^+$ memory T cells is critical to prevent

lung graft rejection after peri-operatively inhibiting the B7-CD28 and CD40-CD40 Ligand pathways.[28] Interestingly, for other transplants $CD8^+$ memory T cells are considered a major barrier to tolerance induction.

Insights gained in experimental models of how innate and adaptive immune responses contribute to lung transplant rejection will allow for the development of immunosuppression that is specifically tailored for this challenging patient population. Recently developed mouse models of obliterative bronchiolitis may provide a platform for mechanistic investigations into the pathogenesis of CLAD.[29] Ex vivo lung perfusion will allow for a therapeutic window to treat the donor organ prior to transplantation, for example though depletion or transfer of cell populations, administration of drugs or targeted downregulation of immune receptors. [30]

References

1. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report--2013; focus theme: age. The Journal of Heart and Lung Transplantation. 2013; 32:965–78. [PubMed: 24054805]
2. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. The Journal of Heart and Lung Transplantation. 2012; 31:1073–86. [PubMed: 22975097]
3. Snell GI, Westall GP, Levvey BJ, et al. A randomized, double-blind, placebo-controlled, multicenter study of rabbit ATG in the prophylaxis of acute rejection in lung transplantation. American Journal of Transplantation. 2014; 14:1191–8. [PubMed: 24618385]
4. Treede H, Glanville AR, Klepetko W, et al. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: results of a prospective, randomized international trial in lung transplantation. The Journal of Heart and Lung Transplantation. 2012; 31:797–804. [PubMed: 22554673]
5. Hachem RR, Yusen RD, Chakinala MM, et al. A randomized controlled trial of tacrolimus versus cyclosporine after lung transplantation. The Journal of Heart and Lung Transplantation. 2007; 26:1012–8. [PubMed: 17919621]
6. King-Biggs MB, Dunitz JM, Park SJ, Kay Savik S, Hertz MI. Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. Transplantation. 2003; 75:1437–43. [PubMed: 12792493]
7. Snell GI, Valentine VG, Vitulo P, et al. Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. American Journal of Transplantation. 2006; 6:169–77. [PubMed: 16433771]
8. Vos R, Vanaudenaerde BM, Verleden SE, et al. A randomised controlled trial of azithromycin to prevent chronic rejection after lung transplantation. The European Respiratory Journal. 2011; 37:164–72. [PubMed: 20562124]
9. Jain R, Hachem RR, Morrell MR, et al. Azithromycin is associated with increased survival in lung transplant recipients with bronchiolitis obliterans syndrome. The Journal of Heart and Lung Transplantation. 2010; 29:531–7. [PubMed: 20133163]
10. Morrell MR, Despotis GJ, Lublin DM, Patterson GA, Trulock EP, Hachem RR. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. The Journal of Heart and Lung Transplantation. 2010; 29:424–31. [PubMed: 19853479]
11. Barr ML, Meiser BM, Eisen HJ, et al. Photopheresis for the prevention of rejection in cardiac transplantation. Photopheresis Transplantation Study Group. The New England Journal of Medicine. 1998; 339:1744–51. [PubMed: 9845709]
12. Hachem RR, Yusen RD, Meyers BF, et al. Anti-human leukocyte antigen antibodies and preemptive antibody-directed therapy after lung transplantation. The Journal of Heart and Lung Transplantation. 2010; 29:973–80. [PubMed: 20558084]

13. Witt CA, Gaut JP, Yusen RD, et al. Acute antibody-mediated rejection after lung transplantation. The Journal of Heart and Lung Transplantation. 2013; 32:1034–40. [PubMed: 23953920]
14. Gelman AE, Li W, Richardson SB, et al. Cutting edge: Acute lung allograft rejection is independent of secondary lymphoid organs. Journal of Immunology. 2009; 182:3969–73.
15. Li W, Bribriesco AC, Nava RG, et al. Lung transplant acceptance is facilitated by early events in the graft and is associated with lymphoid neogenesis. Mucosal Immunology. 2012; 5:544–54. [PubMed: 22549742]
16. Nair N, Gongora E, Mehra MR. Long-term immunosuppression and malignancy in thoracic transplantation: where is the balance? The Journal of Heart and Lung Transplantation. 2014; 33:461–7. [PubMed: 24742695]
17. Palmer SM, Burch LH, Trindade AJ, et al. Innate immunity influences long-term outcomes after human lung transplant. American Journal of Respiratory and Critical Care Medicine. 2005; 171:780–5. [PubMed: 15640363]
18. Kreisel D, Sugimoto S, Zhu J, et al. Emergency granulopoiesis promotes neutrophil-dendritic cell encounters that prevent mouse lung allograft acceptance. Blood. 2011; 118:6172–82. [PubMed: 21972291]
19. Yamamoto S, Nava RG, Zhu J, et al. Cutting edge: Pseudomonas aeruginosa abolishes established lung transplant tolerance by stimulating B7 expression on neutrophils. Journal of Immunology. 2012; 189:4221–5.
20. Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. American Journal of Respiratory and Critical Care Medicine. 2006; 174:566–70. [PubMed: 16741151]
21. Kreisel D, Nava RG, Li W, et al. In vivo two-photon imaging reveals monocyte-dependent neutrophil extravasation during pulmonary inflammation. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107:18073–8. [PubMed: 20923880]
22. Gelman AE, Okazaki M, Sugimoto S, et al. CCR2 regulates monocyte recruitment as well as CD4 T1 allorecognition after lung transplantation. American Journal of Transplantation. 2010; 10:1189–99. [PubMed: 20420631]
23. Burlingham WJ, Love RB, Jankowska-Gan E, et al. IL-17-dependent cellular immunity to collagen type V predisposes to obliterative bronchiolitis in human lung transplants. The Journal of Clinical Investigation. 2007; 117:3498–506. [PubMed: 17965778]
24. Kreisel D, Lai J, Richardson SB, et al. Polarized alloantigen presentation by airway epithelial cells contributes to direct CD8+ T cell activation in the airway. American Journal of Respiratory Cell and Molecular Biology. 2011; 44:749–54. [PubMed: 21653906]
25. Iacono AT, Johnson BA, Grgurich WF, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. The New England Journal of Medicine. 2006; 354:141–50. [PubMed: 16407509]
26. Gelman AE, Okazaki M, Lai J, et al. CD4+ T lymphocytes are not necessary for the acute rejection of vascularized mouse lung transplants. Journal of Immunology. 2008; 180:4754–62.
27. Kirk AD, Guasch A, Xu H, et al. Renal transplantation using belatacept without maintenance steroids or calcineurin inhibitors. American Journal of Transplantation. 2014; 14:1142–51. [PubMed: 24684552]
28. Krupnick AS, Lin X, Li W, et al. Central memory CD8+ T lymphocytes mediate lung allograft acceptance. The Journal of Clinical Investigation. 2014; 124:1130–43. [PubMed: 24569377]
29. Fan L, Benson HL, Vittal R, et al. Neutralizing IL-17 prevents obliterative bronchiolitis in murine orthotopic lung transplantation. American Journal of Transplantation. 2011; 11:911–22. [PubMed: 21521466]
30. Cypel M, Yeung JC, Liu M, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. The New England Journal of Medicine. 2011; 364:1431–40. [PubMed: 21488765]