Immunosuppression for Lung Transplantation
Evidence to Date

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Abstract

With the introduction of ciclosporin (cyclosporine) into routine clinical practice 20 years ago, lung transplantation has become an established treatment for patients with advanced lung disease. Most lung transplant recipients routinely continue to receive a triple-drug maintenance immunosuppressive regimen consisting of a calcineurin inhibitor, an antimetabolite and corticosteroids. The use of antibody-based induction therapy remains common, although there has been a shift away from T cell-depleting agents, such as antithymocyte globulin, towards anti-interleukin-2 receptor monoclonal antibodies. Recent years have seen the introduction of sirolimus and everolimus, immunosuppressive drugs that act by blocking growth factor-driven cell proliferation. While the newer immunosuppressive drugs have been rigorously evaluated in large randomised trials in kidney, liver and cardiac transplantation, such studies are lacking in lung transplantation. Despite a shift towards more potent immunosuppressive regimens that incorporate tacrolimus and mycophenolate mofetil, the development of chronic allograft rejection, as manifested by the bronchiolitis obliterans syndrome, continues to negatively impact on the long-term survival of lung transplant recipients. This article reviews the evidence for the immunosuppressive regimens used during induction and maintenance of patients undergoing lung transplantation, and discusses current strategies in the management of chronic rejection.

Lung transplantation is now an established therapy for the treatment of endstage pulmonary parenchymal and vascular diseases, with >25 000 procedures performed from >210 centres worldwide since 1983.\(^1\) Chronic allograft rejection (in the form of the bronchiolitis obliterans syndrome [BOS]) and infection remain the most significant threats to long-term survival and quality of life.\(^1\) Additionally, with a wide range of indications for lung transplantation, including cystic fibrosis, chronic obstructive pulmonary disease, interstitial lung diseases and pulmonary vascular diseases, recipients are of varying ages and have a varying intrinsic tolerance to immunosuppressive agents and their adverse effects.\(^1\) These factors interweave and interact to a great extent, mandating that immunosuppressive strategies in lung transplantation will always represent a critical individualised balance between the risks of rejection and infection.

Current practice has been derived from other solid organ transplant trials, evolving clinical practice and the limited clinical trial material actually generated from lung transplantations. Many of the randomised clinical trials performed involve small
numbers of patients, such that much of our current clinical practice is based on retrospective case series. Therefore, it is not surprising that the International Society for Heart and Lung Transplantation (ISHLT) Registry describes a wide variety of maintenance immunosuppressive therapies currently in use (almost invariably in combination with a corticosteroid; 2002–5), as follows:

- Tacrolimus + mycophenolate mofetil: 33% of patients at year 1 after lung transplantation, 26% at year 5
- Tacrolimus + azathioprine: 20% at year 1, 18% at year 5
- Ciclosporin + mycophenolate mofetil: 13% at year 1, 14% at year 5
- Ciclosporin + azathioprine: 12% at year 1, 16% at year 5
- Tacrolimus: 9% at year 1, 8% at year 5
- Sirolimus + calcineurin inhibitor: 6% at year 1, 7% at year 5
- Other agents: 7% at year 1, 11% at year 5.

With acute rejection rates in the first year of 50%, and chronic rejection (BOS) rates of 45% by 5 years, clinicians undertake significant switching between immunosuppressive regimens in an attempt to maximise efficacy and avoid toxicity.

1. Clinical Trials of Lung Transplantation Immunosuppression

1.1 Induction Therapy

On the basis of other solid organ transplant results, induction therapy in lung transplantation has potential benefits that could include lower rates of acute rejection, protection from nephrotoxicity due to the delayed introduction of a calcineurin inhibitor, and a decrease in the occurrence of BOS. The polyclonal agents, anti-lymphocyte/anti-thymocyte globulins (ALG/ATG), induce a rapid and profound generalised lymphopenia through Fc receptor-dependent mechanisms, including complement-related cytology and cell-mediated antibody-related cytolytic.

Monoclonal antibodies to CD25 inhibit activation of the interleukin (IL)-2 receptor and thereby selectively target activated T cells. A small number of centres use muromonab-CD3 (OKT3) or campath (monoclonal anti-CD52 antibody) for induction immunosuppression. The use of initial induction therapy with ALG/ATG has decreased to ~12% of all lung transplantations, while the use of IL-2 receptor antagonists (IL-2RA) has risen to 33%. However, the reality is that in lung transplantation, with few randomised trials and the limited available trials and case series showing conflicting or inconclusive results, no firm conclusions are possible. Induction therapy remains an area of active research.

Registry data from the ISHLT suggest that induction therapy with a polyclonal ATG significantly reduced the incidence of acute rejection in the first year after transplantation compared with either no induction or an IL-2RA. In a 44-patient, randomised, single-centre study of rabbit ATG versus conventional triple immunosuppression, Palmer and co-workers noted less acute rejection at 1 year but no difference in 2-year infection, malignancy or survival. Other studies have examined the efficacy of the IL-2RAs versus conventional immunosuppression. There were only subtle effects on acute rejection when daclizumab was used in two studies with historical controls. Similarly, basiliximab has been very recently studied in a 121-patient randomised double-blind trial versus placebo, with no clinically significant differences in outcomes at 1 year. Interestingly, limited head-to-head data comparing ATG and basiliximab suggest ATG may have superiority in terms of reducing acute rejection and BOS. Hopefully these conflicting results will be clarified as part of the outcomes of large multicentre blinded ATG studies currently in progress.

1.2 Maintenance Immunosuppression Therapy

Most lung transplant recipients receive a triple-drug maintenance regimen. The calcineurin inhibitors, ciclosporin (cyclosporine) or tacrolimus remain the cornerstone of long-term immunosuppression. As an antimetabolite, mycophenolate mofetil (MMF) has been increasingly favoured over the use of azathioprine. Although corticosteroids are unver-