Conventional and Novel Approaches to Immunosuppression

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The introduction of potent immunosuppressive agents over the past thirty years is one of the factors that has led to significant improvements in posttransplant survival in the current era of solid organ transplantation. By targeting multiple pathways involved in the alloimmune response to the graft, rates of both acute and chronic rejection have declined. Unfortunately, these agents have not been as effective in lung transplantation where graft rejection remains a major obstacle to long-term survival. In this article, both conventional and novel approaches to preventing graft rejection are reviewed. Immunosuppressive therapy to treat established acute or chronic rejection is discussed elsewhere in this issue.

CONVENTIONAL APPROACHES

Although there is some variability in the medications used at different lung transplant centers, the approach to immunosuppression is generally similar. Maintenance regimens typically involve administration of three distinct classes of immunosuppressive agents: calcineurin inhibitors (CNIs; eg, cyclosporine, tacrolimus), antiproliferative agents (eg, azathioprine, mycophenolate mofetil [MMF], sirolimus), and corticosteroids. In addition, approximately 60% of lung recipients receive induction therapy to augment immunosuppression in the early posttransplant period. Institutional immunosuppression protocols are largely based on evidence from methodologically flawed studies: retrospective single-center experiences and prospective studies that were not randomized, involved small numbers of patients, or compared outcomes to historical data. For many years, the strongest evidence has come from more robust studies in other solid organ transplant populations. In the past decade, however, several large, multicenter clinical trials have been performed in lung transplantation and have informed practice patterns.

Induction Therapy

Induction therapy involves the administration of a potent immunosuppressive agent in the perioperative or early postoperative period to reduce risk of acute rejection and permit more gradual initiation of maintenance immunosuppression. Several types of induction agents are currently in use and specifically target T-lymphocytes, the primary effector cells of the cell-mediated immune system.

The most common induction agents used in clinical practice are humanized or chimeric monoclonal antibodies to CD25 (eg, daclizumab, basiliximab), the alpha subunit of the interleukin-2 receptor (IL-2R).[1] By blocking signaling through the IL-2R, these drugs inhibit T-cell proliferation and differentiation, without inducing depletion. Both daclizumab and basiliximab are generally

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well tolerated. However, there is concern that inhibition of IL-2 mediated signaling, which is also necessary for generation of $CD4^+CD25^+FoxP3^+$ T regulatory cells, may disrupt the delicate balance between alloreactivity and tolerance.[2]

In the latest report from the International Society of Heart and Lung Transplantation (ISHLT), approximately 13% of lung recipients in 2008 received induction therapy with polyclonal antithymocyte globulins (ATG) such as Thymoglobulin or Atgam.[1] These drugs were developed by immunizing rabbits or horses with human thymocytes to induce development of antibodies against a broad range of human T-cell markers.[3] Although the mechanisms responsible for their antirejection properties are not completely understood, administration of these agents results in profound depletion of T-cells, including alloreactive T-cells. It is not clear, however, what effect these drugs have on immunologic mechanisms that promote tolerance to the allograft. For example, animal studies have suggested that repopulation of the T-cell repertoire after initial depletion may consist of lymphocytes with a more alloreactive phenotype.[4] In contrast, other reports indicate that T-cell depletion may spare $CD4^+CD25^+FoxP3^+$ T-regulatory cells and thus promote immunologic tolerance.[5] Better understanding of the pleiotropic effects of antilymphocyte agents on the immune system is required to assess overall impact on the alloimmune response. Numerous clinical side effects associated with polyclonal antilymphocyte agents have been reported and include anaphylaxis, cytokine storm, serum sickness, leukopenia, anemia, and thrombocytopenia as well as increased risk of infection and malignancy.[3]

Alemtuzumab (Campath-1H) is a humanized monoclonal antibody to CD52, a cell surface marker found on all mononuclear lymphocytes. It is used by only a few transplant centers for induction therapy.[1] Alemtuzumab administration results in profound and prolonged T-cell depletion with variable effects on B-lymphocyte, natural killer cells, and monocyte populations. Thus, it is not surprising that infectious complications are among the most common adverse events reported. Similar to the polyclonal agents, a number of side effects have been reported with alemtuzumab use and include infusion-related anaphylaxis and profound cytopenias.[6]

Induction therapy in lung transplantation remains controversial and only about 60% receive this type of immunosuppression.[1] Although reports suggest that increased immunosuppression in the early posttransplant period reduces the risk of acute rejection, this potential benefit may be offset by an increased risk of infection or other induction therapy-associated adverse events. Unfortunately, published information from large, multicenter, prospective, randomized studies comparing induction therapy to placebo is lacking. Similarly, high quality studies comparing one regimen to another are also absent. Thus, transplant center practices regarding induction therapy are based largely on retrospective studies, registry reports, and small prospective single-center investigations as well as institutional experiences and expert opinion.[7–11] A few of these studies are reviewed below.

In the 2010 annual report of the ISHLT registry, induction therapy was associated with a small but statistically significant survival benefit (unadjusted for confounding effects) and decrease in the rate of bronchiolitis obliterans syndrome (BOS) in patients who survived at least 14 days.[1] In a more rigorous retrospective study of almost 4000 lung transplant recipients in the ISHLT registry transplanted between January 2000 and March 2004, induction therapy with either an IL-2R antagonist or polyclonal ATG remained independently associated with improved survival at 4 years (IL2R antagonist, 64%; ATG, 60%; no induction, 57%) even after adjustment for multiple donor and recipient specific variables. Interestingly, no differences in BOS rates were seen in the IL-2R antagonist treatment group compared with the no induction group, whereas BOS rates were slightly higher in the ATG treatment group. There was also a significantly higher rate of infection in both induction therapy groups compared with patients who did not receive induction therapy.[12] In a randomized single-center study of 50 lung transplant patients comparing induction therapy with ATG versus daclizumab, both treatment groups had comparable rates of acute and chronic rejection as well as survival after 1 year. Although cytomegalovirus (CMV) infection rates were higher in the daclizumab group, this may be explained by the significantly greater numbers of CMV-mismatched patients in the daclizumab group.[13]

Alemtuzumab (Campath-1H) induction has recently been studied in lung transplantation after experience in kidney transplantation suggested that it may allow use of lower levels of maintenance immunosuppression without increasing cellular rejection rates or infectious complications.[6] The first report was published by investigators at the University of Pittsburgh. They retrospectively compared short-term outcomes of 48 lung transplant patients who received either ATG or alemtuzumab induction followed by maintenance immunosuppression with tacrolimus with or without low-dose corticosteroids to 28 historical controls who received daclizumab induction and