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Induction therapy in heart transplantation

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Abstract

Survival after heart transplantation (HTx) has improved considerably over the past 20 years. Half of all patients now live more than 13 years, and approximately more than 25% live more than 20 years. The long-term results of cardiac transplantation have continued to improve due to improved peri-operative care and immunosuppression regimens. The risk for acute rejection is highest early after HTx and therefore many transplant centers use a strategy of peri-operative induction therapy in order to provide a rapid and effective protection against acute allograft rejection (1,2).

Key words: heart transplantation, immunosuppression, induction therapy

The rejection of a transplanted organ is primarily a T-lymphocyte (T-cell)-mediated event, although humoral (B-cell) responses also contribute. The exception is hyperacute rejection, which occurs when preformed antibodies to human leukocyte antigens (HLA) result in an immediate rejection. Immune recognition of donor antigens that differ from those of the recipient (allorecognition) begins with the function of antigen-presenting cells (APCs). Donor APCs that are carried passively in the graft express donor alloantigens and may be recognized directly by recipient T cells (direct allorecognition). Additionally, donor alloantigens can be shed by cells in the graft, taken up by the recipient's APCs, and then presented to recipient T cells (indirect allorecognition). The alloantigens on the surface of the APC are recognized by the T-cell receptor (TCR)-CD3 complex on the surface of the T cell. However, optimal T-cell activation occurs only when there is a second or costimulatory signal between the

APC and the T cell. Several costimulatory molecules have been identified that function as receptor-ligand pairs on the APC and T-cell surface that mediate adhesion and mutual activation. Engagement of the TCR-CD3 complex by APC, followed by costimulatory signals, results in activation of calcineurin in the cytoplasm of the T cell. Calcineurin dephosphorylates an important transcription factor, nuclear factor of activated T cells (NF-AT), allowing it to enter the nucleus and bind to the promoters of interleukin-2 (IL-2) and other cytokines. Secreted IL-2 activates the cell-surface IL-2 receptor (IL-2R), stimulating clonal expansion of T cells. IL-2 (along with other cytokines) produced by these T helper cells stimulates expansion of other cells of the immune system, including other T helper cells, cytotoxic T cells, B cells, and natural killer cells. Engagement of the IL-2R, like many other growth factor receptors, activates the enzyme target of rapamycin (TOR). TOR regulates the translation of mRNAs to proteins

that regulate the cell cycle. The lymphocyte cell cycle requires the de novo synthesis of purines, a process controlled by the enzyme inosine monophosphate dehydrogenase. Figure 1 highlights mechanisms of allograft rejection.

Immunologic mechanisms are shown in black; immunosuppressive drugs and their site of action are shown in grey. Acute rejection begins with recognition of donor antigens that differ from those of recipient by recipient APCs (indirect allorecognition). Donor APCs (carried passively in the graft) may also be recognized by recipient T cells (direct allorecognition). Alloantigens carried by APCs are recognized by TCR-CD3 complex on surface of T cell. When accompanied by costimulatory signals between APC and T cells such as B7-CD28, T-cell activation occurs, resulting in activation of calcineurin. Calcineurin dephosphorylates transcription factor NF-AT, allowing it to enter nucleus and

bind to promoters of IL-2 and other cytokines. IL-2 activates cell surface receptors (IL-2R), stimulating clonal expansion of T cells (T helper cells). IL-2, along with other cytokines produced by T helper cells, stimulates expansion of other cells of the immune system. Activation of IL-2R stimulates TOR, which regulates translation of mRNAs to proteins that regulate cell cycle. Sites of action of individual drugs (highlighted in grey) demonstrate multiple sites of action of these drugs, underscoring rationale for combination therapy. AZA indicates azathioprine; MMF, mycophenolate mofetil; GR, glucocorticoid receptor; DAC, daclizumab; and BAS, basiliximab. Rejection of the transplanted heart is a major cause of morbidity and mortality in the first year after heart transplantation. Rejection is classified as hyperacute, acute cellular, acute humoral (vascular), or chronic. Hyperacute rejection occurs within minutes to hours of the blood flow being reestablished and is

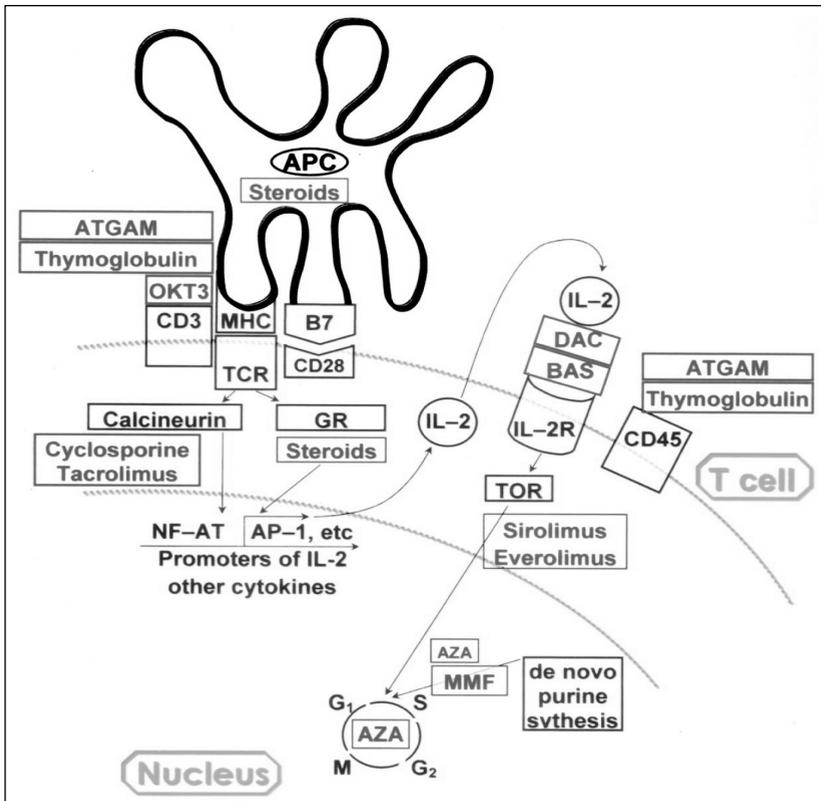


Figure 1: Mechanisms of allograft rejection (see text).

caused by preformed antibodies to ABO blood group antigens, HLA, or endothelial antigens. With ABO matching of recipients to donors and prospective cross-matching of patients who have been previously sensitized to HLA, hyperacute rejection is rare. When it does occur, it is catastrophic because preformed antibodies bind to endothelial antigens on the transplanted heart, resulting in activation of complement. An acute inflammatory infiltrate results in fibrinoid necrosis of the vessels of the grafted organ.

Acute cellular rejection may occur at any time after transplantation but is most common in the first 3 to 6 months. It is a T-cell-mediated response with infiltration of lymphocytes and macrophages and resultant myocytolysis. Acute humoral (also called vascular) rejection occurs days to weeks after heart transplantation and is initiated by antibodies rather than T cells (3,4). The alloantibodies are directed against donor HLA or endothelial cell antigens. Patients at greatest risk of acute humoral rejection include women, patients with a high panel reactive antibody screen and/or a positive cross-match, cytomegalovirus-seropositive recipients, and recipients with sensitization to OKT3. Acute humoral rejection is much less common than acute cellular rejection, occurring in 7% of patients. Its importance stems from its common association with severe ventricular dysfunction, presumably caused by diffuse ischemia secondary to a lack of coronary vasodilatory reserve.

Induction immunosuppression early after heart transplantation is believed to reduce the risk of acute graft rejection and, thus, may have an impact on outcome. More than 50% of centers reporting to the registry of the International Society for Heart and Lung Transplantation (ISHLT) use an induction therapy. Most centers use either an interleukin-2 receptor antagonist (26% of all) or a polyclonal anti-thymocytic (ATG) or an anti-lymphocytic (ALG) antigen (23%); only few centers choose OKT-3 (0,8%) for de novo HTx recipients.

Monoclonal and polyclonal antithyroglobulins are considered the optimal induction agents. Reducing the number of T-cells, which are responsible for graft rejection, is believed to be the most effective method to achieve a rapid and effective immunosuppression early post-transplantation. Most centers administer 1 – 2 mg/kg body weight with an infusion over 4 to 6 hours for 2 to 4 days. Caution should be exercised after the initial dose of monoclonal antithyroglobulins due to the small risk of respiratory and hemodynamic compromise. Antibodies result in substantial lymphocyte depletion (5). These preparations contain antibodies to many surface T- and B-cell molecules, including HLA (6). Antibodies to CD45, a protein that plays a role in T-cell activation, may be particularly important in reversing rejection and inducing tolerance (7). Treatment results in complement-dependent opsonization and eventual cell lysis and may contribute to apoptosis of these cells. Because batches of polyclonal antibodies vary in potency, monitoring of T cells with flow cytometry is helpful in assessing effectiveness and adjusting dosing. There is a risk of allergic reactions. The cytokine release syndrome can occur. Hypertension, diarrhea, and headache are common. Leukopenia and thrombocytopenia may require either a reduction in dose or termination of therapy. There is an increased incidence of either primary or reactivation of cytomegalovirus infections (7).

More recently, IL-2R antagonists have been used for induction therapy. In renal and heart transplant recipients, IL-2R antibodies appear to decrease the risk of rejection in the early postoperative period without increasing infection. Basiliximab is a chimeric (mouse/human) anti-IL-2R monoclonal antibody with mouse variable regions fused to the constant regions of a human IgG and is used as an anti-cytokine receptor antibody for induction therapy in transplantation; usual doses are 20 mg early after HTx and a repeat dose of 20 mg 72 to 94 hours later. Basiliximab binds the subunit of IL-2R expressed on antigen-activated T cells. This prevents binding of IL-2 to the

IL-2R, inhibiting proliferation of T cells (8,9). Few serious common adverse events have been reported. Cytokine release syndrome does not occur after administration of these drugs, and there has been no reported increased risk of infection or malignancy (8-11). Hypersensitivity has been reported with initial exposure and reexposure to basiliximab. The second dose should be withheld if complications such as hypersensitivity occur (12-14). For this reason, in a clinical setting, most centers administer 500 – 1000 mg of methylprednisolone accompanied by histamin blockers (both again H1 and H2) 30 minutes prior to antibody (both ALG/ATG or basiliximab) administration.

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