

# Induction immunosuppression for orthotopic heart transplantation: a review

**Objectives**—To describe the appropriateness and safety of induction immunosuppression for patients at risk for fatal rejection, and to describe the safety and effectiveness profiles of the induction regimens available in the United States.

**Data Sources**—MEDLINE/PubMed database, EMBASE database, Google Scholar; references from pertinent articles were also reviewed to identify additional data.

**Study Selection**—A systematic literature review from January 1, 1980, through June 30, 2008, was performed. Included articles ranged from case series to prospective randomized controlled double-blind placebo-controlled trials that detailed the following topics with respect to induction immunosuppression: risk of fatal rejection, renal sparing, malignancy, OKT3, rabbit or equine antithymocyte globulin, daclizumab, basiliximab, and alemtuzumab.

**Results**—Patients at highest risk for fatal rejection experienced a survival benefit from induction immunosuppression, whereas all other patients experienced no benefit or harm. Most of the early data detail positive experiences with polyclonal antibody regimens. Several newer trials compare the use of polyclonal strategies with the use of anti-CD25 targeted monoclonal antibodies. Few researchers have assessed the usefulness of an anti-CD52 approach. Overall, induction therapy remains a poorly studied and widely variable practice among the major US heart transplant centers.

**Conclusion**—At present, the unrestricted use of induction for all patients does not seem prudent. Induction should be individualized for each patient on the basis of a well-designed protocol, careful analysis of the transplant center's demographics, and the effectiveness and safety profiles of the regimens used. (*Progress in Transplantation*. 2009;19:333-342)

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## Notice to CE enrollees:

A closed-book, multiple-choice examination after this article tests your ability to accomplish the following objectives:

1. Identify patient populations that benefit most from induction immunosuppression
2. Describe 3 untoward effects of drugs used as induction immunosuppression
3. Analyze how the use of induction immunosuppression affects rejection rates in heart transplant recipients

Induction immunosuppression has been used effectively in kidney transplantation for many years; however, similar benefits have not been realized in

orthotopic heart transplant recipients.<sup>1-4</sup> Several groups have attempted to identify the risk factors associated with fatal rejection in patients undergoing heart transplantation, yet no consistent pattern has emerged.<sup>2-7</sup> Many theories have been proposed to account for this disparity, such as a higher rate of death from infectious causes, differences in ischemic time, and variation among recipients in different studies.<sup>5,6</sup> Few associations between these factors have been documented. Accordingly, multiple groups have assessed the large transplant registries in an effort to identify those patients at the highest risk for fatal rejection in whom induction therapy may be beneficial.<sup>2,3</sup> Apart from the populations most appropriate for induction, the optimal regimen is not known, as several induction agents are available in the United States.<sup>1,3</sup> The indications for induction, the

strategies used, and the evidence and controversies surrounding their use are reviewed herein, and recommendations regarding their use are discussed.

### Data Sources and Study Selection

A systematic literature review from January 1, 1980, through June 30, 2008, was performed by using MEDLINE/PubMed and Embase databases and Google Scholar. Included articles ranged from case series to prospective randomized controlled double-blind placebo-controlled trials that detailed the following topics with respect to induction immunosuppression: risk of fatal rejection, renal sparing, malignancy, OKT3, rabbit or equine antithymocyte globulin, daclizumab, basiliximab, and alemtuzumab. Additionally, references from pertinent articles were reviewed to identify additional data.

### Indications for Induction Immunosuppression

Several indications have been suggested for the provision of induction immunosuppression to patients undergoing orthotopic heart transplantation, such as decreasing pretransplant antigenic load, delaying acute rejection, and prolonging graft survival. Induction is commonly provided to prevent early nephropathy induced by calcineurin inhibitors (renal sparing strategy) and fatal rejection.<sup>4-7</sup> However, little evidence has emerged regarding the safety or effectiveness of such induction therapies for these indications in heart transplant recipients.

### Fatal Rejection

Higgins and colleagues<sup>2</sup> published a review of the Cardiac Transplant Research Database in 2005 in an effort to identify those patients at the highest risk for fatal rejection. The authors queried the database from 1990 to 2001 and identified a study group of 5897 patients. During the 11-year study period, 66% of patients received no induction, 19% received muromonab-CD3 (OKT3, Orthoclone-OKT3, Ortho Biotech, Raritan, New Jersey), 9.2% received antithymocyte globulin preparations, and 5% received monoclonal antibodies targeted at interleukin 2 (IL-2). The crude survival rate among patients who received induction was lower than the rate in patients who did not receive induction, with a statistically significant difference ( $P < .001$ ) occurring at 1 year and maintained thereafter.

Induction did provide a significant survival advantage in the patients ( $P < .05$ ) at highest risk for fatal rejection (>5% at 1 year). These recipients were identified as African Americans 25 years old or younger with 4 or more HLA mismatches, African Americans 40 years old or younger with 4 or more HLA mismatches and who received ventricular-assist device (VAD) support for more than 6 months before trans-

plant, or non-African Americans 35 years old or younger with 4 or more HLA mismatches who received VAD support for more than 6 months before transplant.

In light of the Higgins data, Cohen et al<sup>7</sup> published an interesting evaluation of ethnicity as a predictor of graft longevity and recipient mortality in heart transplant recipients. This retrospective database review of 525 patients was conducted between 2000 and 2005. Enrolled patients did not receive induction and were started on standard triple-therapy immunosuppression after transplantation, consisting of a tacrolimus-based regimen, along with an antiproliferative agent such as mycophenolate mofetil, and steroids. Crude mortality was highest among the African American recipients (26.7%), followed by whites (19.5%) and Hispanics (18.9%). The rate of rejection was higher in African American (7.7%) and Asian (10.7%) donors. These findings further support those of Higgins et al and affirm that African Americans are most likely at the highest risk for fatal rejection.

### Renal Sparing Strategy: Delayed Calcineurin Inhibition

Apart from the risk of fatal rejection, the risk of renal failure in the posttransplant population is significant. Several groups have suggested that providing induction therapy to heart transplant patients can safely delay the start of calcineurin inhibition, which in turn may decrease calcineurin-induced renal failure. Moreover, Al Aly et al<sup>8</sup> identified the risk factors for posttransplant renal insufficiency as age, pretransplant glomerular filtration rate, diabetes, and hypertension. Odium et al<sup>9</sup> further specified these findings and determined that patients with a glomerular filtration rate less than 40 mL/min or patients who required posttransplant dialytic support were at a significantly greater risk of death.

Accordingly, several groups have studied induction therapy with either rabbit antithymocyte globulin (rATG, Thymoglobulin, Genzyme Transplant, Cambridge, Massachusetts) or basiliximab (Simulect, Novartis, East Hanover, New Jersey) in an effort to delay the initiation of calcineurin inhibition to prevent renal failure.<sup>10,11</sup> Rosenberg et al<sup>10</sup> performed a prospective trial of basiliximab to delay cyclosporine initiation in patients at high risk of postoperative renal insufficiency versus standard preoperative initiation of cyclosporine on day 0. Patients in the basiliximab arm were defined as those with a serum level of creatinine (SCr) of 2.5 mg/dL or greater or a glomerular filtration rate less than 50 mL/min. Patients in the standard arm were defined as having normal SCr. Twenty-five patients received basiliximab 20 mg on days 0 and +4 with initiation of cyclosporine on day +4 and 33 patients received cyclosporine on day 0. Authors also identified a retrospective group of 32

Table Induction immunosuppression regimens

Strategy	Agent	Dosing schedule	Relative efficacy	Relative safety	Notes
Cytolytic	Antithymocyte globulin, rabbit (Thymoglobulin)	1.5 mg/kg per dose on days 0, +1; +2	+++	++	1. Hypersensitivity reactions, serum sickness, and severe leukopenia possible
	Muronomab-CD3 (OKT3)	5 mg/dose for 7 days	++	+	2. Premedicate 1-4 hours before with methylprednisolone 8 mg/kg intravenously Give the following at the time of dosing Acetaminophen 650 mg orally or rectally Diphenhydramine 50 mg orally or intravenously Famotidine 40 mg orally or intravenously or Ranitidine 150 mg orally or intravenously
Anti-CD25 (IL-2R $\alpha$ )	Daclizumab (Zenapax)	1 mg/kg per dose every 14 days for 5 doses Alternative: 2 mg/kg per dose on days 0, +14	++	+++	1. Well tolerated 2. Premedication not required
	Basiliximab (Simulect)	20 mg/dose on days 0; +4	+	+++	
Anti-CD52	Alemtuzumab (Campath-1H)	Optimal dosing not known	Efficacy not known	+ / ++	1. Poorly studied 2. Potential for cardiotoxic effects 3. Use not currently recommended

patients who met the basiliximab criteria and received standard cyclosporine for comparative purposes (high-risk cyclosporine). The increase in SCr after transplantation was not significantly different in the basiliximab and standard groups, but the difference was significantly less between the basiliximab and high-risk cyclosporine groups (-0.1 vs +0.5,  $P < .02$ ). Furthermore, no patients in the basiliximab group and 13 patients in the cyclosporine group experienced rejection during the 1-year study period.

Similarly, Delgado et al<sup>11</sup> conducted a prospective randomized study to compare the use of basiliximab with rATG induction therapy to delay the initiation of cyclosporine. All patients had pretransplant renal insufficiency, defined as an SCr greater than 2 mol/L. Seven patients were treated with basiliximab 20 mg on day 0 and +4, and an additional 7 patients were treated with rATG beginning on day 0 and continued for 10 days adjusted for absolute lymphocyte count. Cyclosporine was initiated on day +5 in both groups. All patients were alive at the end of the 6-month follow-up and had a similar decrease in SCr. This decrease persisted throughout the entire study follow-up period. These data suggest that the induction-aided delay in calcineurin inhibition may be effective in preventing renal failure and is not associated with an increase in rejection episodes in the first year after transplantation.

### Induction Immunosuppression Regimens

Several agents at different doses and durations have been studied in heart transplantation (see Table). These strategies fall into 1 of 3 categories: cytolytic, anti-CD25 (IL-2R $\alpha$ ) targeted, or anti-CD52 targeted. The cytolytic approach consists of the polyclonal antithymocyte globulins produced in rabbits (Thymoglobulin) or horses (equine, ATGAM, Pharmacia & Upjohn, New York, New York) and the monoclonal antithymocyte antibody muronomab-CD3. The IL-2R $\alpha$  targeted approach consists of the monoclonal antibodies daclizumab (Zenapax, Roche, Nutley, New Jersey) and basiliximab. The anti-CD52 targeted approach consists solely of alemtuzumab (Campath-1H, Genzyme Transplant, Cambridge, Massachusetts).

#### Cytolytic Strategy

##### Antithymocyte Globulins

Two polyclonal globulin formulations are available: equine or rabbit. Polyclonals produce significant lymphocyte depletion by targeting several antibodies on both T and B cells, including HLA antigen.<sup>12,13</sup> Targets of polyclonals include CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR, HLA class 1 heavy chains, and  $\beta$ 2 microglobulin. Polyclonals mediate T-cell suppressive effects via inhibition of proliferative responses to several mitogens. T-cell

depletion is usually observed within 24 hours of the start of polyclonal therapy.<sup>14</sup> Hypersensitivity reactions are possible with repeated exposures to either the equine or the rabbit product. Serum sickness may occur after as little as 1 administration of either product but has been reported at higher frequency with the equine product.<sup>4</sup>

### Monoclonal Antithymocyte Antibody

OKT3 is a murine antibody that is specific for the CD3 molecule on T cells. OKT3 binds to CD3, rendering the T cell unable to respond to antigenic challenge and produces a rapid and significant depletion in circulating CD3+ T cells within minutes after initiation.<sup>15</sup> This binding causes an initial activation of T cells, which upregulate production and release of cytokines, manifesting the cytokine release syndrome.<sup>16</sup> The cytokine release syndrome typically occurs between the first and second doses of OKT3 and is the most life-threatening adverse reaction.

Additionally, Hammond et al<sup>17</sup> identified higher rates of vascular rejection that correlated with the use of OKT3. They studied 20 patients who received a 14- to 21-day course of OKT3 and monitored serum CD3 levels during and after induction. A surge of CD3-expressing cells was seen in as little as 3 days after induction, resulting in rejection in 6 of the 20 patients studied. A strong correlation was found between OKT3 use and vascular rejection with human anti-mouse antibody production ( $P < .01$ ) in these 6 patients.<sup>17</sup>

### Polyclonal Versus Monoclonal Antithymocyte Globulins

Many have suggested that major differences are present in the effectiveness, and particularly the safety profile, of OKT3 versus the polyclonal antithymocyte globulins. Accordingly, Haddad et al<sup>18</sup> performed a meta-analysis of published trials that compared the polyclonal and monoclonal strategies and studied several outcome measures. Studies included 5 trials that enrolled 215 patients who were randomized to receive either rATG or OKT3. No difference between rATG and OKT3 was found in 1-year survival (relative risk [RR], 0.98; 95% confidence interval [CI], 0.91-1.06), infections (RR, 0.85; 95% CI, 0.69-1.05; favors rATG), or graft rejection (RR, 0.97; 95% CI, 0.72-1.3). Significant increases in adverse effects were seen with OKT3, resulting in more pulmonary edema, fever, and hypotension. Particularly alarming was the increase in prevalence of lymphomas with OKT3 compared with rATG.<sup>18</sup>

### Prevention of Coronary Allograft Vasculopathy

Coronary allograft vasculopathy (CAV) is one of many adverse effects of transplantation and can be exacerbated by several available agents used for

maintenance immunosuppression. As a result, induction immunosuppression has been suggested as a method of prolonging the time to CAV development. Accordingly, Zhang et al<sup>19</sup> compared the long-term effects of rATG and OKT3 on mortality and development of CAV. Authors enrolled 75 patients treated with rATG and OKT3 between 1988 and 1991 and followed them up for 10 years. Neither therapy exhibited any effect on long-term survival; however, rATG significantly decreased the incidence of CAV when compared with no induction ( $P = .02$  and  $.05$ , respectively) and rATG significantly extended the time to manifestation of CAV by approximately 3 years ( $P = .03$ ). These benefits were not observed with OKT3, suggesting that in patients at high risk for CAV, induction with rATG may be advisable.<sup>19</sup>

### Adverse Effects of Cytolytic Induction Malignancy

Mortality related to malignancy has eclipsed deaths related to CAV at 5 years and is responsible for nearly one-third of all reported deaths after OHT.<sup>20,21</sup> Both the Haddad<sup>18</sup> and Zhang<sup>19</sup> groups reported the rates of lymphoma, lymphoproliferative disorders, and malignancy in their studies. Haddad et al reported that lymphoma had developed in 0% of patients treated with rATG and 17% of patients treated with OKT3 at 1 year. Zhang et al reported the 10-year incidence of nonskin cancer as 0% in patients who were not induced, 8% in patients induced with rATG, and 16% in patients induced with OKT3. Additionally, Zhang et al reported the total incidence of non-skin cancer in the follow-up period as 12% in patients who were not induced, 20% in patients induced with rATG, and 24% in patients induced with OKT3.

Moreover, Swinnen et al<sup>22</sup> performed a retrospective case-control analysis of 154 patients, 79 of whom were treated with OKT3, at a single center. Lymphoproliferative disorders developed in 1.3% of patients who were not induced, compared with 11.4% of patients induced with OKT3 (odds ratio [OR], 9.5; 95% CI, 1.6-54.7,  $P = .001$ ). The incidence was 5-fold higher in those who received lifetime doses, for induction and rejection, of greater than 75 mg of OKT3.<sup>22</sup>

These findings were broadened by the work of El-Hamamsy et al,<sup>23</sup> who performed a prospective observational analysis of 207 heart transplant patients treated with a 3-day course of rATG for induction from 1982 to 2002. In their study, a neoplasm was diagnosed in 21% of patients; however, multivariate analysis did not identify rATG induction as a significant factor in the development of the neoplasm. In patients treated with rATG, the time to diagnosis of a neoplasm was significantly shorter than the time in patients not induced ( $P = .007$ ). Additionally, time to death after diagnosis of a neoplasm was significantly shorter in patients

treated with rATG than in patients who were not induced ( $P = .006$ ).<sup>23</sup>

### Cytomegalovirus Infections

Infection with cytomegalovirus (CMV) has long been implicated in mortality increase and graft loss after transplantation. However, evidence supporting this claim was not available until the recent publication of the work of Sagedal and colleagues.<sup>24</sup> These authors studied 397 consecutive kidney transplant patients from 1994 to 1997 to identify the effect of asymptomatic and overt CMV infection on mortality and graft loss.<sup>24</sup> Authors concluded that both asymptomatic CMV infection (RR, 2.9; 95% CI, 1.61-5.22;  $P = .001$ ) and overt CMV infection (RR, 2.5; 95% CI, 1.31-4.79;  $P = .006$ ) significantly increased recipient mortality after 100 days. In addition, CMV infection resulted in significantly increased graft loss ( $P = .001$ ).<sup>24</sup>

Problematically, cytolytic induction therapy has been directly implicated in the acquisition of CMV infection.<sup>25-27</sup> San-Juan et al<sup>25</sup> performed a prospective multicenter observational trial to detect factors associated with the development of CMV disease. Authors evaluated 1470 consecutive kidney transplants at 16 different centers from 2003 to 2005. Significant factors associated with acquisition of CMV disease were donor-recipient CMV mismatch (OR, 5.9; 95% CI, 3.7-9.4;  $P < .001$ ), use of OKT3 or rATG for induction (OR, 2.1; 95% CI, 1.14-3.8;  $P = .002$ ), use of cyclosporine (OR, 1.9; 95% CI, 1.22-3.06;  $P = .04$ ), and acute rejection episodes (OR, 2.63; 95% CI, 1.66-4.1;  $P < .001$ ).<sup>25</sup> Adding to this evidence, Mattei et al<sup>27</sup> reported that the incidence of CMV was significantly higher in the group induced with rATG (23.8%) than in the group treated with basiliximab (15.8%).

### Anti-CD25 (IL-2R $\alpha$ ) Strategy

#### IL-2R $\alpha$ Monoclonal Antibodies

There are 2 monoclonal antibodies against the IL-2 receptor, humanized daclizumab and chimeric basiliximab. Since 1995, the use of these monoclonal antibodies has increased by 30%.<sup>28</sup> The IL-2R $\alpha$  monoclonal antibodies do not deplete lymphocytes and block the binding of IL-2 to its receptor, inhibiting the proliferation of T cells.<sup>29</sup> It is speculated that this action alone is not sufficient to inhibit rejection and alternative mechanisms are likely to contribute to the effectiveness of these antibodies.<sup>30,31</sup> The utility of these agents for induction has been attractive since their introduction; as a result, several large trials have been published that detail their safety and effectiveness.

The first landmark study of the IL-2R $\alpha$  monoclonal antibodies was published by Hershberger et al,<sup>5</sup> who performed a prospective randomized blinded placebo controlled trial containing 434 recipients of daclizumab (1 mg/kg every 14 days for 5 doses) for

induction in heart transplantation. Patients with a preoperative requirement for a VAD were excluded. The primary end point of rejection and death was evaluated for a 6-month period. The rate of the primary end point was significantly lower in the daclizumab group (35.6% vs 47.7%,  $P = .007$ ) at 6 months. Alarming, more patients died in the daclizumab group than in the placebo group (6 vs 0) when they received concomitant cytolytic therapy.<sup>5</sup>

As a result of the prospective data provided by Hershberger et al, Kobashigawa et al<sup>32</sup> performed a retrospective database review of the scientific registry of transplant recipients from 1998 to 2003 to characterize the rates of rejection, infection, and death. Patients received daclizumab therapy ( $n = 684$ ) or no induction ( $n = 2525$ ). Patients induced with daclizumab had a significantly lower rate of acute rejection at 6 months (0.77; 95% CI, 0.62-0.94;  $P = .005$ ), 1 year (0.77; 95% CI, 0.67-0.89;  $P < .001$ ), and at 3 years (0.83; 95% CI, 0.73-0.95;  $P = .006$ ). The risk of crude mortality (85.1% vs 85.2%) or infectious death (3.8% vs 3.1%) was no greater with daclizumab than with placebo. These data were reassuring to the heart transplant community and reaffirmed the safety and effectiveness of daclizumab for induction.

#### IL-2R $\alpha$ Dosing Strategies

Basiliximab has a simplified dosing regimen (20 mg on days 0 and +4), whereas the dosing regimen for daclizumab (1 mg/kg per dose every 14 days for 5 doses) is a deterrent to its routine use.<sup>33-35</sup> Several authors have evaluated alternative daclizumab regimens.<sup>6,35,36</sup>

One such alternative was studied by Ortiz et al,<sup>6</sup> who compared the rates of rejection between 2 cohorts of 81 patients treated with daclizumab. The first cohort was treated with 2 doses and the second with 5 doses of 1 mg/kg. Problematically, the patients in the 2 dose group had a significantly shorter ischemic time than did patients in the 5-dose group; however, the crude rate of rejection in the 2-dose group (30%) was consistent with the data from Kobashigawa et al<sup>32</sup> (35%) and Hershberger et al<sup>5</sup> (34%) who studied similar patients.

Not only has the number of necessary doses come under scrutiny, so has the dose itself. Accordingly, Stratta et al<sup>36</sup> conducted a prospective, multicenter, randomized, open label, placebo-controlled study that compared a 2-dose, higher dose, regimen with standard dosing of daclizumab. Stratta et al assessed the rates of rejection, infection, and death in a high-risk group of 297 simultaneous kidney-pancreas transplant recipients. Patients were randomized to daclizumab 2 mg/kg per dose for 2 doses on days 0 and +14, standard 5-dose daclizumab regimen, or no induction. All patients received tacrolimus, mycophenolate, and steroids as maintenance immunosuppression and were followed

up for 6 months. Only the 2-dose regimen resulted in significantly less rejection compared with no induction (17% vs 31%,  $P = .02$ ). No significant difference was found between the 5-dose regimen and no induction (21% vs 31%,  $P = .08$ ). Crude mortality rates and the incidence of serious adverse events, including infectious complications, did not differ significantly among all 3 groups.<sup>36</sup> These data suggest that the 2-dose, higher dose, daclizumab regimen compares favorably with the standard 5-dose regimen.

### Anti-CD52 Strategy

Few case reports have been published that detail limited success with alemtuzumab in isolated cases of OHT induction in children<sup>37</sup> and refractory rejection states.<sup>38,39</sup> In these reports, alemtuzumab has produced a beneficial effect on the detailed overwhelming rejection of these patients.<sup>37-39</sup> Conversely, no safety data have been presented in these populations. Most concerning are the reports of direct cardiotoxic effects and coronary ischemia that have surfaced from the hematology and oncology literature.<sup>40-42</sup> One such retrospective analysis identified use of anthracycline and alemtuzumab as independent predictors of cardiotoxic effects after stem cell transplantation with similar levels of significance ( $P = .002$  and  $P < .001$ , respectively).<sup>42</sup> However, these reports have been limited in scope to the hematology and oncology patients and have not surfaced in publications about solid organ transplantation. This difference may be due, in part, to the approved indication (B-cell chronic lymphocytic leukemia) and the lack of robust trial data in the solid organ transplant population. Accordingly, this agent may be effective for refractory rejection; however, induction with alemtuzumab cannot be recommended until it has been subjected to rigorous clinical trials in OHT, and only after concerns related to cardiotoxic effects have been assuaged.

### Cytolytic Versus Anti-CD25 Strategies

Apart from the debate regarding the need for induction, several pressing questions remain regarding the optimal therapeutic regimen. One such question is the following: Is induction with the IL-2R $\alpha$  monoclonal antibodies as successful as the cytolytic strategies, with respect to effectiveness and safety? In an effort to work toward an answer, Moller et al<sup>29</sup> recently performed a meta-analysis of 9 trials that evaluated the effect of the IL-2R $\alpha$  strategy versus placebo, monoclonal antithymocyte antibodies, and polyclonal antithymocyte antibodies on rejection and death. The authors noted that all of these trials were subject to a high risk of bias, were generally small, and all but 2 had a very short follow-up period. The IL-2R $\alpha$  strategy significantly reduced the risk of acute rejection by their fixed effects model (RR, 0.73; 95% CI, 0.59-0.90);

however, this benefit was not seen when a more-appropriate random effects model was performed (RR, 0.94; 95% CI, 0.46-1.17). Additionally, the IL-2R $\alpha$  strategy significantly increased acute rejection when compared with the polyclonal strategy (RR, 2.99; 95% CI, 1.42-6.28) and was not different when compared with the monoclonal approach (RR, 0.94; 95% CI, 0.74-1.20). These data are interesting, although drawing meaningful conclusions from these data is difficult given the significant heterogeneity ( $I^2 = 56.7\%$ ) and the mediocre quality of the included evidence.

While Moller et al<sup>29</sup> compared the IL-2R $\alpha$  strategy globally, some have suggested that differences may exist between the 2 available agents, daclizumab and basiliximab. Carlsen et al<sup>43</sup> performed a retrospective study of 40 heart transplant patients treated with either daclizumab 1 mg/kg for 5 doses or rATG 2.5 mg/kg for 3 to 5 doses. All patients received standard cyclosporine, azathioprine, and steroid maintenance immunosuppression. The primary end point was the rate of significant rejection (International Society for Heart and Lung Transplantation [ISHLT] grade  $\geq 2$ ). Primary end point occurrence was similar in both groups (daclizumab 9 vs rATG 12,  $P = .05$ ) at 3 months. Significantly more ISHLT grade 1 rejections were seen in the daclizumab group ( $P = .04$ ), the impact of which is unknown. The incidence of infections was significantly higher in the rATG group than in the daclizumab group (10 vs 3, respectively;  $P = .05$ ).<sup>43</sup>

The comparison of cytolytic and IL-2R $\alpha$  strategies was enhanced by the basiliximab data of Flaman et al,<sup>44</sup> who performed a retrospective analysis of 48 adult heart transplant patients at a single center. Patients were treated with basiliximab ( $n = 25$ ) 20 mg on days 0 and +4 or rATG ( $n = 23$ ) 1.5 mg/kg per dose for 3 days beginning on day 0. The primary end point was cellular rejection defined by the average biopsy score. The average biopsy score was significantly lower in the rATG group at 1 month ( $P = .02$ ) and 3 months ( $P = .03$ ) but lost significance at 6 months and thereafter. Significantly more rejection episodes of grade 3A or higher occurred within the first 6 months in the basiliximab group than in the rATG group (17 vs 6,  $P = .02$ ).<sup>44</sup>

The quality of the basiliximab data was elevated by Carrier et al,<sup>45</sup> who performed a prospective, multi-center, parallel-group, open-label, noninferiority trial of 35 patients to compare basiliximab 20 mg on days 0 and +4 with rATG 125 mg on days 0, +1, and +2. All patients received cyclosporine, mycophenolate mofetil, and prednisone for maintenance immunosuppression. Freedom from rejection (ISHLT grade 3A or 4) at 6 months was 83% (15/18) in the rATG group and 65% (11/17) in the basiliximab group. The range of the 1-sided 90% CI on the difference between both groups was higher than the prespecified noninferiority

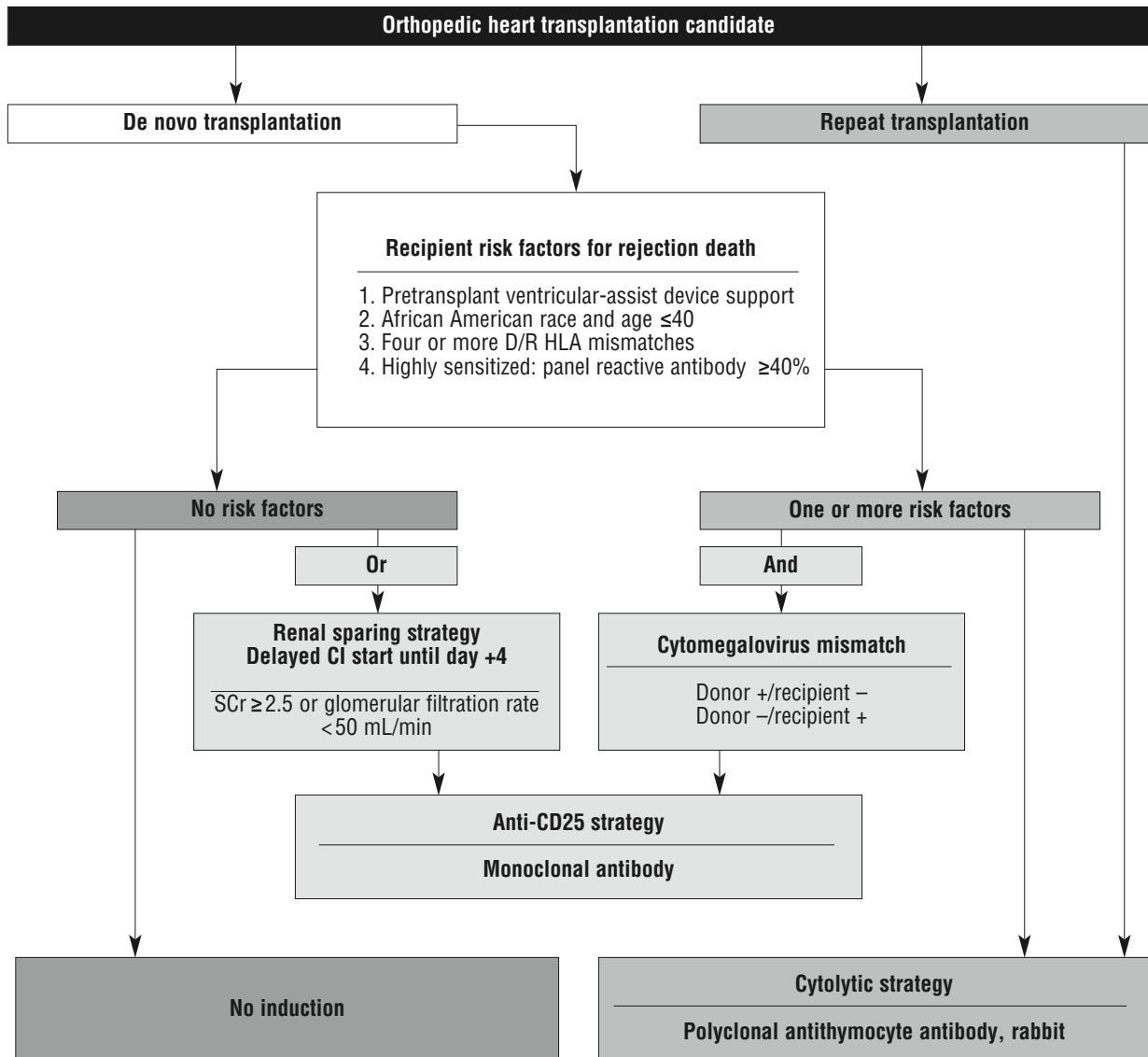


Figure Induction immunosuppression flow chart.

margin; accordingly, the inferiority of basiliximab was not rejected.<sup>45</sup>

Last, given the uniquely different adverse effect profiles of the cytolytic and IL-2R $\alpha$  strategies, it will be interesting to compare the long-term follow-up malignancy risk data when they become available. These data will add significant facets to the discussion about the optimal induction strategy (cytolytic vs IL-2R $\alpha$ ) for OHT.

### Infection-Related Death

Throughout most data comparing the cytolytic and IL-2R $\alpha$  strategies, trends have been seen toward more life-threatening infections with cytolytic induction. Mattei et al<sup>27</sup> compared the rate of infection-related

deaths between basiliximab and rATG for induction in 80 heart transplant patients. About half of all patients enrolled were CMV donor-recipient mismatches. Crude mortality was not different at 6 months between both groups (basiliximab 34.2% and rATG 45.2%,  $P = .05$ ); however, the rate of infection-related death was significantly higher in the rATG group (basiliximab 0% vs rATG 14.3%,  $P < .001$ ). Rates of rejection were similar in both groups (basiliximab 50% and rATG 45.2%,  $P = .05$ ) at 6 months.

### Discussion

At present, the unrestricted use of induction for all patients does not seem prudent. We suggest that induction immunosuppression should only be provided to

patients who have had a significant antigenic challenge and are at significant risk for fatal rejection (see Figure). These patients include those undergoing repeat transplantation, those supported with a VAD before transplantation, African Americans 40 years of age or younger who have 4 or more donor-recipient HLA mismatches, or those who are highly sensitized (panel reactive antibody  $\geq 40\%$ ). Induction for renal sparing should be considered in patients with a preoperative SCr of 2.5 mg/dL or greater or a glomerular filtration rate less than 50 mL/min.

Additionally, several induction immunosuppression agents are marketed in the United States. We suggest that the cytolytic strategy may be more effective than the IL-2R $\alpha$  approach; thus the cytolytic strategy should be regarded as the preferred induction method (see Figure). Cytolytic induction should be performed with rATG; we suggest that the use of ATGAM and OKT3 should be largely abandoned due to the serum sickness and malignancy risks, respectively. Furthermore, we suggest that the anti-CD25 strategy may be advantageous in patients at risk for fatal rejection who exhibit donor-recipient CMV mismatch to minimize the reactivation risk. The anti-CD25 approach may also be advisable in patients who are not at significant risk for fatal rejection and meet the suggested criteria for renal sparing (see Figure). Finally, we suggest that alemtuzumab should not be used for induction immunosuppression because of its overt and well-documented risks of cardiotoxic effects; however, it may be considered as “salvage” therapy for refractory rejection states.

### Conclusions

Induction therapy remains a poorly studied and widely variable practice among the major heart transplant centers in the United States. Induction should be provided to patients who are at significant risk for fatal rejection and should be individualized for each patient on the basis of a well-designed protocol, careful analysis of the transplant center’s demographics, and the effectiveness and safety profiles of the used regimens.

### Financial Disclosures

None reported.

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**CE Test** Test ID 4000.132: Induction immunosuppression for orthotopic heart transplantation: a review

**Learning objectives:** 1. Identify patient populations that benefit most from induction immunosuppression 2. Describe 3 untoward effects of drugs used as induction immunosuppression 3. Analyze how the use of induction immunosuppression affects rejection rates in heart transplant recipients

1. In which of the following patient populations did induction immunosuppression provide a survival advantage?

- a. African Americans  $\leq 25$  years old with  $< 4$  HLA mismatches
- b. Asians  $\leq 40$  years old with preoperative ventricular assist device (VAD) support
- c. Whites  $\leq 25$  years old with  $< 4$  HLA mismatches
- d. African Americans  $\leq 25$  years old with  $\geq 4$  HLA mismatches

2. Which of the following is an evidence-based criterion for the provision of induction immunosuppression with basiliximab for renal sparing?

- a. Serum creatinine  $> 2$  mg/dL
- b. Serum creatinine  $> 2.2$  mg/dL
- c. Glomerular filtration rate  $< 50$  mL/min
- d. Glomerular filtration rate  $< 60$  mL/min

3. A 60-year-old white woman underwent orthotopic heart transplantation with no rejection risk factors; she received daclizumab induction immunosuppression for renal sparing. Which of the following may predispose her to infection-related death?

- a. Concomitant antithymocyte globulin induction
- b. Cyclosporine initiated on day +0
- c. Cyclosporine initiated on day +4
- d. Substitution of basiliximab for induction immunosuppression

4. A 35-year-old African American woman with postpartum cardiomyopathy is about to undergo orthotopic heart transplantation; she is cytomegalovirus (CMV) negative. For this patient, basiliximab be preferred over rabbit antithymocyte globulin for induction immunosuppression in which of the following scenarios?

- a. Donor CMV negative
- b. Preoperative VAD support
- c. Donor CMV positive
- d. Glomerular filtration rate of 85 mL/min

5. A 19-year-old African American man is readmitted with 2R cellular and antibody-mediated rejection with hemodynamic compromise requiring extracorporeal membranous oxygenation. By admission day 3, he has received methylprednisolone 1000 mg daily, intravenous immunoglobulin 1 g/kg daily, and one dose of rituximab without resolution of hemodynamic compromise. Which of the following is a reasonable option for further treatment?

- a. Repeat transplantation, induction with daclizumab
- b. Repeat transplantation, no induction
- c. Treatment with basiliximab
- d. Treatment with alemtuzumab

6. Induction therapy in heart patients can safely delay prescribing which of the following drug therapies?

- a. Steroids
- b. Calcineurin inhibitors
- c. Antiproliferative agents
- d. Intravenous immunoglobulin

7. Induction therapy with rabbit antithymocyte globulin has been demonstrated to decrease the incidence of which of the following problems reported in heart transplant recipients?

- a. Coronary allograft vasculopathy
- b. Cytomegalovirus
- c. Cerebrovascular accident
- d. Epstein-Barr virus

8. Which of the following induction agents has been associated with an increase in malignancies, including lymphoproliferative disorders?

- a. Rabbit antithymocyte globulin
- b. Daclizumab
- c. Muronomab CD-3
- d. Basiliximab

9. Which of the following induction agents was found to have an increased rate of infection-related deaths in orthotopic heart transplant recipients?

- a. Muronomab CD-3
- b. Basiliximab
- c. Rabbit antithymocyte globulin
- d. Daclizumab

10. Which of the following induction therapies was found to have the greatest freedom from rejection at 6 months after heart transplantation?

- a. Daclizumab
- b. Basiliximab
- c. Rabbit antithymocyte globulin
- d. Equine antithymocyte globulin

Test answers: Mark only one box for your answer to each question. You may photocopy this form.

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