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Induction with anti-thymocyte globulin in heart transplantation is associated with better long-term survival compared with basiliximab
Ansari et al, *The Journal of Heart and Lung Transplantation,* Volume 34, Issue 10, May 2015, pp1283-1291

The role of induction immunosuppression in heart transplant has not been clearly identified. According to the 2013 OPTN/SRTR annual report, only about half of all heart transplant recipients (HTRs) receive induction therapy. [1] Conversely, robust literature is available to support the use of induction therapy in kidney transplantation, and is routinely used in this population. Agent selection is based on epidemiologic and immunologic considerations, such as risk of rejection or delayed graft function, desire to delay or avoid calcineurin inhibitors (CNIs), or plan for steroid withdrawal. The most compelling evidence exists for the lymphocyte-depleting agents, anti-thymocyte globulin (ATG) and alemtuzumab, and the interleukin-2 receptor antagonist, basiliximab (BAS), with consensus among experts as to general use criteria for these agents. (2-9)

Several studies assessing the efficacy of BAS and ATG induction in HTRs have demonstrated a reduction in incidence of acute rejection; however, available studies have not shown a difference in long-term survival associated with the use of either drug. [10-15] These studies have also had varying incidence of infectious complications, leaving conflicting evidence for the risk of infections with the use of induction therapy. [11-14]

Ansari et al conducted a review of the ISHLT registry of adult HTRs from 2000 to 2011 who received induction therapy with BAS or ATG. The purpose of this study was to compare long-term outcomes, including survival, incidence of acute rejection, infection, and malignancy. A total of 9,282 patients met criteria and the median follow-up was 3.0 years. One-year survival was similar among the groups (90% vs 91%; p=0.858), but patients receiving ATG induction had improved survival at 5 years (82% vs 77%; p=0.005) and at 10 years (67% vs 64%; p=0.007). BAS was associated with an increased risk of death due to graft failure, cardiovascular events, and infection; however, no difference was found for risk of malignancy between the two groups. The authors concluded that ATG induction may be associated with better long-term outcomes than BAS. [16]

Although this study has a large cohort, the retrospective nature limits the availability of data. Treatment protocols changed during the study, with an increase in BAS induction and a preference for tacrolimus/mycophenolate maintenance in the latter half of the study period. Additionally, the selection criteria used to determine induction therapy and infection prophylaxis regimens were not reported. Despite the higher immunologic risk, patients in the ATG group had a higher rate of survival. Moreover, the BAS group had a higher incidence of infections, which may be related to differences in prophylaxis regimens.

Ansari et al suggest that either ATG or BAS may be reasonable options for induction, but they do not specifically address how the outcomes compare to no induction. Emin et al compared ATG versus no induction in a retrospective study of 2,086 HTRs. Overall survival was similar between the groups; ATG induction was associated with a decreased incidence of acute rejection and an increase in infectious complications. [11] Also, in a study comparing ATG to no induction in 50 HTRs, Zhang et al found no difference in survival

between the groups; however, the results did suggest that ATG may prevent cardiac allograft vasculopathy (CAV). [15]

While current evidence for induction therapy does not show a survival advantage for HTRs, it may provide other benefits for this population. Chronic renal dysfunction is a common post-transplant complication that increases morbidity and mortality. [17] A recent study by Hong et al showed significantly worse survival among HTRs with baseline renal insufficiency. The difference in survival was noted as early as 3 months post-transplant and persisted through the 10-year follow-up period, supporting ISHLTs recommendation that renal dysfunction may be considered a relative contraindication to heart transplant. [14] Delayed initiation of CNIs through use of induction therapy, which has been shown to improve long term renal function in both heart and liver transplant recipients, may be a strategy for patients with baseline and immediate post-transplant renal dysfunction. [19-22]

Prevention and/or delayed progression of CAV is another potential benefit for induction therapy HTR. Jimenez et al and Kobashigawa et al investigated the relationship between rejection and CAV. Jimenez et al showed a significant correlation between rejection severity and the rate of CAV progression ($r=0.42$; $p=0.01$). [23] Kobashigawa et al suggested that recurrent rejection episodes early post-transplant may increase the likelihood of developing CAV. [24] By reducing acute rejection through the use of induction therapy, the potential to develop CAV following recurrent rejection episodes could be minimized.

Despite the outcomes reported by Ansari et al, the question still remains – how do outcomes for patients receiving induction with ATG or BAS differ from patients receiving no induction? A prospective study comparing the induction BAS and ATG to no induction may provide additional information to assist with the development of appropriate induction protocols for HTRs.

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Review provided by:

Jill Krisl, PharmD

Jill Krisl, PharmD is a Transplant Clinical Specialist with the heart and lung transplant programs at Houston Methodist Hospital in Houston, TX. She earned her Bachelor of Arts in technical journalism at Colorado State University, and her PharmD at University of Colorado Anschutz Medical Campus. She then completed her PGY1 and PGY2 critical care specialty residencies at the Medical University of South Carolina, followed by a transplant fellowship at the University of Cincinnati.

Nicole Casciello, PharmD, MBA

Nicole Casciello, PharmD, MBA is a Transplant Clinical Specialist at Indiana University Health Methodist Hospital in Indianapolis, Indiana supporting the heart and lung transplant programs. She earned her PharmD at The University of Texas at Austin College of Pharmacy and her MBA at The Wharton School at the University of Pennsylvania. She completed her clinical training at Duke University Hospital and Houston Methodist Hospital.