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The impact of induction therapy on mortality and treated rejection in cardiac transplantation: A retrospective study

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KEYWORDS:
heart transplantation;
induction therapy;
rejection;
survival

BACKGROUND: Evidence regarding the utility of routine induction therapy on outcomes is not clear. This study aims to evaluate whether induction therapy is associated with a reduced risk of treated rejection and improved overall survival.

METHODS: We retrospectively analyzed all adult patients (age ≥ 18 years) that are included in the UNOS database who underwent heart transplantation between 2000 and 2017. Patients with prior transplants and dual organ transplants were excluded. 34,361 patients were included in the final analysis. We assessed the impact of induction therapy with T cell depleting agents (TC-DA), IL2 receptor antagonists (IL2R antagonist) and compared that to no induction therapy using Cox regression models adjusted for propensity scores. The primary outcome measure was all-cause mortality, whereas treated rejection at one year was analyzed as a secondary outcome measure (available in 77% of patients).

RESULTS: A total of 52% of the cohort did not receive any induction therapy. A total of 27% received IL2R antagonist and the rest received TC-DA. Median age of the recipients was 55 (IQR: 46-62) years. A total of 25% of the population were women and 39% were supported on left ventricular assist device therapy at the time of transplantation. Median follow-up was 4.2 (IQR: 1.1-8.5) years with 32% reported mortality. Multivariate analysis with propensity score adjustment showed that TC-DA induction did not have any effect on mortality (HR = 0.98, 95% CI 0.93-1.03, $p = 0.48$). However, IL2R antagonist was associated with a modestly increased risk of all-cause mortality compared to no induction (HR = 1.06, 95% CI 1.01-1.11, $p = 0.02$, respectively). A total of 25% of patients were found to have treated rejection at one year, TC-DA induction was associated with reduced odds of rejection at one year (OR = 0.82, 95% CI 0.76-0.88, $p < 0.001$). However, induction with IL2R antagonist was not found to have a significant impact (OR = 1.03, 95% CI 0.96-1.11, $p = 0.36$).

CONCLUSIONS: Compared to no induction therapy, induction with TC-DA was associated with reduction in risk of treated rejection at 1 year with no effect on mortality and IL2R antagonist was associated with a small but statistically significant increase in mortality without any impact on risk of rejection.

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The role of induction therapy in adult heart transplant (HTx) patients remains unclear. According to the recent report from Organ Procurement and Transplantation Network (OPTN), the rates of induction therapy have remained relatively steady over the past decade.[1] About 50% of the patients do not receive any induction and the remainder receive either IL2 receptor antagonist or T-cell depleting agents(TC-DA).[1] There is a significant variability in practice amongst centers and the decision to use induction therapy is usually center dependent. This is due in part to the lack of robust randomized control trials to assess the efficacy of induction therapy in patients undergoing HTx and due to concerns for short-term risk of infection and long-term risk of malignancy from these agents.[2-5] Most of the available studies assessing the efficacy of induction therapy are small, single center, observational, or retrospective studies.[6-11] Thus far, none of the available data show any benefit in long-term survival with induction therapy.[8,9] There is also conflicting data on the benefits of induction therapy in reducing the risk of rejection.[2,3,6]

We systematically evaluated the impact of commonly used induction strategies on survival and treated rejection in the UNOS database and reviewed the impact on various patient subgroups.

Materials and methods

Study design

A retrospective analysis of UNOS database was conducted. All adult patients (age≥ 18 years) with available follow-up who underwent HTx between 2000 and 2017 were included in this study. Transplants prior to 2000 were excluded to ensure that our cohort encompassed pre, intra and post-transplant management representing management in the contemporary era. The study cohort was derived from 106,952 patients that were listed for heart transplantation between 1987 and 2017. Of these, 102,397 did not have any previous transplantation. A total of 67,442 patients of this cohort underwent heart transplantation. 58,492 were identified as ≥ 18 years of age and

Table 1 Table of Demographics

	No induction	IL2R antagonist	TC-DA	*p* value
Total number	17,953	9,248	7,160	
Age (years)	55 (46, 62)	55 (46, 62)	55 (45, 62)	0.731
Sex (male)	13551 (75.5)	6974 (75.4)	5247 (73.3)	0.001
Treatment year	2009 [2004, 2013]	2010 [2005, 2014]	2010 [2005, 2014]	<0.001
Race				<0.001
Black	3180 (17.7)	1969 (21.3)	1348 (18.8)	
Other	2104 (11.7)	1062 (11.5)	848 (11.8)	
White	12669 (70.6)	6217 (67.2)	4964 (69.3)	
Creatinine at time of transplant (mg/dl)	1.20 [0.92, 1.50]	1.20 [1.00, 1.60]	1.20 [1.00, 1.60]	<0.001
VAD at time of transplant	6171 (40.0)	2950 (34.4)	2628 (40.5)	<0.001
HLA mismatch ≥ 4	12977 (85.1)	7290 (85.5)	5484 (85.1)	0.71
Ischemia time (hours)	3.10 [2.40, 3.78]	3.20 [2.47, 3.82]	3.27 [2.50, 3.92]	<0.001
ABO blood group				0.11
A group	7499 (41.8)	3756 (40.6)	2952 (41.2)	
B group	2578 (14.4)	1379 (14.9)	996 (13.9)	
AB group	1017 (5.7)	492 (5.3)	375 (5.2)	
O group	6859 (38.2)	3621 (39.2)	2837 (39.6)	
Waitlist status				<0.001
1A	9267 (51.6)	4869 (52.6)	3461 (48.3)	
1B	6296 (35.1)	3221 (34.8)	2755 (38.5)	
2	2386 (13.3)	1157 (12.5)	942 (13.2)	
Donor age (years)	30 (21, 41)	30 (21, 41)	30 (21, 41)	0.15
Diabetes	4423 (24.8)	2528 (27.6)	1815 (25.4)	<0.001
Ischemic cardiomyopathy	6507 (36.6)	3341 (36.5)	2354 (33.1)	<0.001
Body mass index (kg/m^2)	26.57 (23.39, 30.13)	26.74 (23.57, 30.42)	26.76 (23.53, 30.35)	0.006
Immunosuppression at Discharge				
Cell cycle inhibitors				
Azathioprine	643 (3.6)	309 (3.3)	252 (3.5)	0.59
MMF	12807 (71.3)	7142 (77.2)	5509 (76.9)	<0.001
Calcineurin inhibitors				
Cyclosporine	4629 (25.8)	2639 (28.5)	1502 (21.0)	<0.001
Tacrolimus	12034 (67.0)	6365 (68.8)	5383 (75.2)	<0.001
mTOR inhibitors				
Sirolimus	378 (2.1)	190 (2.1)	205 (2.9)	<0.001
Everolimus	124 (0.7)	69 (0.7)	20 (0.3)	<0.001

Variables are summarized as median (25th-75th percentile) or numbers (percentages). Il2R antagonist: interleukin 2-receptor antagonist; MMF: mycophenolate mofetil; TC-DA: T-cell depleting agents; VAD: ventricular assist device.

Table 2 Predictors of Mortality Postcardiac Transplant

Hazard ratio for all-cause mortality (95% confidence interval)	
Without propensity score adjustment	
Age (per 10-year increments)	1.06 (1.04-1.08), $p < 0.001$
Male sex	0.96 (0.92-1.01), $p = 0.21$
Race (ref: white)	
Black	1.24 (1.18-1.31), $p < 0.001$
Other	0.96 (0.90-1.02), $p = 0.23$
Transplant year (per 10-year incr.)	0.86 (0.81-0.90), $p < 0.001$
VAD at time of transplant	1.06 (1.02-1.10), $p = 0.003$
Ischemia time (in hours)	1.08(1.06-1.10), $p < 0.001$
Creatinine at transplant (mg/dl)	1.08 (1.06-1.09), $p < 0.001$
HLA mismatches (≥4 vs <4)	1.02 (0.97-1.08), $p = 0.43$
PRA (≥25% vs <25%)	1.13 (1.05-1.20), $p < 0.001$
Diabetes mellitus	1.29 (1.24-1.35), $p < 0.001$
Recipient infection (2 weeks prior)	1.14 (1.06-1.23), $p < 0.001$
Ventilator need	1.62 (1.45-1.80), $p < 0.001$
ECMO need	2.08 (1.69-2.57), $p < 0.001$
IABP need	1.10 (1.01-1.19), $p = 0.03$
Immunosuppression at discharge Cell cycle inhibitors (ref: none)	
Azathioprine	0.85 (0.77-0.93), P<0.001
Mycophenolate mofetil	0.77 (0.74-0.81), P<0.001
Calcineurin inhibitors (ref: none)	
Cyclosporine	0.33 (0.31-0.36), P<0.001
Tacrolimus	0.28 (0.27-0.30), P<0.001
Induction therapy (ref: none)	
IL2R antagonist	1.06 (1.01-1.11), P=0.01
TC-DA	0.98 (0.93-1.03), P=0.39
With further propensity score adjustment for IL2R antagonist vs no induction	
IL2R antagonist (vs no induction)	1.06 (1.01-1.11), P=0.02
With further propensity score adjustment for TC-DA vs no induction	
TC-DA (vs no induction)	0.98 (0.93-1.03), P=0.48

Abbreviations: ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigens; IABP, intra-aortic balloon pump use; IL2R antagonist, interleukin-2 receptor antagonists; TC-DA, T-cell depleting, ce. Model also adjusted for CMV recipient/donor status.

35,248 of them were transplanted during or after year 2000. They were divided into 3 groups based on the induction strategies. Patients infrequently received induction therapy with cyclophosphamide (n = 19), OKT3 (n = 794), and other rare agents such as anti IL6, anti TNF, Dab486IL2 among others (n = 74) were excluded from the study leaving us with a final cohort of 34,361 patients. Our goal was to compare the 3 most commonly used induction strategies and patients were organized into: Group 1 no induction therapy, Group 2 IL2 receptor antagonists (basiliximab and daclizumab) and Group 3 T cell depleting agents (rabbit anti-thymocyte globulin, ATGAM- equine anti-thymocyte globulin, and alemtuzumab). Risk of treated rejection at 1-year and all-cause mortality was assessed. For this analysis, treated rejection is defined as presence of at least 1 acute rejection episode that was treated with an anti-rejection agent. Cause of death was also assessed based on various induction strategies.

Statistical methods

Continuous variables are presented as mean ± standard deviation (if normally distributed) or median [25th-75th percentile] (when deviating from a normal distribution) with comparisons between independent groups performed using 1-way analysis of variance (ANOVA) or the Kruskal-Wallis test, respectively. Categorical variables are summarized as numbers (percentages) and comparisons between groups were performed by means of a chi-square test.

Propensity risk scores for allocation to TC-DA (vs no induction) and IL2R antagonist (vs no induction) were defined as the probability of treatment allocation derived from a logistic regression model with treatment as the dependent variable and age, sex, race, treatment year, use of VAD, need for extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP) support, mechanical ventilation, recipient infection with need for intravenous drug therapy within 2 weeks of transplantation, history of malignancy creatinine at the time of transplant, HLA mismatch and panel reactive groups (PRA) as the independent predictors. PRA data was collection was variable across the years. PRA before June 2004 and after March 2015 was reported as a combined PRA, and in the in between timeframe was reported as PRA class 1 and class 2. For the sake of our analysis, we divided the PRA data into ≥25% and < 25%. The 25% cut off was used in previous studies as well.[12,13] The probability of receiving TC-DA (as opposed to no induction) and IL2R antagonist (vs no induction) was then included as a covariate in multivariable regression models to adjust for the non-random allocation of the 2 treatments in our observational cohort.

Survival analyses were performed by constructing Cox regression models for all-cause mortality and using our treatment groups as the independent treatment of interest, with further adjustments for the aforementioned covariates as well as propensity risk scores (applied in pairwise comparisons of TC-DA to no treatment, and IL2R antagonist to no treatment) and maintenance immunosuppression with cell cycle inhibitors (none, azathioprine, or mycophenolate mofetil) and calcineurin inhibitors (none, tacrolimus, or cyclosporine). Unadjusted survival graphs were constructed based on the Kaplan-Meier method, whereas adjusted survival plots were derived from the adjusted Cox regression models. For treated rejection at 1 year, a logistic regression model was constructed using the same set of predictors as discussed above. Subgroup analyses were performed, compared by calculating a P value for between-group interaction and graphically presented using forest plots. In sensitivity analyses, we also assessed the association between TC-DA and IL2R antagonist use vs no induction therapy with treated rejection at 1 year after excluding individuals with less than 365 days of follow-up, as well as by modelling a composite endpoint of mortality or treated rejection at one year. This was done to account for the competing risk of mortality during the first year, in the absence of detailed time-to-event data for treated rejection that prevented fitting of a competing hazard risk model.

A 2-tailed p value of <0.05 was considered statistically significant, unless specified otherwise. All analyses were performed using R (version 4.0.2).

Results

Baseline characteristics

A total of 34,361 patients were included in the study cohort. More than half of (52%, n = 17,953) did not receive any

induction therapy. 27% (n = 9,248) received IL2R antagonist as the induction therapy and the remainder (21%, n = 7,160) received TC-DA agents. Of the group that received IL2R antagonist, a quarter received daclizumab and the rest basiliximab. In the TC-DA group, 72% (n = 5,142) received rabbit ATG, 23%(n = 1,685) received equine ATG and 6%(n = 471) received alemtuzimab. Baseline characteristics of these 3 groups are represented in Table 1. 39% of the cohort had a VAD at the time of transplantation. There was greater use of IL2R antagonist in black patients. HLA mismatch was equally distributed across the various groups. Majority of patients had 4 or more HLA mismatches. Fewer patients listed as status 1A received TC-DA therapy. Trends of induction therapy over the years is shown in Figure 1.

Immunosuppression regimen at discharge

The predominant agent for cell cycle inhibition was mycophenolate mofetil (MMF). Less than 4% received azathioprine. Tacrolimus was the calcineurin inhibitor of choice in majority of the patients. A small proportion of patients, less than 3%, received mTOR inhibitor therapy as part of their maintenance immunosuppression. Variation across the 3 induction strategies is shown in Table 1.

Overall mortality

Over a median follow-up of 4.2 (IQR: 1.1-8.5) years, a total of 11,092 death events were recorded. On multivariable analysis, increased age, black (vs white) race, VAD presence at the time of transplantation and longer ischemia times were independently associated with a higher risk of mortality (Table 2). Following multivariable adjustment as well as adjustment for propensity risk scores, use of IL2R antagonist, as opposed to no induction, was associated with a small increase in risk of all-cause mortality (HR = 1.06, 95% CI 1.01-1.11, p = 0.02), whereas no effect on survival was noted with the use of TC-DA compared to no induction (HR = 0.98, 95% CI 0.93-1.03, p = 0.48) (Table 2, Figure 2). In further subgroup analyses, TC-DA was associated with protective effect on overall survival among women (HR=0.86, 95% CI 0.77-0.95 vs 1.02, 95% CI 0.97-1.09 among men) as well as among patients with renal insufficiency (serum creatinine ≥ 2mg/dl) at the time of transplantation and those that were transplanted in recent years (transplant year ≥ 2009) Figure 3). No interactions amongst subgroups were seen for IL2R antagonist agents vs no induction. IL2R antagonist on the other hand was not found to have any mortality benefit in high risk groups such as women, younger patients (age <60 years) or those with renal insufficiency (creatinine >2 mg/dl) at the time of transplant.

Cause of death

The incidence for different causes of death between the induction groups is graphically presented in Figure 4. Cause of death from primary graft failure, rejection, cardiovascular death including coronary artery disease, myocardial infarction, infectious etiology, and malignancy were assessed across treatment strategies. Primary graft failure in the UNOS data collection form is defined as primary non-

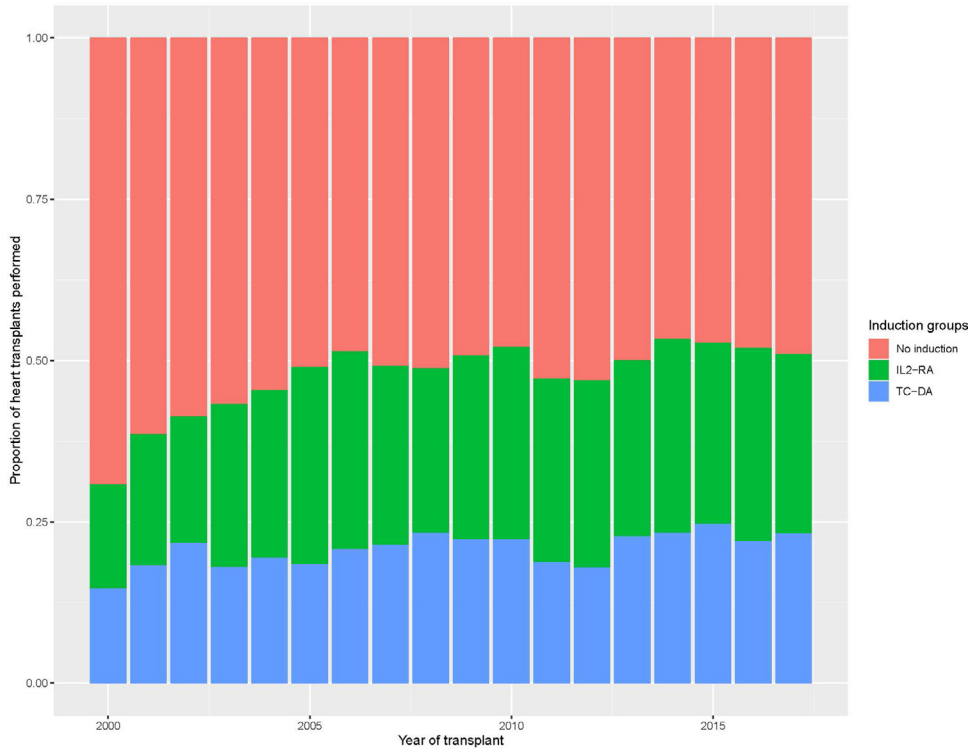

Figure 1 Trends of Induction Therapy over the Years. No induction, red, IL2R antagonist (interleukin 2-receptor antagonists, green), and TC-DA (T-cell depleting agents, blue).

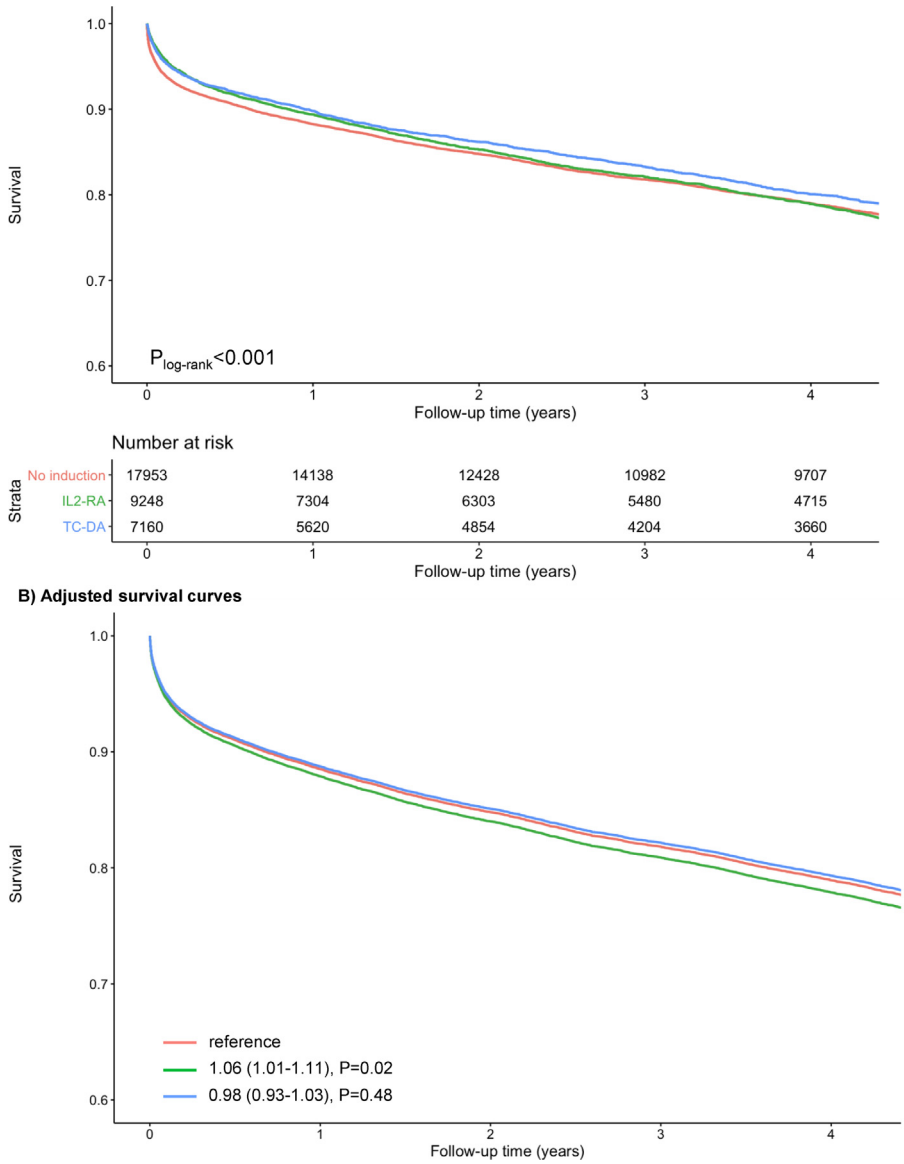

Figure 2 Survival curves for different induction regimens. (A) Unadjusted (Kaplan-Meier) and (B) adjusted survival curves for no induction (red), IL2R antagonist (interleukin 2-receptor antagonists, green) and TC-DA (T-cell depleting agents, red) groups.

function of the graft that is other than rejection. When compared to the no induction group, there was no statistically significant increase in deaths from malignancy (HR = 1.13, 95% CI 0.96-1.31, p = 0.14) or infectious deaths (HR = 1.13, 95% CI 0.98-1.30, p = 0.09) among patients receiving induction with TC-DA agents. However, the risk of cardiovascular deaths was lower in the latter group (HR = 0.86, 95% CI 0.76-0.98, p = 0.03).

Treated rejection at one year

At one year there were a total of 6,591 patients with treated rejection events among 26,356 heart transplant recipients with available information on this outcome. In multivariable analysis younger age, female gender, greater degrees of HLA mismatch (4 or more HLA mismatches), black race, PRA ≥ 25%, and presence of VAD at the time of transplant were associated with increased risk of treated rejection at 1 year (Table 3). Having received a transplant in more recent years as well as induction with TC-DA were associated with a reduction in the risk of treated rejection at one year, with the latter observation remaining significant on further propensity risk analysis (OR = 0.82, 95% CI 0.76-0.88, $p < 0.001$) (Table 3). IL2R antagoniston the other hand did not lower the risk of treated rejection episodes compared to the no induction group (OR = 1.03, 95% CI 0.96-1.11, p = 0.36). Subgroup analyses showed that the association of TC-DA agents with reduced rejection episodes was consistent across most subgroups analyzed Figure 5. Subgroup analysis of IL2R antagonist revealed a significant association with age, transplant era and presence of VAD. Patients older than 60 years benefitted less (OR = 1.17, 95% CI 1.04-1.33) compared to their younger counterparts (OR = 0.98, 95% CI 0.90-1.06). The benefit of IL2R antagonist is also less pronounced in the recent years (transplant in or after 2009

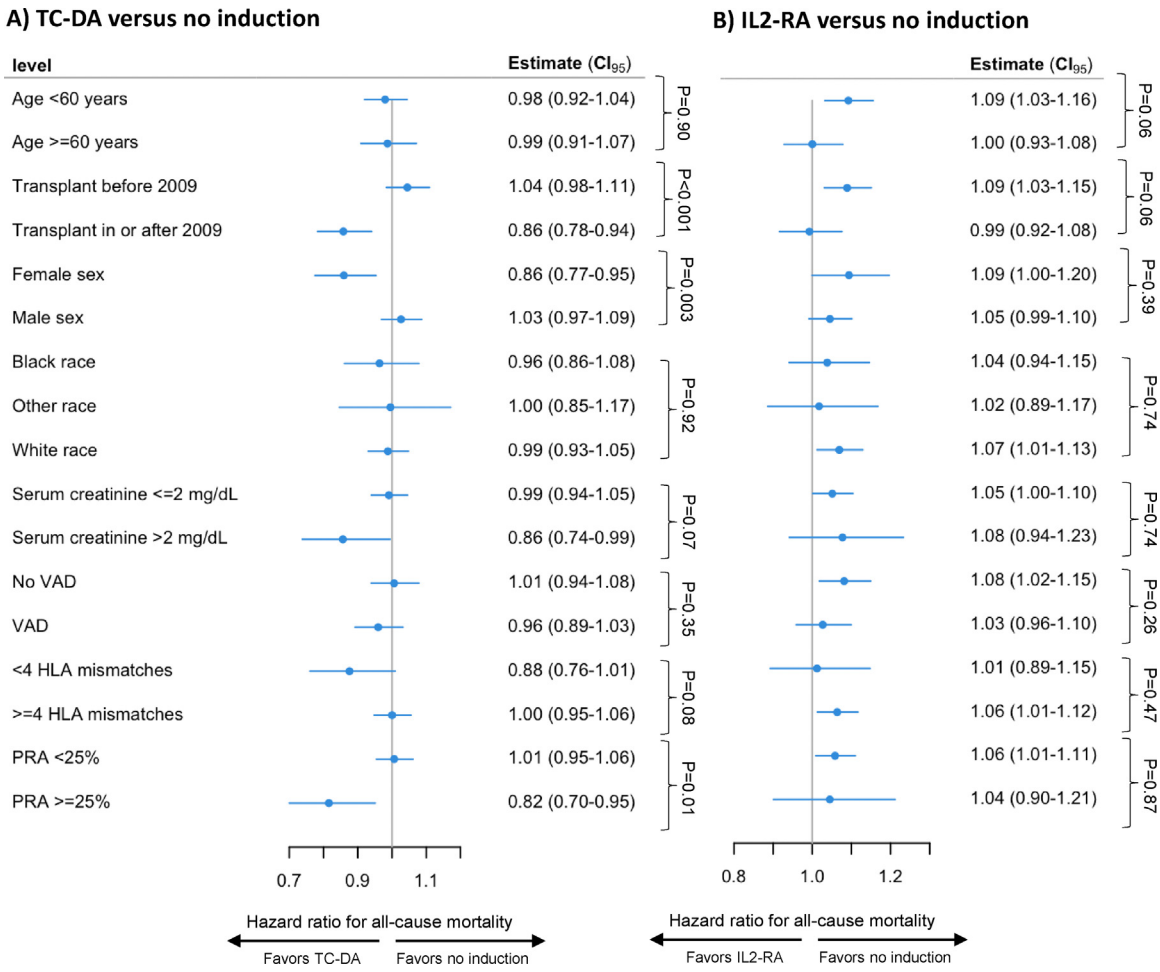

Figure 3 Subgroup analyses for the association between different induction therapy regimens and all-cause mortality. CI_{95}: 95% confident interval; IL2R antagonist: interleukin 2-receptor antagonists; TC-DA: T-cell depleting agents; VAD: ventricular assist device.

OR = 1.13, 95% CI 1.02-1.25 compared to transplant before 2009 OR = 0.95, 95% CI 0.86-1.04).

Sensitivity analyses

In a sensitivity analysis that included patients with available follow-up of at least 365 days, both the lack of association between IL2R antagonist use vs no induction therapy (OR = 1.04, 95% CI 0.97-1.12) and the protective association of TC-DA use vs no induction therapy (OR = 0.82, 95% CI 0.76-0.89) for treated rejection at 1 year persisted. Similarly, when repeating the analysis for a composite endpoint of mortality or treated rejection at 1 year, TC-DA use remained protective when compared to no induction (OR = 0.85, 95% CI 0.79-0.90), whereas again there was no significant difference between IL2R antagonist use vs no induction (OR = 1.04, 95% CI 0.98-1.11).

Discussion

Our analysis of this large UNOS database found that induction therapy with TC-DA was associated with reduced incidence of treated rejection at 1-year and had no impact on all-cause mortality. Others have documented the beneficial effects of TC-DA in reducing or delaying the risk of rejection.[10,14] Similarly, no mortality benefit with TC-DA was seen in previous studies in adult heart transplant recipients.[9] Of note, in subgroup analysis, TC-DA use was associated with survival benefit which was more pronounced in those that were transplanted in recent years. Improvement in survival has been reported with TC-DA induction in the pediatric heart transplantation cohort.[15-17] Using lower doses of ATG and transitioning to adjusted dose protocols have resulted in improved patient survival with TC-DA induction in this population.[18] T-cell-adapted ATG dosing has been shown to reduce total ATG dose and infectious complications without reduction in efficacy in adult transplant patients as well and has been widely adapted in recent years.[19,20] Greater use of newer, less toxic formulations with dose reduction protocols may explain the improvement in survival in recent years.

There was no evidence of increased risk of infection related deaths in the TC-DA group. Similar reduction in rejection risk without an increase in risk of infections was seen in long-term follow up study by Bonaros et al.[3] This may be due to the above stated changes in dosing protocols and routine use of antibacterial and antiviral prophylaxis with TC-DA induction.

Table 3 Predictors of Treated Rejection at One-year Post-cardiac Transplant

Odds ratio for treated rejection at 1 year (95% confidence interval)	
Without propensity score adjustment	
Age (per 10-year increments)	0.97 (0.95-0.98), $p < 0.001$
Male sex	0.95 (0.94-0.96), $p < 0.001$
Race (ref: white)	
Black	1.01 (1.00-1.03), $p = 0.04$
Other	0.98 (0.97-1.00), $p = 0.05$
Transplant year (per 10-year incr.)	0.89 (0.88-0.90), $p < 0.001$
VAD at time of transplant	1.05 (1.04-1.06), $p < 0.001$
Ischemia time (in hours)	1.00(0.99-1.00), $p = 0.19$
Creatinine at transplant (mg/dl)	0.98 (0.98-0.99), $p < 0.001$
HLA mismatches (≥4 vs <4)	1.05 (1.03-1.06), $p < 0.001$
PRA (≥25% vs <25%)	1.02 (1.01-1.04), $p = 0.006$
Diabetes mellitus	1.02 (1.01-1.04), $p < 0.001$
Recipient infection (2 weeks prior)	0.99 (0.97-1.01), $p = 0.46$
Ventilator need	0.96 (0.92-1.00), $p = 0.07$
ECMO need	1.00 (0.92-1.08), $p = 0.98$
IABP need	1.04 (1.02-1.07), $p < 0.001$
Immunosuppression at discharge Cell cycle inhibitors (ref: none)	
Azathioprine	1.03 (1.00-1.06), $p = 0.07$
Mycophenolate mofetil	1.00 (0.99-1.02), $p = 0.56$
Calcineurin inhibitors (ref: none)	
Cyclosporine	1.04 (1.00-1.07), $p = 0.03$
Tacrolimus	0.96 (0.93-0.99), $p = 0.008$
Induction therapy (ref: none)	
IL2R antagonist	1.00 (0.99-1.02), $p = 0.44$
TC-DA	0.97 (0.95-0.98), $p < 0.001$
With further propensity score adjustment for IL2-RA vs no induction	
IL2R antagonist (vs no induction)	1.03 (0.96-1.11), $p = 0.36$
With further propensity score adjustment for TC-DA vs no induction	
TC-DA (vs no induction)	0.82 (0.76-0.88), $p < 0.001$

Abbreviations: ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigens; IABP, intra-aortic balloon pump use; IL2R antagonist, interleukin-2 receptor antagonists; TC-DA, T-cell depleting, agents; VAD, ventricular assist device. Model also adjusted for CMV recipient/donor status.

Furthermore, TC-DA was not associated with increased risk of death from malignancy which was also seen in the data from UK Cardiothoracic Transplant Audit.[6] This may be due to exclusion of patients with older therapies such as OKT3 which is associated with significant risk of PTLD.[21] Additionally, concomitant changes to standard maintenance immunosuppression therapies from azathioprine to mycophenolate and the use of mTOR inhibitors have resulted in the reduction of malignancy risk in the overall cohort.[22,23]

Cardiovascular deaths including deaths from coronary artery disease and myocardial infarction were lower in the TC-DA group. Based on the current database, we are unable to differentiate the effect of TC-DA on cardiac allograft vasculopathy (CAV) alone as CAV was not well documented in this cohort. ATG was shown to be associated with decreased incidence of cardiac allograft vasculopathy in other studies as well.[3,24-26] ATG reduces the risk of CAV and atherosclerosis via immune and non-immune mechanisms including reduction of ischemia-reperfusion injury.[27] This could in turn lead to the overall reduction in cardiovascular deaths in this cohort.

Subgroup analysis on survival did not show any survival benefit with TC-DA amongst black patients (compared to white patients) as was noted in the pediatric heart transplantation.[28] However, women had significant survival benefit with TC-DA induction. Women are in general at higher immunological risk and the polyclonal nature of ATG with the ability to deplete both T and B cells and resulting broader immunosuppressive effect, may explain some of this benefit.[29] TC-DA was also very effective in patients with renal insufficiency at the time of transplant. Using induction therapy may have allowed for delayed initiation of calcineurin inhibitors in these patients.[30] Interestingly, no evidence of increased mortality was seen in patients with VAD with using TC-DA induction. The concerns of increased infectious deaths in patients with VAD receiving induction therapy were not borne out in this study. Truby et al have reported similar safety data with induction therapy in patients with VAD prior to transplantation.[31]

Subgroup analysis also revealed decreased risk of treated rejection across all subgroups with TC-DA induction. This effect was especially pronounced in some of the high-risk groups for rejection such as younger patients, and those with greater degrees of HLA mismatch. The beneficial effect was seen in both sexes and was most evident in those transplanted in the recent years. Of note, the intra and post-operative management strategies along with immunosuppression strategies have evolved over the past 2 decades. It of interest to consider that the beneficial effect of TC-DA therapy on both reduction of mortality and the incidence of treated rejection in this study, was more pronounced in the recent years (transplants≥year2009).

Induction with IL2R antagonist on the other hand was associated with no improvement in risk of treated rejection and there was a modest increase in risk of overall mortality in this cohort. Carrier et al were also unable to show non-inferiority of IL2R antagonist compared to rATG in preventing rejection.[10] A small retrospective study found similar lack of benefit in reducing rejection with basiliximab compared to ATG.[32] In addition, IL2R antagonist are generally considered safer compared to TC-DA due to concerns of increased infections and malignancy with TC-DA. In recent era, these concerns have not translated into increased mortality with TC-DA. Analysis of the International Society for Heart and Lund Transplantation database amongst the pediatric cohort has shown increased mortality with basiliximab compared to ATG.[16] Ansari et al have also found an increased mortality with basiliximab compared to

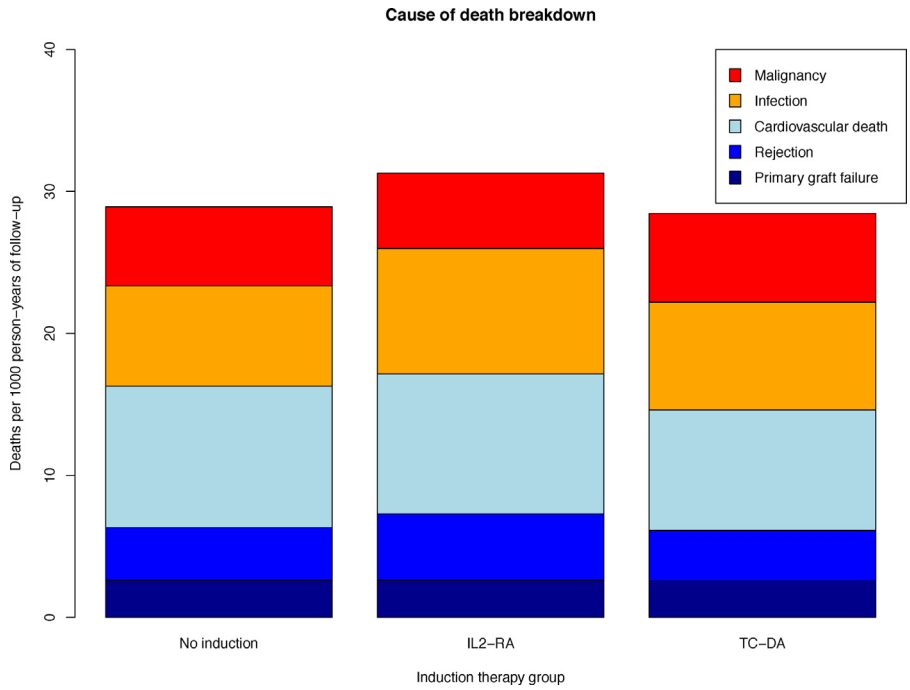

Figure 4 Incidence of different causes of death by induction therapy group. IL2R antagonist: interleukin 2-receptor antagonists; TC-DA: T-cell depleting agents.

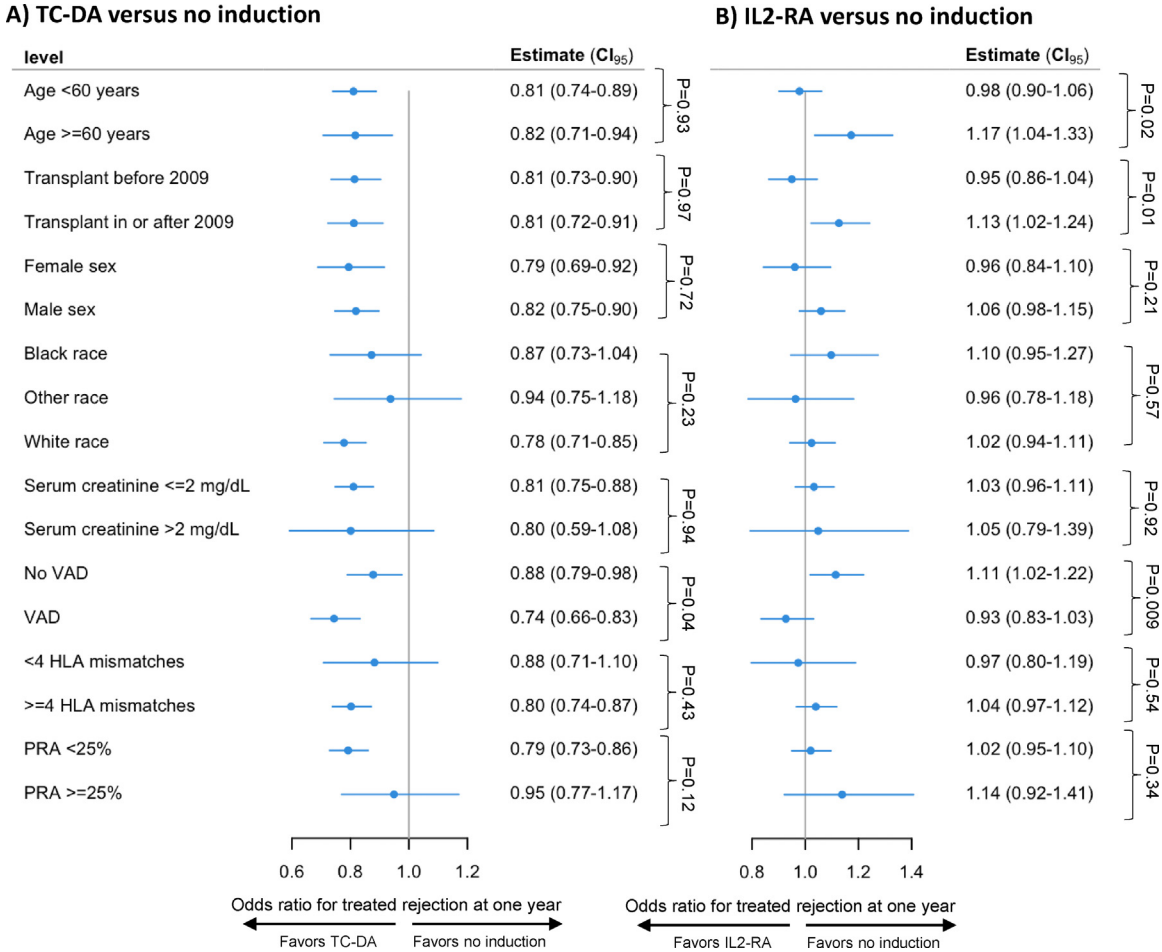

Figure 5 Subgroup analyses for the association between different induction therapy regimens and treated rejection at one year. CI_{95}: 95% confident interval; IL2R antagonist: interleukin 2-receptor antagonists; TC-DA: T-cell depleting agents; VAD: ventricular assist device.

ATG in the adult heart transplant cohort in the International Society for Heart and Lund Transplantation database.[33] Akin to our findings, the concerns of increased risk of deaths from infections or malignancy from ATG were not realized in that study.

To our knowledge, this is the largest study comparing patients treated with the 3 main strategies of no induction, IL2R antagonist induction and TC-DA induction in the contemporary era. The impact of TC-DA on reducing rejection, especially in the high-risk subgroups needs further investigation with randomized control trials. The impact of TC-DA on survival compared to no induction and induction with IL2R antagonist in the current era needs to be confirmed. High risk cohorts such as those with renal insufficiency may have a survival advantage with TC-DA induction.

Limitations: Our study has all the inherent limitations of a retrospective database studies. The decision to use induction therapy is usually center specific and the reasons behind choice of induction therapy cannot be clarified based on this study. We tried to account for this confounding variable by using propensity scoring. Panel reactive antibodies which may contribute towards increased risk of rejection and mortality[13] were not well documented in the UNOS database. There is significant variability in documentation of Class I and Class II Panel Reactive Antibodies (PRAs) and level of Mean Fluorescence Intensity. Previous analysis suggested that only combined elevation of both Class I and Class II PRA was associated with increased risk of rejection and mortality. Only 551 patients in the UNOS database were documented as having combined elevation of PRAs and hence PRA was not included in this analysis. Information regarding dosing of induction therapy and any dosing adjustments made based on clinical condition and lymphocyte count is unavailable in this database. As discussed above, dosing adjustments may have an impact on drug toxicity. Understanding the impact of various induction strategies on CAV would be helpful to understand the potential impact on long-term mortality. However, the extent of CAV is not well documented in this dataset. Cause of death is not always accurately documented in the UNOS database. Cause of death was documented as "unknown" or "other" in 20% of the patients. However, these limitations were to some extent minimized by the large number of patients and the long follow up of these patients. This represents the real-world data and despite the limitations of database studies, adds significantly to our current understanding of induction therapy.

Conclusion

This large retrospective analysis shows that the risk of treated rejection at one-year was reduced with a strategy of induction therapy using T cell depleting agents compared to that of IL2 receptor antagonists or no induction. Of note, this benefit in reduction in rejection was not associated with an increased risk of infectious deaths or deaths from malignancies. There is also a statistically significant reduction in death from cardiovascular causes in this cohort. IL2 receptor antagonists had no impact on reducing treated rejection and was associated with a small but statistically significant increase in all-cause mortality. Randomized controlled studies are needed to confirm these findings. Subgroup analysis in high-risk patients may help individualize treatment strategies and help tailor induction therapies according to the risk groups.

Author contributions

Concept, analysis and drafting of manuscript: LB. Analysis of the data: EO. Interpretation of data: LB, CH, EO. Critical revisions of manuscript: CM, JT, JP.

Disclosure statement

The authors have no conflicts of interest to declare.

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Supplementary materials

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References

1. Colvin M, Smith JM, Hadley N, et al. OPTN/SRTR 2018 annual data report: heart. Am J Transplant 2020;20(suppl s1):340-426.
2. Mattei MF, Redonnet M, Gandjbakhch I, et al. Lower risk of infectious deaths in cardiac transplant patients receiving basiliximab versus anti-thymocyte globulin as induction therapy. J Heart Lung Transplant 2007;26:693-9.
3. Bonaros N, Dunkler D, Kocher A, et al. Ten-year follow-up of a prospective, randomized trial of BT563/bb10 versus anti-thymocyte globulin as induction therapy after heart transplantation. J Heart Lung Transplant 2006;25:1154-63.
4. Beniaminovitz A, Itescu S, Lietz K, et al. Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. N Engl J Med 2000;342:613-9.
5. Segovia J, Rodriguez-Lambert JL, Crespo-Leiro MG, et al. A randomized multicenter comparison of basiliximab and muromonab (OKT3) in heart transplantation: SIMCOR study. Transplantation 2006;81:1542-8.
6. Emin A, Rogers CA, Thekkudan J, Bonser RS, Banner NR, Steering Group UKCTA. Antithymocyte globulin induction therapy for adult heart transplantation: a UK national study. J Heart Lung Transplant 2011;30:770-7.
7. Kobashigawa J, David K, Morris J, et al. Daclizumab is associated with decreased rejection and no increased mortality in cardiac transplant patients receiving MMF, cyclosporine, and corticosteroids. Transplant Proc 2005;37:1333-9.
8. Jarmi T, Patel N, Aslam S, et al. Outcomes of induction therapy with rabbit anti-thymocyte globulin in heart transplant recipients: a single center retrospective cohort study. Ann Transplant 2018;23:422-6.
9. Whitson BA, Kilic A, Lehman A, et al. Impact of induction immunosuppression on survival in heart transplant recipients: a contemporary analysis of agents. Clin Transplant 2015;29:9-17.
10. Carrier M, Leblanc MH, Perrault LP, et al. Basiliximab and rabbit anti-thymocyte globulin for prophylaxis of acute rejection after heart transplantation: a non-inferiority trial. J Heart Lung Transplant 2007;26:258-63.

11. Chin C, Pittson S, Luikart H, et al. Induction therapy for pediatric and adult heart transplantation: comparison between OKT3 and daclizumab. Transplantation 2005;80:477-81.
12. Arnaoutakis GJ, George TJ, Kilic A, et al. Effect of sensitization in US heart transplant recipients bridged with a ventricular assist device: update in a modern cohort. J Thorac Cardiovasc Surg 2011;142:1236-45. 45 e1.
13. Ivey-Miranda JB, Kunnirickal S, Bow L, et al. Differential impact of Class I and Class II panel reactive antibodies on post-heart transplant outcomes. J Card Fail 2021;27:40-7.
14. Zuckermann AO, Grimm M, Czerny M, et al. Improved long-term results with thymoglobuline induction therapy after cardiac transplantation: a comparison of two different rabbit-antithymocyte globulines. Transplantation 2000;69:1890-8.
15. Ansari D, Hoglund P, Andersson B, Nilsson J. Comparison of basiliximab and anti-thymocyte globulin as induction therapy in pediatric heart transplantation: a survival analysis. J Am Heart Assoc 2015;5:1-8.
16. Butts RJ, Dipchand AI, Sutcliffe D, et al. Comparison of basiliximab vs antithymocyte globulin for induction in pediatric heart transplant recipients: an analysis of the International Society for Heart and Lung Transplantation database. Pediatr Transplant 2018;22:e13190.
17. Schweiger M, Zuckermann A, Beiras-Fernandez A, et al. A review of induction with rabbit antithymocyte globulin in pediatric heart transplant recipients. Ann Transplant 2018;23:322-33.
18. Di Filippo S, Boissonnat P, Sassolas F, et al. Rabbit antithymocyte globulin as induction immunotherapy in pediatric heart transplantation. Transplantation 2003;75:354-8.
19. Koch A, Daniel V, Dengler TJ, Schnabel PA, Hagl S, Sack FU. Effectivity of a T-cell-adapted induction therapy with anti-thymocyte globulin (Sangstat). J Heart Lung Transplant 2005;24:708-13.
20. Krasinskas AM, Kreisel D, Acker MA, et al. CD3 monitoring of antithymocyte globulin therapy in thoracic organ transplantation. Transplantation 2002;73:1339-41.
21. Swinnen LJ, Costanzo-Nordin MR, Fisher SG, et al. Increased incidence of lymphoproliferative disorder after immunosuppression with the monoclonal antibody OKT3 in cardiac-transplant recipients. N Engl J Med 1990;323:1723-8.
22. Ingvar A, Smedby KE, Lindelof B, et al. Immunosuppressive treatment after solid organ transplantation and risk of post-transplant cutaneous squamous cell carcinoma. Nephrol Dial Transplant 2010;25:2764-71.
23. Bellumkonda L, Patel J. Recent advances in the role of mammalian target of rapamycin inhibitors on cardiac allograft vasculopathy. Clin Transplant 2020;34:e13769.
24. Zhang R, Haverich A, Struber M, Simon A, Bara C. Delayed onset of cardiac allograft vasculopathy by induction therapy using anti-thymocyte globulin. J Heart Lung Transplant 2008;27:603-9.
25. Zuckermann A, Ploner M, Czerny M, et al. Low incidence of graft arteriosclerosis after cardiac transplantation: risk factor analysis for patients with induction therapy. Transplant Proc 2002;34:1869-71.
26. Azarbal B, Cheng R, Vanichsarn C, et al. Induction therapy with antithymocyte globulin in patients undergoing cardiac transplantation is associated with decreased coronary plaque progression as assessed by intravascular ultrasound. Circ Heart Fail 2016;9:e002252.
27. Mourad G, Morelon E, Noel C, Glotz D, Lebranchu Y. The role of Thymoglobulin induction in kidney transplantation: an update. Clin Transplant 2012;26:E450-64.
28. Carlo WF, Bryant R 3rd, Zafar F. Comparison of 10-year graft failure rates after induction with basiliximab or anti-thymocyte globulin in pediatric heart transplant recipients-The influence of race. Pediatr Transplant 2019;23:e13366.
29. Zand MS. B-cell activity of polyclonal antithymocyte globulins. Transplantation 2006;82:1387-95.
30. Cantarovich M, Giannetti N, Barkun J, Cecere R. Antithymocyte globulin induction allows a prolonged delay in the initiation of cyclosporine in heart transplant patients with postoperative renal dysfunction. Transplantation 2004;78:779-81.
31. Truby LK, Batra J, Jennings DL, et al. Impact of induction immunosuppression on post-transplant outcomes of patients bridged with contemporary left ventricular assist devices. ASAIO J 2020;66:261-7.
32. Flaman F, Zieroth S, Rao V, Ross H, Delgado DH. Basiliximab versus rabbit anti-thymocyte globulin for induction therapy in patients after heart transplantation. J Heart Lung Transplant 2006;25:1358-62.
33. Ansari D, Lund LH, Stehlik J, et al. Induction with anti-thymocyte globulin in heart transplantation is associated with better long-term survival compared with basiliximab. J Heart Lung Transplant 2015;34:1283-91.