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Campath induction in HCV and HCV/HIV-seropositive kidney transplant recipients

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Conflicts of interest
The data reported here have been supplied by the Minneapolis Medical Research Foundation as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the US Government.

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Summary

Alemtuzumab (AZ) induction in hepatitis C-seropositive (HCV+) kidney transplant (KTX) recipients may negatively affect patient survival; however, available information is scant. Using US registry data from 2003 to 2010 of adult HCV+ deceased-donor KTXs (n = 4910), we examined outcomes by induction agent – AZ (n = 294), other T cell-depleting agents, (n = 2033; T cell), IL-2 receptor blockade (n = 1135; IL-2RAb), and no induction (n = 1448). On multivariate analysis, induction therapy was associated with significantly better overall patient survival with AZ [adjusted hazards ratio (aHR) 0.64, 95% confidence interval (CI) 0.45, 0.92], T cell (aHR 0.52, 95% CI 0.41, 0.65) or IL-2RAb (aHR 0.67, 95% CI 0.53, 0.87), compared to no induction. A significant protective effect was also seen with AZ (aHR 0.63, 95% CI 0.40, 0.99), T cell (aHR 0.62, 95% CI 0.49, 0.78), and IL2R-Ab (aHR 0.62, 95% CI 0.47, 0.82) in terms of death-censored graft survival relative to no induction. There were 88 HIV+/HCV+ coinfected recipients. Compared to noninduction, any induction (i.e. three induction groups combined) was associated with similar overall patient survival (P = 0.2255) on univariate analysis. Induction therapy with AZ, other T cell-depleting agents, or IL-2RAb in HCV+ KTX is associated with better patient and death-censored graft survival compared to noninduction. In HCV/HIV coinfected patients, induction is not contraindicated.

Introduction

Kidney transplantation of hepatitis C virus-seropositive (HCV+) patients has been shown to confer a long-term survival advantage over dialysis and is considered the treatment of choice for most end-stage renal disease (ESRD) patients with HCV infection [1,2]. Despite some conflicting reports, however, overall HCV+ patients appear to have lower patient and graft survival compared with HCV-seronegative transplant recipients [3–5]. It has been postulated that kidney transplantation, with its need for immunosuppression, increases the risk of post-transplant liver disease [5–7], infection [2,8,9], and new-onset diabetes [10] among HCV+ patients, all of which may adversely affect patient survival [5,6,11]. However, published experience is scant regarding the potential deleterious impact on the outcome of induction therapy in HCV+ kidney transplant (KTX) recipients [12–14]. In addition, whereas there are some data on induction therapy with thymoglobulin and basiliximab, no studies have evaluated alemtuzumab (AZ)

(Campath-1H), separately. This is important as AZ is a potent induction agent resulting in profound and long-lasting lymphocyte depletion [15–17]. Despite its increasing utilization since its first usage in kidney transplantation in 1999 [16], there is little information with respect to its risk of serious infection, neoplasia, and viral reactivation all of which may impact long-term survival.

Lastly, a clinical challenge in managing kidney transplant recipients with HCV is coinfection with human immunodeficiency virus (HIV+). Hepatitis C progresses more rapidly in patients coinfected with HIV(HCV+/HIV+) [17–19] and the higher risk of rejection in HIV+ kidney transplant recipients might require more potent immunosuppression either as prophylaxis against or treatment of rejection which may in turn further exacerbate hepatitis C infection. No studies have evaluated outcomes associated with induction therapy in HCV+/HIV+ patients.

The purpose of our study was to evaluate Scientific Registry of Transplant Recipients (SRTR) data for the impact of AZ compared to other induction strategies on the long-term patient mortality and graft survival of HCV+ and HCV+/HIV+ kidney transplant recipients.

Materials and methods

Data source

We utilized data from the SRTR. The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Study population

Scientific Registry of Transplant Recipients data was accessed to identify all HCV+ kidney transplant (KTX) recipients between January 2003 and December 2010. Multi-organ recipients were excluded as were pediatric- (<18 years) and live-donor kidney recipients, and recipients from deceased donors <6 years of age.

Hepatitis C virus status is both determined and reported at the time of transplant for donor kidneys and is reported but not necessarily performed at the time of transplant for recipients (reporting refers to any prior positive HCV testing). Recipient induction therapy was determined and classified into four mutually exclusive induction groups. Groups were defined as those receiving (i) AZ (Campath-1H®), (ii) basiliximab (Simulect®) or daclizumab (Zenapax®) (IL-2RAb), (iii) other T cell-depleting agents such as Muromonab-CD3 (Orthoclone OKT®3) and polyclonal antithymocyte globulin (Thymoglobulin®) (T cell), and (iv) no induction (none). Cases with multiple induction medications were excluded except those receiving both AZ and an IL-2Rab were categorized as AZ and those receiving both antithymocyte globulin and IL-2RAb were categorized as T cell.

The primary outcome of this study was overall patient mortality from any cause following transplantation. Time to death was defined as time from the date of transplant until death, censored for loss to follow-up, end of study period (10/31/11), or receipt of subsequent liver transplant. Secondary outcomes were as follows: (i) overall death-censored graft failure (defined as graft failure, return to dialysis, or re-transplantation), and (ii) 1-year acute rejection (indicated by reported acute rejection or treatment for acute rejection in the follow-up forms). Maintenance medication regimen was assessed as initial medication at discharge from the hospital. Missing maintenance medication data (2.6%) was coded as missing.

Statistical analysis

All statistical analysis was conducted using the SAS system version 9.2 (SAS Institute, Inc., Cary, NC, USA). Univariate associations were examined using the chi-square tests for categorical variables. The distribution of continuous variables was examined for normality and for the identification of clinically implausible values – which can result from data entry errors in registries of this size. Clinically implausible body mass index (BMI) values were not included in the analysis of this variable. *t*-Tests and ANOVA were used for the analysis of continuous variables whose distribution approximated normality.

Survival distributions for mortality and graft failure were estimated using the Kaplan–Meier method. Survival curves were compared using the log-rank test. Cox proportional hazards models were used to estimate hazards ratios (HR) and 95% confidence interval (CI) for induction treatment groups after accounting for other factors which were included based on backward selection with the significance level for a variable to remain in the model at <0.2. Induction groups as well as all other covariates were examined for adherence to the proportional hazard assumption. Ties in the failure time were handled using the Efron method. Because of the nonproportionality of our primary independent study variable (induction group), an interaction term with time was included in the models.

The following donor variables were included in the models: age (6–17, 18–39, 40–59, ≥60 years), gender, race (African American, other), cause of death (cerebrovascular accident versus other), history of hypertension, history of diabetes, terminal serum creatinine >1.5 mg/dl, hepatitis C status, and donation after circulatory death (DCD). The

following recipient factors were included in the models: age (continuous), gender, race (African American, other), previous kidney transplantation, previous liver transplantation, duration of maintenance dialysis prior to transplantation (none, ≤3 years, >3 years, missing), number of HLA-A, B, and DR mismatches (≤3, >3), panel-reactive antibody (PRA) level (>30%, ≤30%), BMI (≤30 kg/m^2, >30 kg/m^2, missing), cold ischemia time (hours; ≤12, >12, missing), HIV infection status, insurance status (private, other), and year of transplantation. BMI was calculated as weight (kg)/height (m)^2. Expanded criteria donor (ECD) was defined as age >60 years or age 50–59 years without at least two of three other conditions (cerebrovascular cause of death, terminal serum creatinine >1.5 mg/dl, and hypertension).

The odds of acute rejection at 1 year was estimated with logistic regression using backward selection with the significance level for a variable (same factors as Cox models) to remain in the model at <0.2. Acute rejection data were missing in 2.7% of cases; these cases were not included in the rejection analysis.

All multivariate models were fit with the results from observations that had complete data. Missing data were observed in less than 1%. Imputation methods were not used. All *P*-values were two-sided. This study was approved by the Institutional Review Board of the Albert Einstein College of Medicine.

Results

HCV+ recipients and induction groups

We identified 4910 kidney transplants to HCV+ recipients between January 1, 2003 and December 31, 2010. Among these AZ induction was administered in 6% (n = 294; AZ), other T cell-depleting agents combined in 41% (n = 2033; T cell), IL-2 receptor blockade in 23% (n = 1135; IL-2RAb), and no induction in 30% (n = 1448). The frequency distribution of donor and recipient variables based on induction category is shown in Table 1. Compared to the other three induction categories, transplant recipients in the AZ group were found to have higher rates of recipients who were African American, younger, obese, receiving less maintenance immunosuppression, and had longer dialysis vintage. Transplant recipients treated with AZ were also more likely to have received an organ from donors that were older, ECD, DCD, and with longer cold ischemia times. Those that received no induction had a greater proportion of recipients with HLA mismatch >3, pre-emptive KTX, previous liver transplants, HIV-positive status, and receiving maintenance immunosuppressive therapy minimization. The T-cell group had a greater proportion of recipients with PRA >30% and previous kidney transplants. The IL-2RAb group had a significantly higher proportion of recipients with private insurance compared to the other three groups. The groups were statistically similar in terms of donor race, gender, hypertension, diabetes, death because of CVA, terminal serum creatinine, HCV-positive status, and recipient gender.

For each of the induction groups (AZ, T cell, IL-2RAb, and none), patient survival was 95%, 94%, 92%, and 89%, respectively, at 1 year and 86%, 81%, 76%, and 75%, respectively, at 5 years (Fig. 1). On multivariate analysis, induction therapy was associated with significantly better patient survival when treated with AZ [adjusted HR (aHR) 0.64, 95% CI 0.45, 0.92], T cell (aHR 0.52, 95% CI 0.41, 0.65), and IL-2RAb (aHR 0.67, 95% CI 0.53, 0.87), compared to no induction (Table 2a). A significant protective effect with the use of AZ (aHR 0.63, 95% CI 0.40, 0.99), T cell (aHR 0.62, 95% CI 0.49, 0.78), and IL2R-Ab (aHR 0.62, 95% CI 0.47, 0.82) was also observed in terms of death-censored graft survival relative to no induction (Table 2b).

As a result of the small sample size of the AZ group and its resulting limited statistical power, the original Cox model for patient and graft survival was constructed using backwards elimination at an alpha level of <2.0. As a sensitivity analyses, we modeled the association of specific induction groups including all variables in the Cox model. The results for death-censored graft survival were similar in magnitude and direction (AZ, aHR 0.62, 95% CI 0.39, 0.98; T cell aHR 0.61, 95% CI 0.49, 0.78; IL2R-Ab aHR 0.61, 95% CI 0.46, 0.8). The results for patient survival were similar in direction but did not reach significance for the AZ group (AZ, aHR 0.63, 95% CI 0.39, 1.04; IL2R-Ab aHR 0.68, 95% CI 0.53, 0.87; T cell aHR 0.51, 95% CI 0.41, 0.65).

Acute rejection at 1 year occurred in 8.9% overall, 12.6% of those induced with AZ, 9.6% with other T-cell therapies, 9.1% with IL-RAb, and 7.1% with no induction (P = 0.0085). On multivariate analysis, the odds of acute rejection was higher with AZ [adjusted odds ratio (aOR) 1.70, 95% CI 1.12, 2.56), and other T cell-depleting agents (aOR 1.32, 95% CI 1.02, 1.72), but not IL-2RAbs (aOR 1.27, 95% CI 0.95, 1.71) compared to noninduction. Other risk factors for acute rejection were donor HCV+ status (aOR 1.38, 95% CI 1.10, 1.74), recipient HIV coinfection (aOR 2.27, 95% CI 1.28, 4.01), whereas increasing recipient age was protective (aOR 0.98, 95% CI 0.97, 0.99 per year).

HCV/HIV-coinfection (HCV+/HIV+) versus HCV-monoinfection (HCV+)

A total of 88 HCV+ recipients were coinfected with HIV (HCV+/HIV+). Transplantation of HIV coinfected patients, within this HCV cohort, steadily increased from 2 cases in 2002 to 24 cases in 2010 (Table 3). Compared to those with HCV monoinfection, the HCV+/HIV+ group was comprised of significantly greater proportions of recipients of

Table 1. Donor and recipient characteristics by induction group.*

Characteristic % or mean ± SD	Alemtuzumab (*n* = 294)	T cell (*n* = 2033)	IL-2RAb (*n* = 1135)	None (*n* = 1448)	*P*-value
Donor age, years					
6–17	5.8	6.1	6.1	5.1	0.0022
18–39	31.6	36.7	36.7	41.4	
40–59	54.8	51.4	51.4	48.7	
≥60	7.8	5.8	5.8	4.8	
Donor African American	19.1	15.7	14.2	14.2	0.1211
Donor female	34.7	38.6	37.4	38.0	0.5999
Donor hypertension	31.1	29.2	27.9	26.1	0.1424
Donor diabetes	4.4	5.9	5.8	5.8	0.7979
Donor death because of CVA	40.1	40.2	40.1	39.4	0.9740
Donor DCD	12.6	8.5	5.4	5.4	<0.0001
Donor expanded criteria	18.7	15.1	13.8	13.0	0.0483
Donor serum Cr > 1.5 mg/dl	12.6	14.8	13.8	12.9	0.4061
Donor HCV positive	34.7	29.2	28.9	29.6	0.2497
Recipient age, years	51.8 ± 10.3	52.4 ± 9.4	53.4 ± 9.4	53.1 ± 9.0	0.0076
Recipient ESRD diagnosis					
Glomerulonephritis	13.3	16.1	16.9	11.1	<0.0001
Diabetes	29.6	24.3	26.0	22.4	
Hypertension	37.1	31.7	25.7	27.8	
Other/unknown	20.1	27.9	31.4	38.8	
Recipient African American	59.9	52.8	42.3	45.4	<0.0001
Recipient female	27.6	27.1	23.5	26.5	0.1526
Recipient kidney re-transplant	16.3	19.6	9.3	12.0	<0.0001
Recipient dialysis					
No dialysis	6.8	8.0	10.9	8.0	<0.0001
≤3 years	33.0	37.3	43.3	45.5	
>3 years	58.5	52.9	44.0	38.7	
Recipient BMI > 30 kg/m^2	33.7	25.8	24.5	25.2	0.0157
Recipient PRA > 30%	30.7	32.4	20.0	24.3	<0.0001
Recipient CIT > 24 h	32.0	21.9	18.0	16.7	<0.0001
Recipient HLA MM > 3	79.6	73.5	72.9	71.8	0.0500
Recipient HIV positive	1.4	0.7	1.9	3.3	<0.0001
Recipient insurance, private	23.5	24.5	32.1	30.5	<0.0001
Recipient previous LTX	2.0	5.6	8.4	11.2	<0.0001
Maintenance immunosuppression at discharge <3 drugs	63.0	32.9	18.9	26.3	<0.0001

CVA, cerebrovascular accident; DCD, donation after circulatory death; ESRD, end-stage renal disease; BMI, body mass index; CIT, cold ischemia time; PRA, panel-reactive antibodies; HLA, human leukocyte antigen mismatch; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LTX, liver transplant.

*Data not shown for waiting-list candidates and recipients missing information on BMI, panel-reactive antibody, cold ischemia time, and duration of diabetes.

African American race, ESRD because of diabetes or glomerulonephritis, nonprivate insurance, HLA mismatch >3, longer vintage, and fewer prior liver or kidney transplants; donors were more likely to be HCV+ (Table 4). Maintenance immunosuppression was minimized in 13% of those with HCV monoinfection and 16.3% of those with HCV/HIV coinfection ($P = 0.3900$). On multivariate analysis HCV+/HIV+ was associated with a somewhat increased hazard for patient mortality (aHR 1.55, 95% CI 0.98–2.46) and DCGL (aHR 1.40, 95% CI 0.89, 2.19) compared to HCV+. Acute rejection at 1 year occurred in 8.5% of HCV+ and 18.2% of HCV+/HIV+ cases.

Induction and HCV+/HIV+ recipients

Utilization of induction therapy in HCV+/HIV+ patients increased from 0% in 2003 to a usage of 20–50% between 2004 and 2008, and 67% in 2010 (Table 3). Four patients received induction with AZ, 22 with other T cell-depleting agents, 15 with IL2R-Ab, and 47 did not receive induction. The mean recipient age at transplantation was not significantly different between the four groups (48.0 ± 10.7, 52.0 ± 7.3, 50.7 ± 9.2, and 51.1 ± 8.1, respectively; $P = 0.8229$). Patient and graft survival curves of the HCV/HIV coinfected cases are depicted in Fig. 2a for each

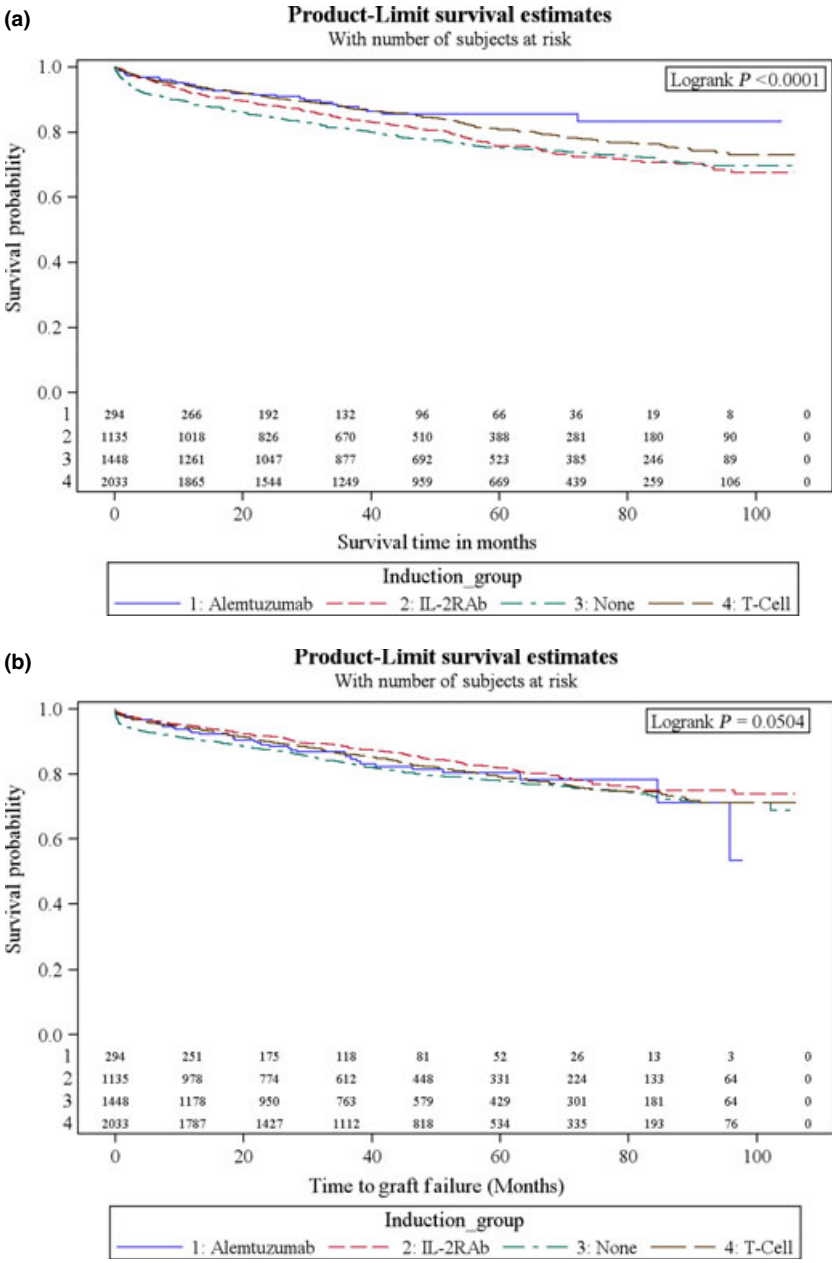

Figure 1 Kaplan–Meier plots of (a) overall patient survival and (b) death-censored graft survival for hepatitis C-seropositive kidney transplant recipients by induction group.

induction category and in Fig. 2b for the three induction groups combined compared to noninduction. Compared to those that did not receive induction, those that received any induction (i.e. three induction groups combined) demonstrated similar overall patient survival (overall $P = 0.2255$; 85% and 94% at 1 year and 68% and 75% at 3 years ($P = 0.1094$) (Fig. 2b) and death-censored graft survival (overall $P = 0.4030$; 85% vs. 94% at 1 year and 67% vs. 74% at 3 years, respectively).

Discussion

This analysis of HCV+ KTX recipients supports an association between induction therapy either with AZ, IL-2RAbs, or other T-cell depleting and better overall patient and death-censored graft survival when compared to no induction. These improved outcomes were seen in all three induction groups when compared to noninduction which had the lowest acute rejection.

Table 2. Final multivariable Cox model* after backwards elimination for (a) post-transplant mortality and (b) post-transplant death-censored graft failure.

Parameters (reference group)	Patient mortality Adjusted hazards ratio (95% CI)
(a) Post-transplant mortality	
Induction (no induction)	Reference
Alemtuzumab	0.64 (0.45–0.92)
Other T-cell depleting	0.52 (0.41–0.65)
IL-2RAb	0.68 (0.53–0.87)
Donor age, years (6–17)	Reference
18–39	1.20 (0.88–1.63)
40–59	1.42 (1.05–1.92)
≥60	1.63 (1.12–2.38)
Donor gender, female (male)	1.17 (1.02–1.33)
Donor, African American (non-African American)	1.18 (0.99–1.40)
Recipient age, continuous per year	1.03 (1.02–1.04)
Recipient race, African American (other)	0.89 (0.77–1.03)
Recipient BMI > 30 kg/m^2 (other)	1.03 (0.87–1.20)
Recipient PRA > 30% (PRA ≤ 30)	1.02 (0.86–1.20)
Recipient HLA-mismatches >3 (≤3)	1.11 (0.95–1.29)
Recipient, prior kidney transplant (primary)	1.52 (1.26–1.84)
Recipient, HIV positive	1.55 (0.98–2.46)
Recipient, prior liver transplant	1.48 (1.20–1.84)
Recipient insurance, nonprivate	1.13 (0.97–1.31)
Recipient ESRD diagnosis (glomerulonephritis)	
Diabetes	1.21 (0.97–1.51)
Hypertension	0.97 (0.77–1.21)
Other/unknown	1.17 (0.95–1.44)
Dialysis duration prior to transplant (none)	Reference
<3 years	1.07 (0.86–1.33)
≥3 years	0.99 (0.78–1.25)
(b) Post-transplant death-censored graft failure	
Induction (no induction)	Reference
Alemtuzumab	0.63 (0.40–0.99)
Other T-cell depleting	0.62 (0.49–0.78)
IL-2RAb	0.62 (0.47–0.82)
Donor age, years (6–17)	Reference
18–39	1.10 (0.77–1.59)
40–59	1.59 (1.10–2.30)
≥60	2.03 (1.31–3.14)
Donor gender, female (male)	1.13 (0.98–1.31)
Donor, African American (non-African American)	1.32 (1.11–1.57)
Donor, death because of cerebrovascular accident	1.22 (1.05–1.43)
Donor, diabetes history	1.38 (1.07–1.78)
Donor, terminal serum creatinine > 1.5 mg/dl	1.14 (0.93–1.39)
Donor, HCV seropositive	1.19 (1.01–1.40)
Donor, human immunodeficiency virus seropositive	1.40 (0.89–2.19)
Donor, cold ischemia time ≥ 12 h (<12 h)	0.84 (0.70–1.02)
Recipient age, continuous per year	0.98 (0.98–0.99)
Recipient race, African American (other)	1.51 (1.29–1.76)
Recipient, dialysis time pretransplant (none)	
<3 years	1.45 (1.07–1.95)
≥3 years	1.53 (1.13–2.08)
Recipient PRA > 30% (PRA ≤ 30)	1.32 (1.12–1.57)
Recipient HLA-mismatches >3 (≤3)	1.15 (0.96–1.36)
Recipient, prior kidney transplant (Primary)	1.34 (1.10–1.63)
Recipient insurance, nonprivate	1.23 (1.03–1.47)

BMI, body mass index; ESRD, end-stage renal disease; HLA, human leukocyte antigen; PRA, panel-reactive antibody; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

*The following donor variables were included in this model: age, gender, race, cause of death, history of hypertension, history of diabetes, terminal serum creatinine, donation after circulatory death, and HCV status. The following recipient factors were included in this model: age, gender, race, ESRD diagnosis, previous kidney transplantation, time on dialysis therapy prior to transplantation, number of HLA-A, B, and DR mismatches, panel-reactive antibody level, body mass index, insurance type, HIV status, cold ischemia time, previous liver transplantation, and the following interaction variables: alemtuzumab × time, IL-2RAb × time, and T cell × time.

Whether induction therapies have a deleterious impact on the outcome of HCV+ KTX recipients has been a subject of ongoing debate. The main reason for using induction therapy is to reduce the incidence and severity of acute rejection, which is associated with decreased graft survival. However, a major risk factor for infectious complications after solid organ transplantation is immunosuppression, including both maintenance therapy and agents used for induction or rejection. Some small studies have shown promising results with antithymocyte globulin or basiliximab in terms of viral infection, cirrhosis, and patient mortality in HCV+ renal transplant recipients [2,12–14]. In a SRTR analysis, Luan *et al.* [12] showed that induction with either depleting or nondepleting antibodies was associated with a 25% lower risk for mortality in 3708 HCV+ recipients as compared to those not receiving induction therapy. Another SRTR analysis observed similar patient survival in HCV+ recipients receiving depleting and nondepleting agents [13]. In a retrospective review of 104 HCV-infected kidney transplant recipients, patients who received induction with antithymocyte globulin had similar HCV viral load on follow-up as compared to patients without induction [14]. In a recent single-center study that evaluated long-term outcomes of 110 HCV-infected patients after KTX, a subset analysis of 31 recipients showed that patients who received daclizumab had a worse progression of liver fibrosis score than patients receiving a lymphocyte-depleting agent [2]. Whereas various single and multicenter studies, both randomized and nonrandomized, are reasonably consistent in demonstrating the effectiveness of AZ as an induction or preconditioning agent in renal transplant recipients [20–25], no studies have investigated the use of AZ induction – separate from other T cell-depleting

Table 3. HIV+/HCV+ recipients and induction therapy by year

Year	HIV+/HCV+ cases ($N = 88$) (%)	Induction therapy, *n* (%)	Induction type		
			AZ	T cell	IL-2RAb
2003	2 (2.3)	0 (0)	0	0	0
2004	6 (6.8)	3 (50)	0	0	3
2005	5 (5.7)	1 (20)	0	1	0
2006	10 (11.4)	4 (40)	0	1	3
2007	10 (11.4)	2 (20)	0	1	1
2008	15 (17.1)	5 (33)	0	2	3
2009	16 (18.2)	10 (62)	1	2	7
2010	24 (27.3)	16 (67)	3	8	5

therapies – on HCV(+) recipients. Given the findings of these reports and our study, it appears that induction therapy, even with AZ, may result in better outcomes, and at very least not worse ones, compared to noninduction.

Our study highlights that the patient survival benefit of induction therapy is maintained over time. Given that the effect of HCV on patient survival after KTX may follow a slow time trajectory and that liver disease can develop slowly or late after transplantation [26], a study of HCV(+) recipients must include long-term outcomes. Studies mostly focusing on 5-year survival rates have generally failed to find significant differences in patient survival between HCV-seropositive and HCV-seronegative recipients [27–31]. However, the majority of studies with large sample size and adequate follow-up have demonstrated a detrimental effect of HCV+ on patient and graft survival [3,4,32–37].

The potential impact of induction therapy on graft survival of HCV+ recipients is unclear. Increased graft loss associated with HCV status has been attributed to the occurrence of HCV-related renal disease [38], glomerulonephritis [4], post-transplant diabetes mellitus [10], chronic allograft nephropathy [4], and liver-related mortality [4,5]. In the liver transplant literature, immunosuppression causes an early increase in HCV replication after liver transplantation resulting in progression of recurrent HCV and liver fibrosis [39–41]. Conceivably immunosuppression related increases in HCV replication could increase the risk of glomerular damage of the kidney graft; however, it remains unknown whether the influence of immunosuppression in HCV+ liver recipients can be extrapolated to kidney recipients. A few studies looking at the impact of induction on graft failure in HCV+ patients have failed to find any differences in terms of any induction versus noninduction [12], and depleting versus nondepleting agents [13]. The traditional paradigm is that a patient and graft survival benefit in HCV+ KTX recipients is best derived from minimization of immunosuppression and avoidance of acute rejection (and the subsequent requirement for additional immunosuppression) resulting in a reduced net state of immunosuppression that over the long term may allow host defenses against HCV.

In contrast, our results demonstrate that the group with the lowest acute rejection (noninduction group) had the worst patient and graft survival. Our results are consistent with induction therapy offering a protective effect against graft failure. Although recipient selection bias cannot be discounted as a cause for the disparity in the observed and expected outcomes, it may be that the prognosis of kidney recipients with HCV is complex and beyond simply choice of induction and/or maintenance therapy.

A clinical challenge in managing kidney transplant recipients with HCV is coinfection with HIV. The presence of HIV results in more rapid progression of hepatitis C in coinfected patients [18,19]. HIV is also a strong risk factor for allograft rejection compared to those without HIV [42,43] with acute rejection rates ranging from 13 to 67% [42–46]. The higher risk of rejection might require more potent immunosuppression either as prophylaxis against or treatment of rejection which may in turn further exacerbate hepatitis C infection. Compared to HCV monoinfection, we found that HCV/HIV coinfection was associated with a somewhat increased risk for patient mortality and death-censored graft loss, and a significantly increased likelihood of acute rejection. Results of smaller studies have found coinfection to be a risk factor for patient survival, graft survival, or infectious complications relative to monoinfection [47,48]. Stock *et al.* [47] found a marginally higher hazard of death and significantly more serious infections in 16 HCV+/HIV+ patients compared to 80 HIV monoinfected patients. Time to event curves for graft loss and graft rejection did not differ. In an observational, multicenter, retrospective case–control study of 20 HIV+ and 40 HIV patients in Spain, Mazuecos *et al.* [48] noted that eight HCV+/HIV+ coinfected patients had significantly lower death-censored graft survival compared to the monoinfected groups on early follow-up [vs. HCV+/HIV− ($n = 8$); log-rank $P = 0.009$; vs. HCV−/HIV+ ($n = 12$); log-rank $P = 0.02$]. The authors suggested that the higher risk of pharmacologic nephrotoxicity or the possible effect of HIV infection on either HCV infection or on the development of rejection could, among other factors, explain the increased susceptibility to graft loss. However, the meaningfulness of the conclusions from these reports is limited by small sample size, short follow-up and lack of risk-adjusted analyses.

Most transplantation centers have been historically reluctant to use lymphocyte-depleting agents for induction in HIV+ recipients (and there is no information available regarding HCV+/HIV+ patients), as these agents severely deplete $CD4^+$ T cells for several months [43]. In the initial clinical trials of organ transplantation in patients with HIV infection, immunosuppressive regimens focused on maintenance therapy using agents with known

Table 4. Donor and recipient characteristics of cases with HCV alone compared to those with HIV/HCV coinfection.

Characteristic % or mean ± sd	HIV/HCV (n = 88)	Isolated HCV (n = 4823)	P-value
Donor age, years			
6–17	3.4	6.2	0.1283
18–39	48.8	37.6	
40–59	40.9	50.3	
≥60	6.8	5.8	
Donor African American	13.6	15.2	0.6933
Donor female	37.5	37.9	0.9386
Donor hypertension	20.9	28.2	0.1369
Donor diabetes	4.6	5.8	0.6263
Donor death because of CVA	34.1	40.1	0.2590
Donor DCD	5.7	7.1	0.5997
Donor serum Cr > 1.5 mg/dl	15.9	13.8	0.5735
Donor HCV positive	54.6	29.1	<0.0001
Recipient age, years	51.1 ± 8.1	52.8 ± 9.3	0.0849
Recipient ESRD diagnosis			
Glomerulonephritis	18.2	25.6	<0.0089
Diabetes	4.6	14.8	
Hypertension	37.5	29.3	
Other/unknown	39.8	31.3	
Recipient African American	77.3	48.1	<0.0001
Recipient female	23.9	26.1	0.6321
Recipient kidney re-transplant	6.8	15.1	0.0313
Recipient dialysis			
No dialysis	5.7	10.9	0.0015
≤3 years	27.3	40.7	
>3 years	65.9	46.3	
Recipient BMI > 30 kg/m^2	18.2	23.2	0.5657
Recipient PRA > 30%	21.6	25.9	0.4163
Recipient CIT > 24 h	18.2	18.0	0.9252
Recipient HLA MM >3	83.0	73.0	0.0368
Recipient insurance, private	85.2	71.8	0.0054
Recipient previous LTX	1.1	7.9	0.0191

CVA, cerebrovascular accident; DCD, donation after circulatory death; ESRD, end-stage renal disease; BMI, body mass index; CIT, cold ischemia time; PRA, panel-reactive antibodies; HLA, human leukocyte antigen mismatch; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LTX, liver transplant.

antiretroviral qualities [43,47]. This therapy consisted of a combination of steroids, a calcineurin inhibitor and mycophenolate mofetil. However, because of high rejection rates, induction therapy with interleukin-2 receptor blocker was next introduced [44–46]. Data from a prospective study by Kumar *et al.* [45] demonstrated that induction therapy by anti-CD25 antibody administration and maintenance therapy with sirolimus resulted in a decreased rejection rate; however, the 1-year patient and graft survival rates were in the range of other high-risk populations – 85% and 75%, respectively. Another small retrospective study by Gruber *et al.* [46] that examined outcomes in eight HIV+ KTXs receiving induction therapy with an anti-interleukin-2 receptor antibody and maintenance therapy with cyclosporine, mycophenolate mofetil and prednisone found patient and graft survival rates of 100% and 88%, respectively, and the rate of acute rejection was 13% at a median follow-up of 15 months. Despite an initial reluctance, recent reports are supporting the use of thymoglobulin induction in HIV+ recipients [47,49]. A study of 150 HIV+ KTX recipients found that thymoglobulin induction was significantly associated with an increased risk of graft loss on multivariate analysis (HR 2.1, 95% CI 1.1–5.6, P = 0.03). Thymoglobulin induction was also associated with twice as many serious infections per follow-up year as patients receiving IL-2RAb induction or no induction (0.9 vs. 0.4, P = 0.002) [47]. Another study reported that 2-year patient survival was less than 50% in the elderly (>60 years old) who had DGF and received thymoglobulin induction [49]. Tan *et al.* [50] described three HIV-infected live-donor kidney transplant recipients that were successfully preconditioned with AZ, all of whom had good graft function and no incidence of acute rejection, while requiring only maintenance with low-dose tacrolimus monotherapy. Our report found a shift in the United States toward the use of more potent induction therapy in patients with HCV+/HIV+. In contrast to other reports, we show on univariate analysis that overall patient survival among those that received any induction therapy was comparable to those that did not receive induction. The modest sample size did not allow for the conduct of a multivariate analysis.

Our results are subject to the limitations inherent in observational data. Because kidney transplant recipients are often not randomly selected to receive specific types of induction strategies, it is possible that they are in some unmeasured way systemically less (or more) healthy than those that received other types of induction or no induction. There is the possibility for residual confounding as a result of donor, recipient, or transplant factors not included in the analysis (not available in SRTR dataset) such as HCV genotype, administration of HCV therapy, duration and severity of HCV infection, liver histology, HCV viral load and, if HIV+, CD4 counts and HIV therapy. The intensity of maintenance immunosuppressive regimens may have a significant impact on the post-transplant course and although we assessed drug number, drug levels are not available in the SRTR database. In addition, it is challenging to assess the impact of a specific immunosuppressive drug on the outcome of HCV infection in kidney transplant recipients as immunosuppressive drugs are generally given in combination. Potential issues relating to the determination of acute rejection include missing or incomplete data, reporting bias, sampling and technique errors, measures of quantification and subjective interpretation. One systematic limitation of this and other previous studies is the use of HCV antibody screening to label

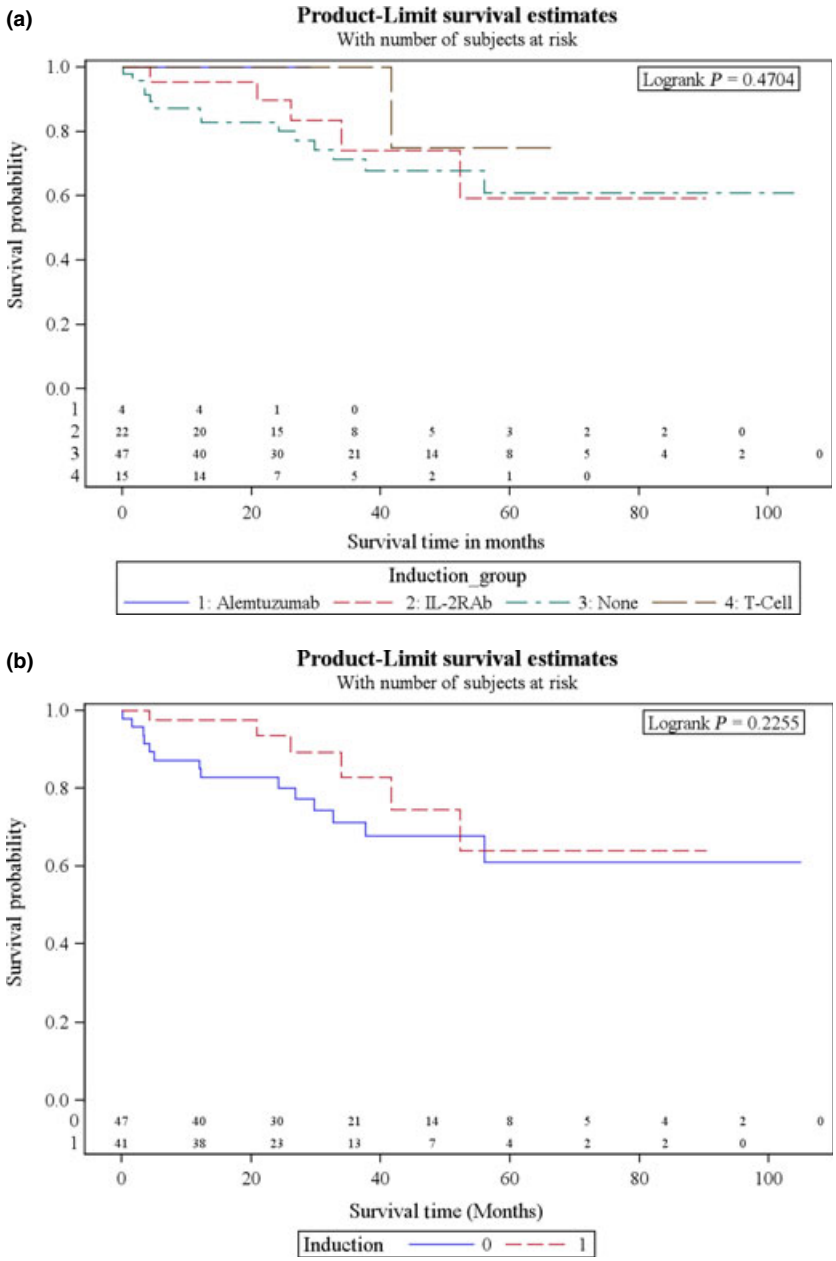

Figure 2 Kaplan–Meier plots of (a) overall patient survival by induction group (b) overall patient survival by induction versus no induction for hepatitis C-seropositive/human immunodeficiency virus coinfected kidney transplant recipients.

patients as 'HCV+'. In the absence of PCR analyses, patients may have false-positive HCV antibody results. Lastly, registry data is somewhat limited towards gaining an understanding of the causes of graft or patient loss; as such it is difficult to assess the direct association of failures that would be more reflective of induction therapy, donor risk factors, recipient characteristics, or the interaction of these. The results of the HCV/HIV coinfected group are largely descriptive. As a result of small sample size comparisons of donor and transplant characteristics between the four groups were not meaningful and a multivariate analysis was not possible.

In conclusion, this analysis supports not only that the use of induction therapy either with AZ, IL2R-Abs, or other T cell-depleting agents is not contraindicated but that it may be beneficial in HCV+ kidney transplant recipients. Inferences are limited because of the potential for patient selection bias; nevertheless, the large sample size and long follow-up allows for informative evaluation of causal factors associated with key outcomes. HCV/HIV-coinfection

represents a somewhat higher risk group compared to HCV-monoinfection with regard to long-term outcomes. The findings for this subgroup are less clear. More definitive studies are necessary to clarify the role of induction therapy in patients with HCV+ and HCV/HIV+.

Authorship

MV: wrote the paper, designed research/study. PF: designed research/study, performed research/study, analyzed data. YX: collected data. TK: wrote the paper, collected data. KM: contributed important reagents. SG: contributed important reagents. JC-F: contributed important reagents. MK: contributed important reagents. MA: contributed important reagents. EA: contributed important reagents. LKK: wrote the paper, designed research/study, analyzed data.

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