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Anti-Thymocyte Globulin versus Interleukin-2 Receptor Antagonist in Kidney Transplant Recipients with Hepatitis C Virus

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Abstract

Background: Hepatitis C virus-positive (HCV+) kidney transplant (KT) recipients are at increased risks of rejection and graft failure. The optimal induction agent for this population remains controversial, particularly regarding concerns that anti-thymocyte globulin (ATG) might increase HCV-related complications.

Methods: Using SRTR and Medicare claims data, we studied 6780 HCV+ and 139,681 HCV-KT recipients in 1999–2016 who received ATG or interleukin-2 receptor antagonist (IL2RA) for induction.

We first examined the association of recipient HCV status with receiving ATG (vs. IL2RA) using multilevel logistic regression. Then, we studied the association of ATG (vs. IL2RA) with KT outcomes (rejection, graft failure, and death) and hepatic complications (liver transplant registration and cirrhosis) among HCV+ recipients using logistic and Cox regression.

Results: HCV+ recipients were less likely to receive ATG than HCV- recipients (living donor, $aOR=_{0.64}0.77_{0.91}$; deceased donor, $aOR=_{0.71}0.81_{0.92}$). In contrast, HCV+ recipients who received ATG were at lower risk of acute rejection compared to those who received IL2RA (1-year crude incidence=11.6% vs. 12.6%; $aOR=_{0.68}0.82_{0.99}$). There was no significant difference in the risks of

graft failure (aHR=$_{0.86}1.00_{1.17}$), death (aHR=$_{0.85}0.95_{1.07}$), liver transplant registration (aHR=$_{0.58}0.97_{1.61}$), and cirrhosis (aHR=$_{0.73}0.92_{1.16}$).

Conclusions: Our findings suggest that ATG, as compared to IL2RA, may lower the risk of acute rejection without increasing hepatic complications in HCV+ KT recipients. Given the higher rates of acute rejection in this population, ATG appears to be safe and reasonable for HCV+ recipients.

INTRODUCTION

In the United States, 6.3% of deceased-donor kidney transplant (DDKT) recipients have hepatitis C virus (HCV) infection.[1] HCV+ KT recipients have been reported to have higher rates of rejection, graft failure, and mortality compared to their HCV- counterparts.[2–6] A possible approach to address these elevated risks among HCV+ recipients is to use anti-thymocyte globulin (ATG), a more potent induction immunosuppression agent that has been shown in randomized trials to reduce acute rejection in HCV- recipients.[7–9] Kidney Disease: Improving Global Outcomes (KDIGO) guidelines also suggest using a lymphocyte-depleting agent for recipients at high immunologic risk.[10] Nonetheless, some have questioned the use of such agents in HCV+ recipients because potent immunosuppression may possibly promote HCV replication, leading to cirrhosis, liver transplantation (LT), and death.[11–14] Anecdotally, HCV+ recipients often receive less potent induction agents, namely interleukin-2 receptor antagonists (IL2RA), despite their higher risk of rejection.[4,15]

When selecting an induction agent, clinicians must balance the risk of rejection against the risk of HCV-related hepatic complications, both of which have conflicting management and long-term effects on patient and graft survival. It is therefore essential to understand how each of the two risks is associated with the induction agent selection. For rejection, the key question is whether the superiority of ATG over IL2RA in preventing rejection, which was demonstrated in multiple HCV- populations,[7–9] could be generalized to HCV+ recipients. For hepatic complications, the key question is whether ATG, which may promote HCV replication, is actually associated with higher risks of hepatic complications compared to IL2RA. However, there are limited published data on both topics, hindering clinicians from accurately balancing the risk and benefit of ATG compared to IL2RA for HCV+ recipients.[15,16]

We sought to address these knowledge gaps in induction agent selection for HCV+ KT recipients using national registry data. The objectives of this study were to characterize the current practice regarding the selection of ATG versus IL2RA in HCV+ KT recipients, and to compare KT outcomes (acute rejection, graft failure, and mortality) as well as hepatic complications (LT registration and cirrhosis) by induction agent among HCV+ KT recipients.

MATERIALS AND METHODS

Data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted 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 (HRSA), US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors. Cirrhosis was ascertained and analyzed using Medicare inpatient claims from the United States Renal Data System (USRDS).

Study population

First, we studied all HCV+ kidney-only transplant recipients (termed "entire HCV+ cohort") between January 1, 1999 and December 31, 2016. We used HCV serology status to determine HCV+ status. After excluding recipients with human immunodeficiency virus (n=258; 1.8%), multi-organ transplant recipients (n=2196; 15.9%) and those with no available immunosuppression data (n=260; 2.2%), this population included 11,391 HCV+ KT recipients. We also created a cohort of 236,322 HCV- kidney-only transplant recipients using the same criteria as above (termed "entire HCV- cohort"). We used these cohorts to examine the temporal trends in the use of induction agents among KT recipients by recipient HCV status.

Then, we restricted the entire HCV+ cohort to those who used either of the study agents (termed "ATG/IL2RA HCV+ cohort"). We excluded those who received no antibody-based induction agent (n=2537; 22.3%), induction agents other than ATG or IL2RA (n=1145; 12.9%), or both ATG and IL2RA (n=396; 5.1%). We also excluded those who did not receive maintenance immunosuppression with a calcineurin inhibitor and anti-metabolite (n=533; 7.3%). This population included 6780 HCV+ KT recipients and was used as the primary study population in our outcomes analyses. We also created a cohort of 139,681 HCV- kidney-only transplant recipients using the same criteria as above (termed "ATG/IL2RA HCV- cohort"). The ATG/IL2RA HCV- cohort was used to compare the usage pattern of ATG versus IL2RA between HCV+ and HCV- recipients.

Usage pattern of induction agent

Using the ATG/IL2RA HCV+ and HCV- cohorts, we investigated whether recipient HCV status was associated with the use of ATG over IL2RA, and whether this practice varied between KT centers. We first compared the crude proportion of recipients who received ATG by HCV status at each KT center. Then, we conducted a multi-level logistic regression to examine whether recipient HCV status was associated with the use of ATG (versus IL2RA), after adjusting for other clinical factors. This model also included a random intercept term and a random slope term to account for the variation between transplant centers. The random intercept represented each transplant center's overall tendency to use ATG. The random slopes represented how, at each transplant center, recipient HCV status was associated with the use of ATG. We fitted this model using Gibbs sampler with uninformative diffuse priors under the Bayesian framework.[17] Lastly, we identified factors associated with the use of ATG (versus IL2RA) among the HCV+ recipients by conducting another multi-level logistic regression on the ATG/IL2RA HCV+ cohort.

Acute rejection

Using the ATG/IL2RA HCV+ cohort, we conducted multi-level multivariable logistic regressions to compare the odds of acute rejection at 1 year post-KT by induction agent. We adjusted for recipient variables (age, race, sex, panel reactive antigens (PRA), previous transplant, body mass index (BMI), cause of ESRD, years on dialysis, serum albumin, diabetes, hypertension, malignancy, peripheral vascular diseases, hepatitis B virus core antibody, education level, insurance, and previous history of LT registration), donor variables (age, race, sex, BMI, and HCV), and transplant variables (calendar year of transplant and human leukocyte antibody (HLA) mismatches), and maintenance immunosuppression agent (steroid at discharge, tacrolimus versus cyclosporine, and mycophenolates versus mTOR inhibitors). We also adjusted for variables specific to deceased donors: cause of death, history of hypertension and diabetes, donation after cardiac death (DCD), machine perfusion, terminal serum creatinine, and cold ischemic time. We conducted subgroup analyses by donor type (living vs. deceased) to examine any differences in the association between ATG and acute rejection. A random intercept term was included in the models to account for center-level clustering.

Graft and patient survival

Graft survival was defined as the time from transplant to graft failure (return to dialysis or re-KT), censoring for death. Patient survival was defined as the time from transplant to death. Death was ascertained from multiple sources, including follow-up reports from transplant centers, Centers for Medicare & Medicaid Services ESRD Death Notification Form (CMS 2746), and the Social Security Death Master File. All recipients were administratively censored at the end of follow-up on December 31, 2016. Using the ATG/IL2RA HCV+ cohort, we conducted multivariable Cox regressions to compare the hazards of graft failure and death by induction agent, adjusting for the same set of variables as used in the acute rejection model. We stratified the baseline hazard functions by transplant center: in other words, the baseline hazard functions were allowed to differ between transplant centers to account for center-level clustering. This technique is analogous to including random intercept terms in mixed-effects models.[18,19] We also conducted subgroup analyses by donor type to examine any differences in the association between ATG and survival.

Liver transplant registration

LT registration was defined as being registered as a recipient of or a waitlisted candidate for LT. We used LT registration as a surrogate indicator for end-stage liver disease (ESLD). We ascertained LT registration using the SRTR data of LT recipients and waitlisted candidates. Among 6780 KT recipients in the ATG/IL2RA HCV+ cohort, 461 (6.8%) recipients had a history of LT registration before their KT. Having a history of LT registration was included as a covariable in our KT outcome models, as the history of advanced liver disease may have influenced induction agent selection as well as post-KT outcomes.

Among the remaining 6319 KT recipients with no previous history of LT registration, 78 (1.2%) underwent LT registration after their KT. LT registration after KT was studied as a surrogate outcome for post-KT ESLD. Using these 6319 recipients with no previous history of LT registration, we compared the hazard of LT registration by induction agent using Cox

models, adjusting for the same set of variables as used in the acute rejection model (except for previous history of LT registration). Recipients were censored at death, graft failure, or the end of follow-up on December 31, 2016. We conducted subgroup analyses by donor type to examine any differences in the association between ATG and post-KT LT registration.

Cirrhosis

We ascertained cirrhosis using an ICD-9-CM diagnosis code 571.5 from Medicare inpatient and outpatient claims. Previous studies reported high validity of using ICD-9-CM codes for ascertainment of cirrhosis.[20,21] This analysis was restricted to 3114 (45.9%) recipients in the ATG/IL2RA HCV+ cohort who received KT between January 1, 1999 and December 31, 2014 (due to an additional 2-year lag in Medicare claims data availability), used Medicare as primary insurance, and had no previous history of cirrhosis or LT registration at the time of KT. We first estimated the cumulative incidence of cirrhosis using the Fine and Gray method, treating death as a competing risk.[22,23] Then, we compared the hazard of new onset cirrhosis by induction agent using multivariable Cox models, adjusting for the same set of covariables as used in the acute rejection model. Recipients were censored at death, graft failure, the end of Medicare primary coverage, or the end of follow-up on December 31, 2014. We conducted subgroup analyses by donor type to examine any differences in the association between ATG and cirrhosis.

Post-transplant lymphoproliferative disorder and cytomegalovirus infection

In addition to cirrhosis, we studied post-transplant lymphoproliferative disorder (PTLD; ICD-9-CM code: 200, 202, 204, and 238.77)[24] and cytomegalovirus (CMV) infection (ICD-9-CM code: 078.5) with Medicare claims data. This analysis was restricted to 3708 (54.7%) recipients in the ATG/IL2RA HCV+ cohort who received KT between January 1, 1999 and December 31, 2014, and used Medicare as primary insurance. The data were analyzed using the same methods as cirrhosis, except that the combination of donor and recipient CMV status (D+/R+, D+/R-, D-/R+, and D-/R-) was added as a covariable to the CMV analysis.

Statistical analysis

All analyses were performed using Stata 15.0/MP for Unix (College Station, Texas) and JAGS version 4.2.[25] 95% confidence intervals are reported as per the method of Louis and Zeger.[26] Missing values were handled using missing indicators (Table S1).

RESULTS

Temporal trends in induction agent use

In the entire HCV+ and HCV- cohort, the use of ATG increased during the study period (Figure 1). Among all HCV+ LDKT recipients during the study period (n=2479), the use of ATG increased from 2.9% in 1999 to 37.6% in 2004 and remained similar thereafter. The use of IL2RA was largely unchanged, from 34.5% in 1999 to 35.0% in 2016. Among all HCV+ DDKT recipients during the study period (n=8912), the use of ATG steadily increased from 5.1% in 1999 to 59.7% in 2016. The use of IL2RA slightly decreased from 30.8% in 1999 to 17.1% in 2016. In addition, the use of no antibody-based induction

decreased substantially (54.0% in 1999 to 7.7% in 2016, LDKT; 48.8% in 1999 to 8.1% in 2016, DDKT). Similar secular trends were observed in HCV- recipients, except that the use of ATG was more common compared to HCV+ recipients (see below).

Population characteristicsc

In our primary study population, the ATG/IL2RA HCV+ cohort (n=6780), 1410 received LDKT and 5370 received DDKT. Among the LDKT recipients, 652 (46.2%) received ATG and 758 (53.8%) received IL2RA. Among the DDKT recipients, 3342 (62.2%) received ATG and 2028 (37.8%) received IL2RA. Overall, several risk factors were more common in the ATG group (Table 1). Compared to the IL2RA group, the ATG group had higher proportions of recipients with PRA>80 (11.1% in ATG vs 4.7% in IL2RA, LDKT; and 18.8% in ATG vs 7.5% in IL2RA, DDKT), previous transplants (24.4% in ATG vs 19.5% in IL2RA, LDKT; and 19.5% in ATG vs 16.9% in IL2RA, DDKT), female sex (35.7% in ATG vs 31.7% in IL2RA, LDKT; and 27.1% in ATG vs 24.7% in IL2RA, DDKT), and donation after cardiac death (DCD) cases (10.9% in ATG vs 6.9% in IL2RA). However, the ATG group also had a higher proportion of preemptive transplants (24.5% in ATG vs 20.4% in IL2RA, LDKT; and 7.2% in ATG vs 6.3% in IL2RA, DDKT).

Usage pattern of induction agent

In the ATG/IL2RA cohorts, KT centers showed a wide variation in the overall ATG use in HCV+ recipients, which was comparable to that in HCV- recipients (Figure 2a). Among 85 KT centers that performed 5 or more HCV+ LDKT, 16 (18.9%) centers used ATG in greater than 80% of their HCV+ LDKT recipients, whereas 22 (25.9%) did in less than 20%. Similarly, among 177 centers that performed 5 or more HCV+ DDKT, 63 (35.6%) used ATG in greater than 80% of their HCV+ DDKT recipients, whereas 19 (10.7%) did in less than 20%.

In our multi-level logistic model, we found that HCV+ recipients were significantly less likely to receive ATG (aOR=$_{0.64}0.77_{0.91}$, LDKT; and aOR=$_{0.71}0.81_{0.92}$, DDKT) compared to HCV- recipients after adjusting for clinical characteristics. When estimated specifically to each transplant center, these odds ratios were narrowly distributed around the population odds ratios, with standard deviations of 0.14 in LDKT and 0.25 in DDKT, suggesting that the strength of the association between recipient HCV+ status and ATG use was generally similar across transplant centers (Figure 2b).

Several clinical factors, most of which indicated higher immunological risk, were associated with ATG use in HCV+ recipients (Table 2). Among LDKT recipients, higher peak PRA (10–79 vs 0–9, aOR=$_{1.16}1.68_{2.48}$; 80–100 vs 0–9, aOR=$_{1.59}3.19_{6.49}$), history of previous transplant (aOR=$_{1.33}2.18_{3.55}$), and HLA-A mismatches (1 mismatch vs none, aOR=$_{1.04}1.63_{2.56}$; 2 vs none, aOR=$_{1.02}1.75_{3.11}$) were associated with the use of ATG. Among DDKT recipients, factors including African American recipient (aOR=$_{1.12}1.39_{1.71}$), higher peak PRA (10–79 vs 0–9, aOR=$_{1.32}1.60_{1.95}$; 80–100 vs 0–9, aOR=$_{3.64}4.98_{6.88}$), history of previous transplant (aOR=$_{1.55}2.08_{2.78}$), stroke as the cause of donor death (aOR=$_{1.06}1.29_{1.56}$), kidney on machine perfusion (aOR=$_{1.14}1.44_{1.80}$), and longer cold ischemic time (per 12-hour increase, aOR=$_{1.00}1.12_{1.25}$) were associated with the use of

ATG. On the other hand, older recipient age (per 10-year increase after 55; aOR=$_{0.49}$0.59$_{0.72}$), Medicare as primary insurance (aOR=$_{0.68}$0.81$_{0.97}$), and donor HCV+ (aOR=$_{0.62}$0.77$_{0.96}$) were associated with lower odds of using ATG.

Acute rejection

In the ATG/IL2RA HCV+ cohort, 11.4% in the ATG group (10.4% among LDKT and 11.6% among DDKT) and 12.6% in the IL2RA group (12.0% among LDKT and 12.9% among DDKT) developed acute rejection within 1-year post-KT. After adjusting for potential confounders, the odds of acute rejection were significantly lower (aOR=$_{0.68}$0.82$_{0.99}$) in the ATG group compared to the IL2RA group (Table 3). When stratified by donor type, the odds of acute rejection still tended to be lower in the ATG group in both subpopulations (aOR, $_{0.50}$0.75$_{1.13}$ in LDKT and $_{0.68}$0.84$_{1.04}$ in DDKT).

Graft and patient survival

In the ATG/IL2RA HCV+ cohort, the risk of graft failure was not significantly different between the ATG and IL2RA groups in the entire population (aHR=$_{0.86}$1.00$_{1.17}$) or in the subpopulations stratified by donor type (aHR=$_{0.64}$0.98$_{1.52}$ in LDKT and $_{0.81}$0.97$_{1.16}$ in DDKT). Similarly, the risk of death was not statistically significantly different between the ATG and IL2RA groups in the entire population (aHR=$_{0.85}$0.95$_{1.07}$) or in the subpopulations stratified by donor type (aHR=$_{0.67}$0.92$_{1.26}$ in LDKT and $_{0.85}$0.98$_{1.12}$ in DDKT; Table 3). Cause-specific mortality rates were also generally similar between the groups (Figure S1).

Liver transplant registration

In the ATG/IL2RA HCV+ cohort, 92.7% of LDKT and 93.3% of DDKT recipients had no previous LT registration by the time of their KT. Among these recipients, LT registration after KT was rare: 3 (0.5%) in the ATG group and 17 (2.5%) in the IL2RA group among LDKT recipients, and 40 (1.3%) in the ATG group and 18 (1.0%) in the IL2RA group among DDKT recipients. After adjusting for confounders, the risk of LT registration was not significantly different between the ATG and IL2RA groups (aHR=$_{0.58}$0.97$_{1.61}$). However, when stratified by donor type, ATG was associated with a significantly lower risk (aHR=$_{0.02}$0.10$_{0.40}$) among LDKT recipients but with a non-significantly higher risk (aHR=$_{1.00}$1.88$_{3.55}$) among DDKT recipients, although these estimates should be interpreted with caution due to the small number of events within each stratum.

Cirrhosis

Among the 3114 HCV+ recipients included in this analysis, the cumulative incidence of cirrhosis was 3.1% at 1-year post-KT, 8.2% at 3-year, 12.3% at 5-year, and 21.1% at 10-year, treating death as a competing risk. After adjusting for confounders, there was no significant difference between the ATG and IL2RA groups in the entire population (aHR=$_{0.73}$0.92$_{1.16}$; Table 3) or in the subpopulations stratified by donor type (aHR=$_{0.33}$0.66$_{1.31}$ in LDKT and $_{0.78}$1.01$_{1.30}$ in DDKT).

Post-transplant lymphoproliferative disorder and cytomegalovirus infection

The cumulative incidence of PTLD was 0.8% at 1-year post-KT, 1.4% at 3-year, 2.0% at 5-year, and 2.6% at 10-year, and that of CMV infection was 7.7% at 1-year post-KT, 9.9% at 3-year, 11.2% at 5-year, and 12.5% at 10-year, treating death as a competing risk. After adjusting for confounders, ATG was not associated with either PTLD (aHR=$_{0.36}0.63_{1.13}$) or CMV infection (aHR=$_{0.70}0.88_{1.11}$) (Table S2).

DISCUSSION

In this national study of ATG versus IL2RA for induction immunosuppression in HCV+ KT recipients, we observed that HCV+ recipients were at approximately 20% lower odds of receiving ATG for induction immunosuppression than comparable HCV- recipients. This practice seemed common among the majority of transplant centers. However, somewhat contrary to this practice, HCV+ KT recipients who received ATG were at lower odds of acute rejection (1-year crude incidence=11.4% vs. 12.6%; aOR=0.82) with no increase in cirrhosis, LT registration, graft failure, or mortality compared to their counterparts who received IL2RA.

There is limited evidence on the association between ATG and KT outcomes in HCV+ KT recipients. Previous studies on induction therapy in this population have mainly focused on the comparison of any versus no antibody-based induction therapy using national registry data, and found lower mortality associated with induction therapy.[16,27] However, these studies provide limited guidance to the current clinical practice in which most KT recipients undergo antibody-based induction immunosuppression: in our study, more than 90% of the HCV+ KT recipients in 2016 received antibody-based induction therapy. Another national registry study[28] compared HCV+ DDKT recipients who used a depleting agent (ATG or alemtuzumab) with those who used a non-depleting agent (IL2RA). This study found no difference between the groups in graft and patient survival: however, it did not include acute rejection as an endpoint. Conversely, it is well established in various HCV- KT recipient populations that ATG, compared to IL2RA, lowers acute rejection but does not affect graft failure or mortality.[7–9] The findings from these studies correspond with our results, suggesting that the benefit of ATG over IL2RA in lowering the risk of acute rejection could also be expected in the HCV+ population.

Another important clinical question particular to the HCV+ KT recipient population is whether ATG increases the risk of HCV-related hepatic complications. As maintaining an adequate level of immunity is necessary to suppress HCV replication,[29] it has been speculated that the potent immunosuppression rendered by ATG might be harmful for HCV+ KT recipients.[11–14] This speculation is corroborated by earlier studies in HCV+ LT recipients that reported a higher risk of HCV recurrence associated with OKT3 and IL2RA compared to no induction.[13,30] However, more recent studies that specifically examined the effect of ATG in HCV+ KT recipients have found no increase in hepatic complications. Rodrigues and colleagues reported no increase in HCV viral load among HCV+ KT recipients who received ATG compared to those who did not.[31] Roth and colleagues observed a slower progression of liver fibrosis among HCV+ KT recipients who received ATG or OKT3 compared to those who received IL2RA.[15] These findings are in accordance

with our results in that we found no association between ATG and LT registration or cirrhosis.

Induction agent selection in the HCV+ recipients was associated with each center's preference as well as patient-level clinical characteristics. First, center preference appears to play a key role in induction agent selection in HCV+ population, as evidenced by the large center-level variation in the use of ATG versus IL2RA (Figure 2a). This finding is consistent with our previous study on induction agent selection in the entire KT recipient population.[32] In contrast, the impact of recipient HCV+ status on induction agent selection does not seem to vary greatly across centers, given the relatively small center-level variation in the association between recipient HCV+ status and ATG use. In other words, a majority of KT centers seem to consider recipient HCV+ status as a reason to select IL2RA over ATG. Lastly, patient-level characteristics associated with receiving ATG in HCV+ KT recipients, such as higher peak PRA, history of previous transplant, and longer cold ischemic time, were similar to those from the previous study on the entire KT recipient population.[32]

Direct-acting antivirals (DAA) are increasingly used in HCV+ KT recipients. It is unclear how DAA will influence the risk-benefit balance of induction agent selection in HCV+ KT recipients. Our study was not specifically equipped to address this question, as our data source did not have HCV treatment information. Even if we had the information, those who received DAA are yet few in numbers and have not been followed up long enough. Bearing these in mind, we speculate DAA may have fairly limited impacts on our findings, which suggest that the effect of ATG in HCV+ recipients resembles that in HCV- recipients. DAA would render HCV+ recipients aviremic, probably narrowing the clinical differences between HCV+ and HCV- recipients. Additionally, DAA is usually initiated after the conclusion of induction therapy,[33,34] reducing the chance of induction-DAA interaction. Further research on these topics are warranted.

Our study has some limitations. Confounding by indication, i.e., biases caused by the differences in clinical factors that lead to the selection of a certain agent over another, may still be present due to the observational nature of our study. However, we adjusted for a wide range of donor, recipient, and transplant variables to minimize any residual confounding. In addition, induction agent selection seems to have been significantly driven by each center's own preference rather than by individual patients' characteristics, likely reducing the impact of this type of confounding.[32,35] Another limitation of our registry study was that not all of the HCV-related clinical variables were available in our datasets. Particularly, our study could not identify viremic status, which is a potential effect modifier between induction and clinical outcomes. Viremic status may also change post-KT due to treatment, spontaneous clearance, or reinfection.[36] However, the clinical importance of viremic status has decreased after the advent of DAA, as the recipients can now be rendered aviremic.

Finally, our ascertainment of some outcomes have limitations. LT registration is a proxy outcome, which may not capture all ESLD or advanced liver diseases. Our analyses on cirrhosis, PTLD, and CMV infection were limited to Medicare beneficiaries as these outcomes were ascertained using Medicare claims data. However, we speculate our findings still hold important implications, as all kidney transplant recipients are eligible for Medicare,

about half of them use it, and treatment effects in studies limited to Medicare beneficiaries have commonly been consistent with those in non-Medicare beneficiaries (in other words, findings from studies of Medicare claims data are considered to generalize well to the entire KT population).

Despite the higher rates of acute rejection in this population, the use of ATG for induction immunosuppression for HCV+ KT recipients has remained controversial, due to the possible adverse effect of ATG in HCV management. We found that the HCV+ KT recipients were less likely to receive ATG (versus IL2RA) compared to their HCV- counterparts at the majority of KT centers across the US. Contrary to this practice, our outcomes analyses showed an association between ATG and a lower risk of acute rejection compared to IL2RA, similar to the results from previous studies in HCV- KT recipients. In addition, we found no evidence of increased LT registration or cirrhosis following induction therapy with ATG. These findings suggest that, at least under the current clinical practice, ATG is a safe and reasonable option for induction immunosuppression in HCV+ KT recipients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

ABBREVIATIONS

ATG	anti-thymocyte globulin
BMI	body mass index
CMV	cytomegalovirus
DAA	direct-acting antivirals
DCD	donation after cardiac death
DDKT	deceased donor kidney transplant
DGF	delayed graft function

ECD	expanded criteria donor
ESLD	end-stage liver disease
ESRD	end-stage renal disease
HCV	hepatitis C virus
HLA	human leukocyte antigen
IL2RA	interleukin-2 receptor antagonist
KDIGO	Kidney Disease: Improving Global Outcomes
KT	kidney transplant
LDKT	living donor kidney transplant
LT	liver transplant
PRA	panel reactive antigen
PTLD	post-transplant lymphoproliferative disorder
SRTR	Scientific Registry of Transplant Recipient
USRDS	United States Renal Data System

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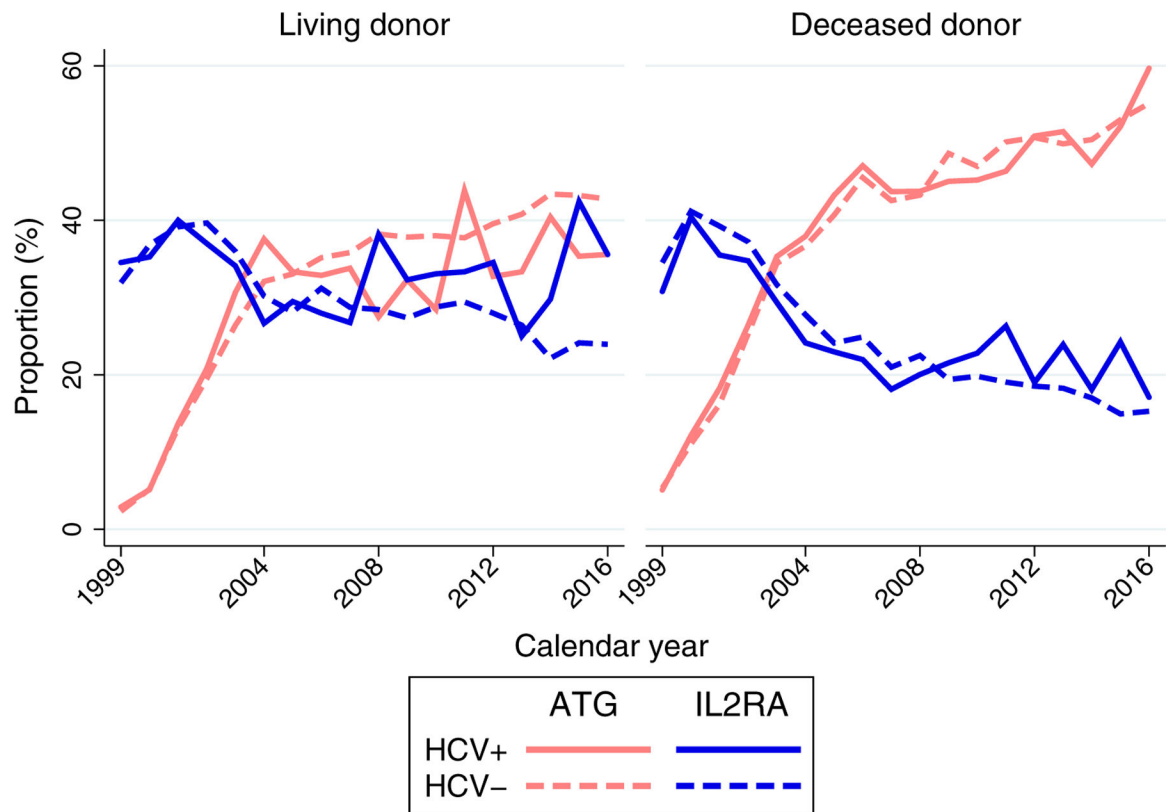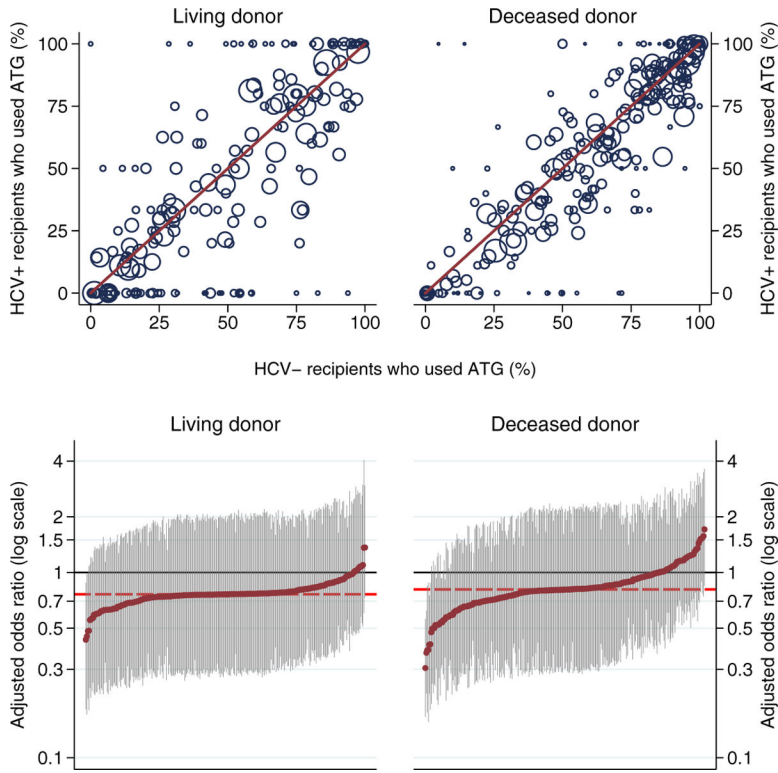
Figure 1.

Trends in the use of induction agents for kidney transplant recipients by donor type and recipient hepatitis C virus status

ATG, anti-thymocyte globulin; IL2RA, interleukin-2 receptor antagonist; and HCV, hepatitis C virus.

Solid lines represent trends in the HCV+ recipients and dashed lines represent those in the HCV- recipients.

Figure 2.
Variation between transplant centers in anti-thymocyte globulin (ATG) use in kidney transplant recipients with and without hepatitis C virus (HCV)

(a) Comparison of ATG use by recipient HCV status at each transplant center

(b) Center-specific odds ratio for ATG use in HCV+ recipients compared to HCV- counterparts

Each dot represents a transplant center and gray bars represent 95% confidence intervals. Analyses presented here includes eligible HCV+ and HCV- kidney transplant recipients who used either ATG or interleukin-2 receptor antagonist. (a) The y-axis represents the proportion of HCV+ recipients at each transplant center who used ATG for induction immunosuppression. The x-axis represents the same proportion of HCV- recipients. Markers are sized proportionally to the number of HCV+ kidney transplant recipients at the center. (b) The estimates represent the association of recipient hepatitis C virus-positive (HCV+) status with the use of ATG (versus IL2RA) at a transplant center after adjusting for confounders. Across the entire population, the HCV+ recipients were significantly less likely to receive ATG compared to HCV- recipients (LDKT, aOR=$_{0.64}0.77_{0.91}$; and DDKT, aOR=$_{0.71}0.81_{0.92}$; shown in dashed horizontal lines). This association did not vary greatly between transplant centers: i.e., the majority of the centers showed a similar tendency.

Table 1.

Population characteristics by donor type and induction agent

	Living donor		Deceased donor	
	ATG (n=652)	IL2RA (n=758)	ATG (n=3342)	IL2RA (n=2028)
Recipient variables				
Age (y)	52 (44, 58)	52 (44, 59)	55 (48, 61)	54 (47, 61)
Female sex	35.7%	31.7%	27.1%	24.7%
Race				
White	60.3%	53.7%	27.7%	31.3%
African American	24.4%	27.4%	57.0%	49.2%
Hispanic/Latino	10.6%	13.5%	10.9%	13.8%
Other/multi-racial	4.8%	5.4%	4.4%	5.8%
Years on dialysis	1.0 (0.0, 2.6)	1.1 (0.2, 2.2)	3.6 (1.6, 6.2)	3.3 (1.6, 5.8)
Preemptive transplant	24.5%	20.4%	7.2%	6.3%
Cause of ESRD				
Glomerulonephritis	23.6%	21.2%	16.0%	16.7%
Diabetes	23.9%	25.1%	28.4%	28.6%
Hypertension	16.6%	16.6%	31.5%	25.0%
Others	35.9%	37.1%	24.0%	29.7%
Peak PRA				
0–9	64.0%	75.4%	54.8%	68.1%
10–79	24.8%	20.0%	26.4%	24.5%
80–100	11.1%	4.7%	18.8%	7.5%
BMI (kg/m^2)	25.9 (22.6, 29.8)	26.1 (22.8, 30.0)	26.6 (23.4, 30.5)	26.0 (22.9, 30.0)
Previous transplants	24.4%	19.5%	19.5%	16.9%
Donor variables				
Age (y)	40 (31, 49)	41 (31, 49)	39 (26, 49)	39 (26, 49)
Female sex	57.4%	60.6%	38.4%	38.1%
Race				
White	65.2%	58.1%	71.4%	70.9%
African American	20.9%	24.2%	14.2%	12.4%
Hispanic/Latino	9.5%	13.3%	11.6%	13.6%
Other/multi-racial	4.4%	4.4%	2.8%	3.2%
BMI (kg/m^2)	26.9 (23.7, 29.8)	26.6 (23.8, 29.8)	25.8 (22.6, 29.8)	25.6 (22.4, 29.7)
Terminal serum creatinine (mg/dl)			0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
Cold ischemic time (hr)			17.6 (12.0, 23.2)	18.0 (12.1, 24.0)
Donation after cardiac death			10.9%	6.9%

ATG, anti-thymocyte globulin; IL2RA, interleukin-2 receptor antagonist; IQR, interquartile range; ESRD, end-stage renal disease; PRA, panel reactive antigen; and BMI, body mass index. Continuous variables are shown in median (IQR). Data on terminal serum creatinine, cold ischemic time, and donation after cardiac death were only available for deceased donor cases.

Table 2.

Factors associated with the use of anti-thymocyte globulin versus interlukin-2 receptor antagonist among kidney transplant recipients with hepatitis C

	Living donor (n=1410)			Deceased donor (n=5370)		
Recipient variables						
Age (per 10-year increase)						
<40	0.50	0.79	1.19	0.81	1.06	1.40
40–55	0.83	1.23	1.81	0.90	1.11	1.36
55	0.46	0.72	1.10	0.49	**0.59**	0.72
Female	0.94	1.34	1.91	0.87	1.05	1.26
Race						
White		(Ref)			(Ref)	
African American	0.51	1.06	2.32	1.12	**1.39**	1.71
Hispanic/Latino	0.52	1.22	2.89	0.71	0.94	1.28
Other/multi-racial	0.29	0.78	2.07	0.57	0.83	1.21
Peak PRA						
0–9		(Ref)			(Ref)	
10–79	1.16	**1.68**	2.48	1.32	**1.60**	1.95
80–100	1.59	**3.19**	6.49	3.64	**4.98**	6.88
Previous transplants	1.33	**2.18**	3.55	1.55	**2.08**	2.78
BMI (kg/m^2)						
<17.5	0.25	0.66	1.65	0.53	0.93	1.70
17.5–25		(Ref)			(Ref)	
25–30	0.70	1.02	1.47	1.02	**1.23**	1.47
30	0.67	1.04	1.60	0.95	1.16	1.42
Diabetes	0.42	0.74	1.34	0.64	0.84	1.11
Hypertension	0.69	1.24	2.19	0.71	0.92	1.20
Cause of ESRD						
Diabetes		(Ref)			(Ref)	
Glomerulonephritis	0.35	0.68	1.39	0.63	0.87	1.21
Hypertension	0.30	0.58	1.18	0.73	0.99	1.34
Others	0.30	0.56	1.12	0.52	**0.72**	0.98
Preemptive transplant	1.02	**1.57**	2.48	0.74	1.05	1.47
Time on dialysis (per 1-year increase)						
<6	1.00	1.13	1.27	0.97	1.02	1.07
6	0.98	1.06	1.16	0.96	0.99	1.02
Serum albumin (per 1-g/dL increase)						
<3	0.44	1.19	2.85	0.29	0.63	1.31
3	0.80	1.17	1.70	0.96	1.17	1.42
Symptomatic peripheral vascular disease	0.79	1.17	1.74	0.83	0.98	1.17

	Living donor (n=1410)			Deceased donor (n=5370)		
Pre-transplant malignancy	0.75	1.00	1.33	0.90	1.05	1.24
HBV+	0.97	1.04	1.12	1.01	**1.05**	1.08
Medicare as primary insurance	0.55	0.79	1.13	0.68	**0.81**	0.97
Donor variables						
Age (per 10-year increase)						
<25	0.28	1.55	7.19	0.74	0.97	1.26
25	0.77	0.90	1.06	0.92	1.01	1.10
Female	0.57	0.77	1.06	0.79	0.94	1.12
Race						
White		(Ref)			(Ref)	
African American	0.38	0.83	1.79	0.82	1.04	1.32
Hispanic/Latino	0.25	0.59	1.39	0.78	1.00	1.27
Other/multi-racial	0.36	1.05	2.95	0.74	1.18	1.87
BMI (kg/m^2)						
<17.5	0.23	1.93	17.02	0.49	0.75	1.15
17.5–25		(Ref)			(Ref)	
25–30	0.71	1.03	1.53	0.87	1.04	1.25
30	0.54	0.83	1.26	0.85	1.05	1.30
HCV+	0.23	1.11	4.67	0.62	**0.77**	0.96
Number of mismatches, HLA-A						
0		(Ref)			(Ref)	
1	1.04	**1.63**	2.56	0.94	1.26	1.71
2	1.02	**1.75**	3.11	0.87	1.17	1.61
Number of mismatches, HLA-B						
0		(Ref)			(Ref)	
1	0.45	0.75	1.25	0.75	1.10	1.62
2	0.39	0.71	1.31	0.72	1.05	1.52
Number of mismatches, HLA-DR						
0		(Ref)			(Ref)	
1	0.77	1.22	1.94	0.88	1.15	1.52
2	0.86	1.51	2.59	0.81	1.07	1.41
Donation after cardiac death				0.93	1.25	1.69
Diabetes				0.67	0.95	1.36
Hypertension				0.82	1.01	1.25
Stroke as the cause of death				1.06	**1.29**	1.56
Kidney on machine perfusion				1.14	**1.44**	1.80
Terminal serum creatinine (per 1-mg/dL increase)						
<1.8				0.84	1.06	1.32
1.8				0.88	1.01	1.17
Cold ischemic time (per 12-hour increase)				1.00	**1.12**	1.25

Subscript indicates upper and lower bounds of 95% confidence interval. Bold face indicates statistical significance (p<0.05). PRA, panel reactive antigen; BMI, body mass index; ESRD, end-stage renal disease; HBV, hepatitis B virus; HCV, hepatitis C virus; and HLA, human leukocyte antigen.

Table 3.

Association of anti-thymocyte globulin versus interleukin-2 receptor antagonist with kidney transplant outcomes and hepatic complications in kidney transplant recipients with hepatitis C virus

	Overall (n=6780)			Donor type					
				Living donor (n=1410)			Deceased donor (n=5370)		
Acute rejection	0.68	**0.82**	0.99	0.50	0.75	1.13	0.68	0.84	1.04
Graft failure	0.86	1.00	1.17	0.64	0.98	1.52	0.81	0.97	1.16
Death	0.85	0.95	1.07	0.67	0.92	1.26	0.85	0.98	1.12
Liver transplant registration	0.58	0.97	1.61	**0.02**	**0.10**	**0.41**	1.00	1.88	3.55
Cirrhosis [*]	0.73	0.92	1.16	0.33	0.66	1.31	0.78	1.01	1.30

Liver transplant registration was defined as being registered as a waitlisted candidate for or a recipient of a liver transplant. Estimates are adjusted odds ratios for acute rejection and adjusted hazard ratios for others. Subscript indicates upper and lower bounds of 95% confidence interval. Bold face indicates statistical significance (p<0.05).

[*] This analysis was restricted to 3114 (45.9%) recipients in the ATG/IL2RA HCV+ cohort who received KT in 1999–2014 (due to Medicare claims data availability), used Medicare as primary insurance, and had no previous history of cirrhosis or LT registration at the time of KT.