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Outcome of induction immunosuppression for liver transplantation comparing anti-thymocyte globulin, daclizumab, and corticosteroid

Tadahiro Uemura,[1] Eric Schaefer,[2] Christopher S. Hollenbeak,[2,3] Akhtar Khan[4] and Zakiyah Kadry[1]

1 Division of Transplantation, Department of Surgery, Penn State University, College of Medicine, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA
2 Department of Public Health Sciences, Penn State University, College of Medicine, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA
3 Division of Outcomes Research and Quality, Department of Surgery, Penn State University, College of Medicine, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA
4 Division of Transplantation, Department of Surgery, Allegheny General Hospital, Pittsburgh, PA, USA

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Correspondence
Tadahiro Uemura MD, PhD, Department of Surgery, H062, Penn State Milton S. Hershey Medical Center, 500 University Drive, Hershey, PA 17033, USA. Tel.: +717 531 5921; fax: +717 531 5851; e-mail: tuemura@hmc.psu.edu
Zakiyah Kadry MD, Department of Surgery, H062, Penn State Milton S. Hershey Medical Center, 500 University Drive, Hershey, PA 17033, USA. Tel.: +717 531 5921; fax: +717 531 5851; e-mail: zkadry@psu.edu

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Summary

In addition to standard corticosteroid induction, anti-thymocyte globulin (ATG) or daclizumab as induction immunosuppression has been reported for liver transplantation. However, the effects and long-term outcomes of antibody induction therapy are not well known, especially for hepatitis C (HCV). The United Network for Organ Sharing (UNOS) database was utilized to analyze 16 898 adult primary liver transplant patients who received ATG alone ($n = 452$), ATG and steroids (ATG + S) ($n = 1758$), daclizumab alone ($n = 683$), or steroid alone ($n = 14\ 005$), listed as induction immunosuppression. Graft and patient survival, and donor and recipient factors for survival were analyzed for HCV and all liver diseases. For patients with HCV, ATG + S had significantly inferior graft survival compared with daclizumab ($P = 0.01$) and steroids ($P = 0.03$). The Cox proportional hazards model also showed that ATG + S was a marginal risk factor for graft failure ($P = 0.05$). On the other hand, for patients with all the liver diseases, graft and patient survival were not significantly different between induction regimens. ATG induction appeared to be preferentially used in patients with renal dysfunction, with improvement in renal function after liver transplantation. Thus, ATG induction can be used for patients with renal dysfunction in non-HCV diseases. Daclizumab induction achieved satisfactory short-term and long-term outcomes of liver transplantation in all the liver diseases including HCV disease.

Introduction

Corticosteroid induction has traditionally been the standard immunosuppression treatment for liver transplantation for many years. Recently, however, induction therapy with antibodies has been increasingly used [1,2]. Induction immunosuppression provides potential benefits through preservation of renal function, reduction in maintenance immunosuppression, and reduction in the number of acute rejection episodes [3–6]. However, issues with the use of antibody induction are an increased risk of over-immunosuppression, especially for hepatitis C patients. Thus, the use of induction therapy with antibodies in liver transplantation remains controversial.

End stage of liver disease secondary to hepatitis C has become one of the leading indications for liver transplantation worldwide [7]. Recurrent hepatitis C is universal after liver transplantation, and it is associated with a significant reduction in graft and patient survival [8,9]. The use of antibodies, such as OKT3 or anti-thymocyte globulin (ATG), for steroid resistant rejection has been shown to worsen hepatitis C recurrence [10–13]. Furthermore, it has been suggested that immunosuppressive induction therapy could increase the risk of aggressive hepatitis C recurrence [7,14]. On the other hand, small single center analyses have shown that induction therapy with ATG can be safely given by delayed initiation of calcineurin inhibitor and decreased maintenance immunosuppressive therapy, thus reducing the risk of hepatitis C recurrence [15–17]. Thus, the impact of profound immunosuppressive effects from induction agents on liver transplantation for hepatitis C recipients is yet to be determined. The objective of this study was to analyze the effect and outcome of induction therapy (ATG and daclizumab) on liver transplantation in a population-based data set from the United Network for Organ Sharing (UNOS).

Patients and methods

This is a registry study based on data from the United Network for Organ Sharing/the Organ Procurement and Transplantation (UNOS/OPTN). Adult patients (≥18 years of age) who underwent liver transplantation after initiation of the Model for End-Stage Liver Disease (MELD) scoring system between 3/1/2002 and 12/31/2007 as reported to UNOS/OPTN were used in this analysis. Patients receiving multiple organ transplants and re-transplants were excluded. We first selected those patients who received ATG, daclizumab, or steroids listed as induction immunosuppression in the UNOS files. We then retained for analysis those patients who received ATG alone ($n = 452$), ATG in combination with steroids (ATG + S) ($n = 1758$), daclizumab alone ($n = 683$), or steroids alone ($n = 14\,005$). Patients who received a combination of these induction agents were excluded: daclizumab and steroids ($n = 743$); and ATG and daclizumab ($n = 32$). HCV positive patients were those with a positive serologic test for hepatitis C. A total of 6612 patients were HCV positive: 207 received ATG, 786 received ATG + S, 251 received daclizumab alone, and 5386 received steroids alone.

Patient survival was defined as the time from the date of primary transplant until the date of death. Patients alive at the last recorded follow-up were considered censored for patient survival. Graft survival was defined as the time from the date of primary transplant until the date of graft failure or death. A re-transplantation constituted graft failure. Patients alive and without a graft failure at the time of last follow-up were considered censored for graft survival. Both graft survival and patient survival were censored at 5 years as a result of limited follow-up after 5 years post-transplant in some groups.

Demographics for recipients were age, gender, ethnicity, HCV status, the MELD score, status 1 assignment, medical condition pretransplant, history of transjugular intrahepatic portosystemic shunt (TIPS), spontaneous bacterial peritonitis, portal vein thrombosis, previous upper abdominal surgery, and the following at the time of transplant: total bilirubin, creatinine, international normalized ratio (INR), and albumin. Donor factors were status (living or deceased), age, gender, ethnicity, cold ischemia time and warm ischemia time.

Recipient and donor factors were compared among the induction groups using chi-square tests for categorical variables and Kruskal–Wallis tests for continuous variables. In unadjusted analysis for patient and graft survival, the Kaplan–Meier method was used to estimate survival curves, and the log-rank test was used to test for differences among curves. The Cox proportional hazards model was used to evaluate patient mortality and graft loss among recipient and donor factors. Patients with a complete set of factors (complete cases) were used in the Cox models. For all the patients, there were 13 948 (83%) complete cases with 406 (90%) in the ATG group, 1409 (80%) in the ATG + S group, 564 (83%) in the daclizumab group, and 11 569 (83%) in the steroids group. For HCV patients, there were 5859 (89%) complete cases, with 198 (96%) in the ATG group, 641 (83%) in the ATG + S group, 220 (88%) in the daclizumab group, and 4800 (89%) in the steroids group.

Renal and liver functions were analyzed in the first year after transplant using the set of patients who were alive and without a graft failure at their 1-year follow-up after primary transplant. Follow-up data at 6 months (±30 days) and 1 year (±60 days) post-transplant were used; follow-up data outside these ranges were excluded. Generalized linear models assuming a Gamma distribution were used to model mean renal and liver function levels over time, with the method of generalized estimating equations (GEE) used to account for correlation within the patients.

Analysis was also conducted to assess overall survival and graft survival by induction and maintenance group combinations at 30 days postliver transplantation. Tacrolimus, mycophenolate mofetil (MMF) and steroid maintenance were predominantly used in the registry data. Therefore, four maintenance groups were of principal interest: tacrolimus, MMF and steroids; tacrolimus and MFF; tacrolimus and steroids; and tacrolimus alone. We compared survival end points between all pairs of

induction and maintenance group combinations using unadjusted and adjusted Cox models. *P*-value was adjusted by Bonferonni correction because of the large number of comparisons. Patients alive (overall survival) and without a graft failure (graft survival) at a landmark of 30 days post-transplant were used for this analysis. The landmark is set as the patients may have started their third course of maintenance therapy (e.g. steroids) some days after transplant. For hepatitis C patients, the analysis for maintenance immunosuppression could not be performed because of small sample size.

Results

All recipients

The characteristics of all recipients and donors are presented in Table 1. Approximately 30–40% of the patients were positive for HCV in all groups. The ATG group had a higher creatinine level at the time of liver transplantation ($P < 0.001$). Steroid induction was used more frequently in living donor liver transplantation ($P < 0.001$).

Graft and patient survival

Figure 1a shows graft survival in the unadjusted analysis. The ATG induction group had a graft survival of 85% at 1 year and 69% at 5 years compared to the ATG + S (84% and 67%, respectively), daclizumab (86% and 71%, respectively), and steroid groups (86% and 70%, respectively) ($P = 0.26$) (Fig. 1a). Patient survival also showed no significant difference in all groups (ATG: 1-year 88%, 5-year 72%, ATG + S: 1-year 87%, 5-year 71%, daclizumab: 1-year 89%, 5-year 75%, steroids: 1-year 89%, 5-year 73%) ($P = 0.16$). Table 2 presents the Cox proportional hazard models for patient mortality and graft loss that included donor and recipient factors. Hepatitis C, age of patient, African–American, creatinine ≥2 mg/dl, pretransplant ICU status, portal vein thrombosis, previous upper abdominal surgery, donor age, and Hispanic donors were significant risk factors for both graft survival and patient survival. There was no significant difference among the induction groups for patient mortality and graft loss (Table 2), although ATG + S versus steroids was close to significance for patient survival (HR = 1.12, $P = 0.07$) and graft survival (HR = 1.12, $P = 0.05$).

Renal function

A total of 11 603 patients were identified for this analysis as per criteria described in the Patients and Methods section. A total of 11 600 patients (99%) had a creatinine value documented at the time of liver transplantation, 8805 patients (76%) had a creatinine value at 6 months, and 10 118 patients (87%) had a creatinine value at 1 year after liver transplantation. Figure 1b shows the creatinine level before and after liver transplantation among all groups. The ATG group had a significantly higher mean level of creatinine at 1.82 ± 0.10 mg/dl before transplant compared with the daclizumab group at 1.37 ± 0.06 mg/dl ($P < 0.01$) and the steroid induction group at 1.47 ± 0.01 mg/dl ($P < 0.01$), and showed a trend for significance compared with the ATG + S group at 1.62 ± 0.04 ($P = 0.05$). The ATG + S group had a significantly higher mean level than the daclizumab ($P < 0.01$) and steroids ($P < 0.01$) groups. However, the creatinine level in the ATG and ATG + S groups improved after liver transplant, and there were no significant differences at 6 and 12 months among the three groups (Fig. 1b).

Maintenance immunosuppression

We analyzed the effect of combination of maintenance immunosuppression with each induction on graft and patient survival. The tacrolimus, MMF, and corticosteroid groups encompassed 43.3% of patients; tacrolimus and MMF (12.0%); tacrolimus and corticosteroids (24.5%); tacrolimus alone (8.8%); and other maintenance immunosuppression (11.3%). There were no significant differences at the Bonferonni level for graft and patient survival in adjusted analysis for any combination of maintenance immunosuppression involving tacrolimus with ATG, ATG + S, daclizumab, or steroid induction.

Hepatitis C recipients

The characteristics of recipients with hepatitis C and donors are presented in Table 3.

Graft and patient survival in HCV recipients

Figure 2a shows graft survival in unadjusted analysis. The ATG induction group had 84% graft survival at 1 year and 62% graft survival at 5 years, compared to the ATG + S (82% and 61%), daclizumab (90% and 73%), and steroid groups (85% and 66%), respectively ($P = 0.03$) (Fig. 2a). ATG + S had significantly worse graft survival compared with daclizumab ($P = 0.01$) and steroids ($P = 0.03$). ATG alone showed a trend for worse graft survival compared with daclizumab ($P = 0.09$) and steroids ($P = 0.08$). There was also a significant difference among the groups ($P = 0.03$) in the patient survival (ATG: 1-year 86%, 5-year 64%, ATG + S: 1-year 86%, 5-year 65%, daclizumab: 1-year 92%, 5-year 77%, steroids: 1-year 88%, 5-year 70%). ATG + S had significantly worse patient survival than daclizumab ($P = 0.01$) and steroids ($P = 0.03$), and ATG alone trended toward worse patient survival compared with daclizumab ($P = 0.05$) and steroids ($P = 0.08$). Table 4 presents Cox proportional hazard models for patient mortality and

Table 1. Demographics of all recipients and donors.

	ATG (n = 452)	ATG + steroid (n = 1758)	Daclizumab (n = 683)	Steroid (n = 14 005)	P-value
Recipients					
Age (years)	52.0 ± 10.6	52.4 ± 10.1	52.1 ± 9.3	52.5 ± 10.1	0.42
Female (%)	33.6	31.8	31.8	33.2	0.59
Diagnosis (%)					
HCV	34.3	37.9	40.7	33.5	<0.001
HBV	3.5	1.8	2.5	3.8	
Alcoholic	19.7	20.4	16.0	8.0	
Cholestatic	7.5	9.2	7.0	9.2	
Other	35.0	34.3	33.8	35.5	
Race					
White	72.8	76.6	75.0	72.1	<0.001
Black	12.2	10.6	10.0	7.5	
Hispanic	10.2	9.1	11.3	14.3	
Asian	4.2	3.2	3.4	4.8	
Other	0.6	0.5	0.4	1.3	
MELD Score	21.8 ± 9.8	19.8 ± 9.8	18.9 ± 8.2	20.4 ± 9.7	<0.001
Bilirubin (mg/dl)	6.8 ± 9.6	6.7 ± 10.3	5.2 ± 7.0	7.4 ± 10.2	<0.001
Creatinine (mg/dl)	1.9 ± 1.6	1.6 ± 1.5	1.4 ± 1.2	1.5 ± 1.3	<0.001
INR	1.9 ± 1.2	1.7 ± 0.9	1.7 ± 0.9	1.8 ± 1.7	<0.001
Albumin (g/dl)	3.0 ± 0.7	2.9 ± 0.7	2.9 ± 0.6	2.9 ± 0.7	<0.001
Status 1 (%)	4.4	2.4	2.6	3.8	0.01
Pretransplant in ICU (%)	12.4	9.3	5.9	12.0	<0.001
History of SBP (%)	6.6	8.1	5.9	7.8	<0.001
History of TIPS	7.1	9.7	4.8	8.4	<0.001
Portal vein thrombus	3.8	4.5	2.5	4.0	<0.001
Donor					
Donor status (%)					
Deceased donor	96.9	96.3	97.7	93.7	<0.001
Living donor	3.1	3.7	2.3	6.3	
Age (years)	40.4 ± 16.2	40.4 ± 16.3	40.7 ± 17.5	40.6 ± 17.1	0.99
Cause of death (%)					
Anoxia	13.9	17.3	12.9	12.7	<0.001
CVA	43.4	40.6	39.9	43.3	
Trauma	39.3	38.2	44.7	41.4	
CNS tumor	0.7	1.5	0.4	0.8	
Other	2.7	2.4	2.1	1.8	
Female (%)	43.6	42.9	41.9	40.1	0.06
Race					
White	69.0	75.1	65.2	69.7	<0.001
Black	14.2	15.2	16.8	12.5	
Hispanic	12.8	7.1	15.8	14.0	
Asian	2.2	1.9	1.5	2.4	
Other	1.8	0.7	0.6	1.4	
Cold ischemia time (h)	7.1 ± 4.8	7.2 ± 3.3	7.6 ± 2.9	7.4 ± 3.6	<0.001
Warm ischemia time (min)	37.7 ± 13.3	41.5 ± 20.6	43.7 ± 21.1	40.2 ± 19.1	<0.001

ATG, anti-thymocyte globulin; TIPS, transjugular intrahepatic portosystemic shunt; SBP, spontaneous bacterial peritonitis; MELD, model for end-stage liver disease; INR, international normalized ratio; CVA, cerebrovascular accident; CNS, central nervous system.

graft loss including donor and recipient factors for HCV patients. African–American patients, female recipients, creatinine ≥2 mg/dl, previous upper abdominal surgery, donor age, Hispanic donor, and Asian donor were significant risk factors for HCV for both graft loss and patient mortality. There was no significant difference among the induction groups for HCV patients in either model (Table 4). However, ATG + S versus steroids trended toward worse patient mortality (HR = 1.18, $P = 0.05$) and graft loss (HR = 1.15, $P = 0.08$).

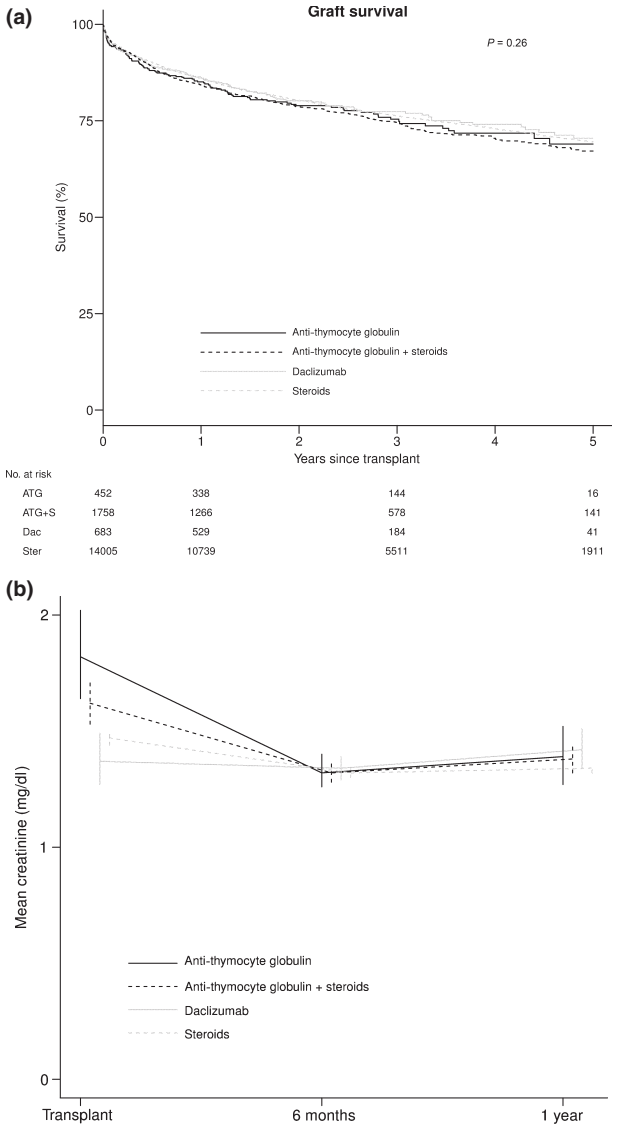

Figure 1 (a) Kaplan–Meier curves for graft survival (all subjects). (b) Mean creatinine levels in the first year post-transplant (all patients).

Renal function in HCV recipients

A total of 4459 patients were identified for this analysis as per criteria described in the Patients and Methods section. A total of 4458 patients (99%) had a documented creatinine value at the time of liver transplantation, 3401 patients (76%) had a creatinine value at 6 months, and 3859 patients (87%) had a creatinine value at 1 year after liver transplantation. Figure 2b shows renal function in recipients with hepatitis C before and after liver transplant among all groups. The ATG group had a mean level of creatinine of 1.53 ± 0.09 mg/dl before transplant compared to ATG + S at 1.57 ± 0.07 mg/dl ($P = 0.72$), daclizumab at 1.29 ± 0.09 mg/dl ($P = 0.06$), and steroids at 1.44 ± 0.02 mg/dl ($P = 0.31$). ATG + S had a significantly higher mean level of creatinine at baseline compared with daclizumab ($P = 0.01$), and showed a trend for a higher creatinine level compared with steroid ($P = 0.06$). Creatinine in the ATG and ATG + S groups improved after liver transplant and there were no significant differences between the groups at 6 and 12 months (Fig. 2b).

Total bilirubin in the first year in HCV recipients

We compared mean total bilirubin at preliver transplant, 6 months, and 12 months after liver transplantation. A total of 4459 patients were identified for this analysis as per the criteria described in Patients and Methods. A total of 4452 patients (99%) had documented bilirubin value at the time of liver transplantation, 3391 patients (76%) had bilirubin value at 6 months, and 3874 patients (87%) had bilirubin value at 1 year after liver transplantation. The bilirubin levels were normalized after liver transplant in all groups, and there were no significant differences among the groups at 6 months or 1 year (Fig. 3).

Discussion

As the liver is considered to be an immunologically privileged organ, the use of antibody to prevent rejection has been perceived as unnecessary and could carry the risk of over-immunosuppression. On the other hand, antibody induction has some advantage over standard corticosteroid induction. Ramirez *et al.* reported that anti-IL2 induction achieved excellent graft and patient survival with a low incidence of acute rejection [1]. Furthermore, recent studies have shown that antibody induction (daclizumab or ATG) with delayed initiation of calcineurin inhibitors had significant benefits in preserving renal function after liver transplantation [3,15,18]. Thus, the use of antibody induction for liver transplantation is still controversial and the long-term outcome is not well studied. In this study, we followed graft and patient survival up to 5 years postliver transplantation. ATG or daclizumab achieved survivals that statistically did not differ from the results of corticosteroid induction in all liver diseases, but not in HCV disease. This result suggests that ATG or daclizumab could be valid choices for induction immunosuppression in liver transplantation in non-HCV disease. Indeed, there was a tendency for ATG induction to be chosen for patients with pretransplant renal dysfunction, and renal function significantly improved by 6 months postliver transplant. ATG induction with delayed initiation or lower dose of calcineurin inhibitors has been reported to improve renal function after the liver transplantation [15].

Table 2. Cox proportional hazard model adjusting for donor and recipient factors in all patients.

	Patient survival			Graft survival		
Variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Induction						
Anti-thymocyte globulin	1.12	(0.90–1.39)	0.32	1.11	(0.91–1.36)	0.29
Anti-thymocyte globulin + steroids	1.12	(0.99–1.27)	0.07	1.12	(1.00–1.26)	0.05
Daclizumab	1.01	(0.82–1.24)	0.94	1.02	(0.85–1.23)	0.82
Steroids	(ref)			(ref)		
Age						
10-year increase	1.17	(1.12–1.22)	<0.001	1.08	(1.04–1.12)	<0.001
Gender						
Female	1.00	(0.92–1.09)	0.97	1.00	(0.92–1.08)	0.94
Male	(ref)			(ref)		
Race						
White	(ref)			(ref)		
Black	1.35	(1.19–1.53)	<0.001	1.32	(1.17–1.48)	<0.001
Hispanic	0.88	(0.78–0.99)	0.04	0.89	(0.80–1.00)	0.04
Asian	0.89	(0.74–1.08)	0.25	0.90	(0.76–1.08)	0.27
Other	1.44	(1.07–1.93)	0.02	1.37	(1.04–1.81)	0.03
HCV status						
Positive	1.38	(1.28–1.50)	<0.001	1.35	(1.26–1.46)	<0.001
Not positive/ unknown	(ref)			(ref)		
Total bilirubin (mg/dl)						
≥8	0.97	(0.86–1.09)	0.60	1.08	(0.96–1.20)	0.19
<8	(ref)			(ref)		
Creatinine (mg/dl)						
≥2	1.13	(1.01–1.28)	0.04	1.11	(0.99–1.24)	0.07
<2	(ref)			(ref)		
INR						
≥2	0.93	(0.83–1.04)	0.21	0.95	(0.85–1.05)	0.33
<2	(ref)			(ref)		
Albumin (g/dl)						
≥3	0.92	(0.85–0.99)	0.04	0.96	(0.89–1.03)	0.25
<3	(ref)			(ref)		
MELD						
<20	(ref)			(ref)		
20–30	1.14	(1.02–1.28)	0.03	1.11	(0.99–1.23)	0.07
>30	1.32	(1.08–1.63)	0.01	1.18	(0.98–1.43)	0.08
UNOS status						
Status 1	0.92	(0.73–1.17)	0.50	1.00	(0.81–1.24)	0.99
Other	(ref)			(ref)		
Medical condition pretransplant						
ICU	1.53	(1.33–1.75)	<0.001	1.41	(1.24–1.60)	<0.001
Hospitalized	1.06	(0.94–1.19)	0.38	1.03	(0.92–1.15)	0.60
Not hospitalized	(ref)			(ref)		
TIPS						
Yes	1.06	(0.93–1.21)	0.40	1.00	(0.89–1.14)	0.96
No/unknown	(ref)			(ref)		
Portal vein thrombosis						
Yes	1.42	(1.20–1.69)	<0.001	1.38	(1.17–1.62)	<0.001
No/unknown	(ref)			(ref)		
Prev upper abdominal surgery						
Yes	1.15	(1.06–1.25)	<0.001	1.14	(1.06–1.23)	<0.001
No/unknown	(ref)			(ref)		
Donor status						
Deceased	1.05	(0.84–1.32)	0.65	0.80	(0.67–0.97)	0.02
Living	(ref)			(ref)		
Donor age						
10-year increase	1.12	(1.10–1.15)	<0.001	1.14	(1.12–1.17)	<0.001
Donor sex						
Female	1.01	(0.94–1.10)	0.75	1.04	(0.97–1.12)	0.25
Male	(ref)			(ref)		
Donor race						
White	(ref)			(ref)		
Black	1.08	(0.96–1.21)	0.19	1.15	(1.04–1.28)	0.01
Hispanic	1.23	(1.10–1.37)	<0.001	1.21	(1.09–1.34)	<0.001
Asian	1.21	(0.96–1.53)	0.11	1.16	(0.93–1.45)	0.18
Other	1.12	(0.81–1.56)	0.49	1.05	(0.76–1.44)	0.78
Cold ischemia time (h)						
<8	(ref)			(ref)		
8–12	1.02	(0.94–1.11)	0.56	1.06	(0.98–1.14)	0.14
>12	1.17	(0.99–1.37)	0.06	1.29	(1.12–1.49)	<0.001

INR, international normalized ratio; MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt; UNOS, United Network for Organ Sharing.

Several factors have been proposed to predict poor survival in HCV patients, such as high pretransplant viral titers, genotype 1b, early and severe recurrence of HCV, acute rejection, steroid bolus, use of monoclonal antibody (OKT3) or ATG, cytomegalovirus, and human immunodeficiency virus infection [10,19]. The effects of current immunosuppressive regimens on HCV disease remain unclear. The use of any antibody induction in liver transplantation for HCV has also remained controversial [15]. Rosen *et al.* reported that approximately 40% of patients with minimal or self-limited recurrent HCV infection showed a proliferative T-cell response to HCV antigens, whereas none of the patients with severe recurrence showed a T-cell response to HCV antigens [20]. These data suggest that the T-cell response to HCV antigens is important and T-cell depleting antibodies such as OKT-3 or ATG may not be the appropriate immunosuppressive drugs for HCV disease. Indeed, ATG is viewed with caution because of the possible increased risk of HCV recurrence and severe side effects [10,21]. On the other hand, recent single center analyses have shown that ATG was

Table 3. Demographics of recipients with hepatitis C and donors.

	ATG (*n* = 207)	ATG + steroids (*n* = 768)	Daclizumab (*n* = 251)	Steroid (*n* = 5386)	*P*-value
Recipients					
Age (years)	52.8 ± 6.8	52.4 ± 7.2	51.9 ± 6.6	53.0 ± 7.2	0.01
Female (%)	26.1	22.8	25.9	24.0	0.66
Race (%)					
White	73.9	72.9	71.3	69.0	<0.001
Black	12.1	14.5	11.6	8.4	
Hispanic	10.1	10.3	13.5	17.8	
Asian	3.4	1.8	3.2	3.4	
Other	0.5	0.5	0.4	1.3	
MELD Score	20.4 ± 9.5	19.0 ± 9.5	17.2 ± 7.8	19.6 ± 9.2	<0.001
Bilirubin (mg/dl)	5.6 ± 8.1	5.7 ± 8.8	4.4 ± 6.4	6.4 ± 9.5	<0.001
Creatinine (mg/dl)	1.7 ± 1.3	1.6 ± 1.6	1.3 ± 1.0	1.5 ± 1.2	<0.001
INR	1.9 ± 1.5	1.7 ± 0.7	1.6 ± 0.4	1.8 ± 0.9	<0.001
Albumin (g/dl)	3.0 ± 0.7	2.9 ± 0.7	2.9 ± 0.5	2.9 ± 0.6	0.04
Status 1 (%)	0.5	0.1	0	0.1	0.53
Pretransplant in ICU (%)	7.2	7.0	2.4	7.9	0.001
History of SBP (%)	7.9	8.1	6.7	9.1	0.22
History of TIPS	5.3	7.4	3.2	9.0	<0.001
Portal vein thrombus	2.9	3.3	3.2	4.3	0.02
Donors					
Donor status (%)					
Deceased	97.6	95.8	94.8	95.9	0.52
Living	2.4	4.2	5.2	4.1	
Age (years)	41.3 ± 15.1	40.7 ± 15.7	40.5 ± 16.2	39.9 ± 16.1	0.22
Cause of death (%)					
Anoxia	15.3	15.0	11.8	13.1	0.03
CVA	46.5	41.5	40.3	42.6	
Trauma	34.2	39.3	45.0	42.0	
CNS tumor	0.5	1.4	0.4	0.7	
Other	3.5	2.9	2.5	1.6	
Female (%)	46.4	39.8	45.0	37.8	0.001
Race					
White	70.5	74.5	65.3	67.0	<0.001
Black	11.6	15.6	19.1	12.7	
Hispanic	11.6	7.4	14.3	16.2	
Asian	3.9	1.4	1.2	2.4	
Other	2.5	1.1	0	1.7	
Cold ischemia time (h)	7.3 ± 5.3	7.1 ± 3.2	7.6 ± 3.0	7.2 ± 3.4	0.02
Warm ischemia time (min)	35.8 ± 17.1	44.1 ± 22.1	43.2 ± 19.0	41.2 ± 19.0	<0.001

ATG, anti-thymocyte globulin; TIPS, transjugular intrahepatic portosystemic shunt; SBP, spontaneous bacterial peritonitis; MELD, Model for End-Stage Liver Disease; INR, international normalized ratio; CVA, cerebrovascular accident; CNS, central nervous system.

not associated with an increased incidence of hepatitis C recurrence [6,22,23]. Furthermore, ATG induction provided a benefit by reducing maintenance immunosuppression compared with steroid induction alone [6]. There are also conflicting data regarding daclizumab induction in liver transplantation for HCV disease. Nelson *et al.* have reported that patients who received daclizumab in combination with MMF developed an early onset hepatitis associated with high viral titers and more rapid progression of HCV disease [24]. On the other hand, the recent HCV-3 study showed that daclizumab induction with steroid free immunosuppression was safe and beneficial for HCV positive liver transplant patients [4]. Recently, Moonka *et al.* analyzed outcomes of liver transplantation comparing antibody-based induction therapy with no induction [25]. In their report, they concluded that induction significantly improved patient and graft survival for HCV as well as non-HCV patients. However, in our study, ATG + S group had significantly inferior graft and patient survival compared with daclizumab and steroids alone. The Cox proportional hazards model also showed that ATG + S was a marginal risk factor for graft

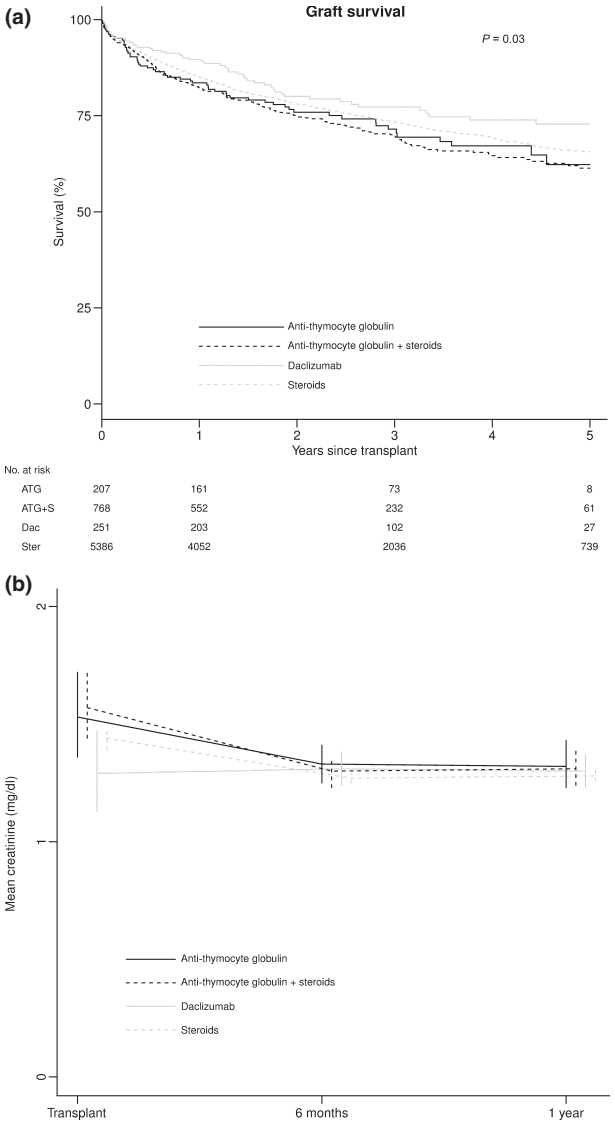

Figure 2 (a) Kaplan–Meier curves of graft survival (HCV patients). (b) Mean creatinine levels in the first year post-transplant (HCV patients).

loss for HCV disease. In our study, the ATG alone and daclizumab groups achieved graft and patient survival that did not differ statistically compared with steroid induction for HCV disease. The 5-year graft survival in the daclizumab group was 11% higher than that in the ATG alone group. Although this difference was not statistically significant, a type II error may not be ruled out because of the relatively small number of patients. The strongest risk factor was African–American recipients compared with White patients. It has been reported that African–American patients have inferior outcomes of liver transplantation for HCV disease compared to White patients [26], and this racial difference needs to be further analyzed including medical and socio-economic factors.

We recognize that maintenance immunosuppression has a more important role for long-term outcome. Therefore, we analyzed the combination of maintenance immunosuppression with ATG, daclizumab, or steroid induction for all liver transplant recipients at 30 days postliver transplantation. In this study, we did not find any difference in graft or patient survival when tacrolimus-based maintenance immunosuppression was used in combination with ATG, daclizumab, or steroid induction, although there was the limitation that maintenance immunosuppression may experience substantial changes over time. For HCV disease, there are a few studies on maintenance immunosuppression regarding MMF focusing on survival benefit. Iacob *et al.* reported that longer administration of MMF had a beneficial effect on graft and patient survival [14]. Lake *et al.* also reported that liver transplant recipients with HCV on a MMF-containing regimen had a lower risk for progressive renal dysfunction and death [27]. An analysis of the Scientific Registry of Transplant Recipients data has shown that recipients treated at discharge with MMF, tacrolimus, and corticosteroids are associated with improved long-term outcomes after liver transplantation compared with tacrolimus and corticosteroids alone in patients with and without HCV, in spite of the fact that less than one-half of patients discharged on MMF remained on MMF at 12 months [28]. Future prospective trials regarding MMF in liver transplantation for HCV in larger patient cohorts may provide further data to that effect.

Acute rejection is one of the most important risk factors that has been shown to significantly increase the severity of recurrent hepatitis C because of steroid boluses and subsequent increases in immunosuppression [29]. Steroid boluses have been associated with elevations in serum HCV levels of 4- to 100-fold [30]. In this analysis, these factors were not included in the Cox hazard model because of missing or unavailable data. The UNOS database does not include liver biopsy data or HCV PCR and we acknowledge that our results do not provide the state of HCV recurrence. In addition, post-transplant lymphoproliferative disorders (PTLD) is a serious complication after liver transplantation [31], and anti-lymphocyte induction has been reported as a risk factor for PTLD [32]. However, in this study, we also could not analyze PTLD among the induction agents because of limitations in the data collected by UNOS. We recognize that there are limitations to this study using the UNOS database, but we do believe that the large UNOS database used for this study is robust enough to compare trends in patient and graft survival. Moreover, this large data set allowed us to adjust for donor and recipient confounders and

Table 4. Cox proportional hazard model for donor and recipient factors in HCV patients.

	Patient survival			Graft survival		
Variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Induction						
Anti-thymocyte globulin	1.17	(0.89–1.55)	0.27	1.09	(0.83–1.43)	0.53
Anti-thymocyte globulin + steroids	1.18	(1.00–1.39)	0.05	1.15	(0.98–1.35)	0.08
Daclizumab	0.85	(0.62–1.17)	0.32	0.80	(0.59–1.07)	0.14
Steroids	(ref)			(ref)		
Age						
10-year increase	1.10	(1.02–1.19)	0.01	1.02	(0.95–1.09)	0.63
Gender						
Female	1.17	(1.03–1.33)	0.01	1.18	(1.05–1.33)	0.01
Male	(ref)			(ref)		
Race						
White	(ref)			(ref)		
Black	1.36	(1.15–1.61)	<0.001	1.35	(1.15–1.58)	<0.001
Hispanic	0.86	(0.74–1.01)	0.07	0.88	(0.76–1.03)	0.10
Asian	0.90	(0.66–1.23)	0.51	1.05	(0.79–1.39)	0.74
Other	0.96	(0.58–1.57)	0.86	0.99	(0.63–1.56)	0.96
Total bilirubin (mg/dl)						
≥8	1.05	(0.87–1.27)	0.62	1.12	(0.94–1.34)	0.21
<8	(ref)			(ref)		
Creatinine (mg/dl)						
≥2	1.31	(1.09–1.57)	0.004	1.25	(1.05–1.48)	0.01
<2	(ref)			(ref)		
INR						
≥2	0.98	(0.83–1.17)	0.86	0.98	(0.84–1.16)	0.87
<2	(ref)			(ref)		
Albumin (g/dl)						
≥3	1.01	(0.91–1.13)	0.84	1.02	(0.92–1.13)	0.68
<3	(ref)			(ref)		
MELD						
<20	(ref)			(ref)		
20–30	1.19	(1.00–1.41)	0.05	1.13	(0.96–1.32)	0.15
>30	1.16	(0.84–1.59)	0.36	1.09	(0.81–1.47)	0.56
Medical condition pretransplant						
ICU	1.24	(1.00–1.54)	0.05	1.12	(0.91–1.38)	0.27
Hospitalized	0.93	(0.78–1.11)	0.43	0.93	(0.79–1.10)	0.42
Not hospitalized	(ref)			(ref)		
TIPS						
Yes	0.98	(0.81–1.20)	0.88	0.91	(0.75–1.10)	0.34
No/unknown	(ref)			(ref)		
Portal vein thrombosis						
Yes	1.07	(0.81–1.42)	0.64	1.00	(0.76–1.31)	0.99
No/unknown	(ref)			(ref)		
Prev upper abdominal surgery						
Yes	1.14	(1.02–1.28)	0.03	1.13	(1.02–1.26)	0.02
No/unknown	(ref)			(ref)		
Donor status						
Deceased	1.24	(0.83–1.87)	0.30	0.79	(0.57–1.08)	0.14
Living	(ref)			(ref)		
Donor age						
10-year increase	1.23	(1.18–1.27)	<0.001	1.24	(1.20–1.28)	<0.001
Donor sex						
Female	1.00	(0.90–1.12)	0.97	1.03	(0.93–1.14)	0.60
Male	(ref)			(ref)		
Donor race						
White	(ref)			(ref)		
Black	0.96	(0.81–1.14)	0.62	1.03	(0.88–1.20)	0.71
Hispanic	1.27	(1.08–1.48)	0.003	1.22	(1.06–1.42)	0.01
Asian	1.65	(1.24–2.20)	<0.001	1.55	(1.18–2.05)	0.002
Other	1.10	(0.71–1.72)	0.66	1.00	(0.65–1.54)	0.99
Cold ischemia time (h)						
<8	(ref)			(ref)		
8–12	1.05	(0.94–1.18)	0.37	1.07	(0.96–1.19)	0.25
>12	0.99	(0.76–1.27)	0.91	1.22	(0.97–1.53)	0.08

INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt.

to better understand better trends in survival compared with smaller single center studies.

In summary, we have shown satisfactory short and long outcomes of ATG and daclizumab induction in liver transplantation compared with steroid induction in all liver diseases. Daclizumab and steroids alone induction appeared to provide better graft survival for HCV patients compared with ATG + S or ATG alone group. These results suggest that less immunosuppressive induction is important for HCV disease. ATG induction showed significant improvement in renal function after liver

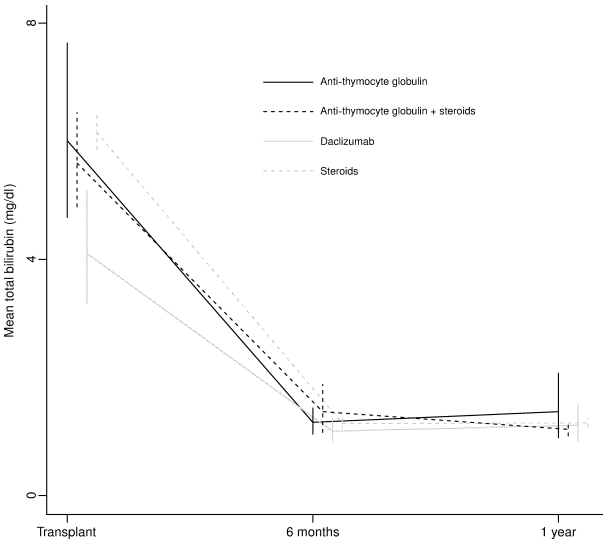

Figure 3 Mean total bilirubin levels in the first year post-transplant (HCV patients).

transplantation and ATG can be a choice for patients with renal dysfunction in non-HCV disease.

Authorship

TU: participated in research design, obtaining database, performance of research, data analysis, and writing the paper. ES and CH: participated in data analysis. AK: participated in research design. ZK: participated in research design, data analysis, and writing the paper.

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