Decreased chronic cellular and antibody-mediated injury in the kidney following simultaneous liver-kidney transplantation

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In simultaneous liver-kidney transplantation (SLK), the liver can protect the kidney from hyperacute rejection and may also decrease acute cellular rejection rates. Whether the liver protects against chronic injury is unknown. To answer this we studied renal allograft surveillance biopsies in 68 consecutive SLK recipients (14 with donor-specific alloantibodies at transplantation [DSA+], 54 with low or no DSA, [DSA–]). These were compared with biopsies of a matched cohort of kidney transplant alone (KTA) recipients (28 DSA+, 108 DSA–). Overall 5-year patient and graft survival was not different: 93.8% and 91.2% in SLK, and 91.9% and 77.1% in KTA. In DSA+ recipients, KTA had a significantly higher incidence of acute antibody-mediated rejection (46.4% vs. 7.1%) and chronic transplant glomerulopathy (53.6% vs. 0%). In DSA– recipients at 5 years, KTA had a significantly higher cumulative incidence of T cell–mediated rejection (clinical plus subclinical, 30.6% vs. 7.4%). By 5 years, DSA+ KTA had a 44% decline in mean GFR while DSA+SLK had stable GFR. In DSA– KTA, the incidence of a combined endpoint of renal allograft loss or over a 50% decline in GFR was significantly higher (20.4% vs. 7.4%). Simultaneously transplanted liver allograft was the most predictive factor for a significantly lower incidence of cellular (odds ratio 0.13, 95% confidence interval 0.06–0.27) and antibody-mediated injury (odds ratio 0.11, confidence interval 0.03–0.32), as well as graft functional decline (odds ratio 0.22, confidence interval 0.06–0.59). Thus, SLK is associated with reduced chronic cellular and antibody-mediated alloimmune injury in the kidney allograft.

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The liver can protect a simultaneously transplanted kidney allograft (termed simultaneous liver-kidney transplants, SLK) against hyperacute antibody-mediated rejection even when high levels of donor-specific alloantibody (DSA) are present at the time of transplantation.[1,2] Two recent studies of the United Network for Organ Sharing database have further suggested that the incidence of acute rejection of the kidney is lower in SLK and that the kidney allograft survival is superior to that in kidney transplant alone (KTA), suggesting that chronic injury also may be affected by SLK.[3,4]

Our program has employed protocol renal allograft biopsies and detailed kidney function studies to investigate the extent of subclinical and chronic immunologic injury in solitary kidney allografts.[5,6] Comparable studies have not previously been performed in SLK patients.

The goal of the current study was to examine protocol biopsy findings, *de novo* DSA formation and changes in renal function over time in SLK recipients. Given that kidney transplant recipients with high levels of DSA (DSA+) at the time of transplantation tend over time to have much different graft histology and renal function than do those without DSA (DSA–), we separated SLK into 2 groups: those with high levels of DSA at baseline (DSA+ SLK) ($n = 14$) and those with low levels or no DSA at the time or transplantation (DSA– SLK; $n = 54$). Each SLK group was then compared with a matched cohort (1:2) of KTA recipients (DSA+ KTA and DSA– KTA).

RESULTS

Overall survival

Of the 82 sequential SLK, 14 were not functioning as SLK at 1 year including 4 kidney allografts lost to technical complications (4.9%), 7 recipient deaths (8.5%), 2 liver retransplants (2.4%), and 1 kidney allograft lost to foscarnet toxicity (1.2%). Thus, the overall 1-year kidney allograft survival in SLK was 82.3% and patient survival was 91.5%.

Sixty-eight SLK were functioning at 1 year and were evaluable for long-term outcomes with both surveillance biopsy and kidney function with a follow-up of 80 months. One hundred and thirty-six matched KTA recipients were also followed for an average of 80 months. For these groups, the overall 5-year recipient survival was 93.8% SLK and 91.9% in KTA ($P = 0.71$). Similarly, the overall death-censored kidney graft survival was comparable (91.2% in SLK vs. 77.1% in KTA, $P = 0.12$).

SLK versus KTA: DSA+ recipients

Patients. Of the 68 SLK recipients who were censored for 1-year graft survival of both the liver and kidney, 14 were DSA+ (had a mean fluorescence intensity [MFI] >2000 by LABScreen software [One Lambda, Canoga Park, CA]) at the time of transplantation. Nine of the 14 patients had a positive T- and/or B-cell flow cytometric crossmatch, whereas 5 were crossmatch negative. Two patients with the highest T- and B-cell flow crossmatch levels had positive antihuman globulin enhanced cytotoxicity. Of the 14 patients, 2 had DSA to donor class I human leukocyte antigen (HLA) only, 8 to donor class II only, and 4 to both donor classes I and II (Table 1).

DSA+ SLK were then matched 1:2 with 28 DSA+ KTA recipients based on transplant era, age, sex, and race. Patient demographics were similar otherwise (Table 2) except there were more HLA mismatches in DSA+ SLK, induction with T cell depletion was more common in the DSA+ KTA (96.4% vs. 7.1%; $P = 0.0001$), and the cold ischemia time was shorter in the DSA+ KTA group (245 ± 355 vs. 555 ± 76 minutes; $P = 0.002$). The DSA levels varied within the groups at the time of transplantation (Supplementary Tables S1 and S2), with MFIs ranging from slightly >2000 to >10,000. A higher percentage of patients had a baseline DSA MFI >10,000 in the DSA+ SLK group (6 of 14; 42.9%) than in the DSA+ KTA group (6 of 28; 21.4%). None of the DSA+ KTA patients had positive antihuman globulin enhanced cytotoxicity.

The indications for kidney transplantation in the DSA+ SLK patients were calcineurin-inhibitor [CNI] toxicity ($n = 5$; 35.7%), primary oxaluria ($n = 4$; 28.6%), hepatorenal syndrome ($n = 2$; 14.3%), primary glomerular disease ($n = 2$; 14.3%), and diabetic nephropathy ($n = 1$; 7.1%). In the DSA+ KTA group, the indications were primary glomerular disease ($n = 11$, 39.3%), polycystic kidney disease ($n = 6$; 21.4%), diabetic nephropathy ($n = 3$; 10.7%), obstructive nephropathy ($n = 2$; 7.1%), secondary oxaluria ($n = 1$; 3.6%), and other/unknown ($n = 5$; 17.9%).

Clinical outcomes. Delayed graft function (defined as needing dialysis within 1 week of transplantation) did not happen in either group. The mean follow-up was 74 months (range 31–120) in DSA+ SLK and 64 months (range 13–120) in DSA+ KTA. Five-year patient survival was similar, 100% in DSA+ SLK and 95.3% in DSA+ KTA ($P = 0.34$) (Figure 1a).

Table 1 | DSA+ recipients: crossmatch and DSA specificity at the time of transplantation

	SLK	KTA	*P*
Preoperative FC-XM	9	18	NS
T cell	0	4	
B cell	3	7	
T and B cell	6	7	
Pre-existing DSA	14	28	NS
Class I	2	11	
Class II	8	13	
Classes I and II	4	4	

DSA, donor-specific alloantibody; DSA+, high levels of donor-specific alloantibody; FC-XM, flow cytometric crossmatching; KTA, kidney transplant alone; NS, not significant; SLK, simultaneous liver-kidney transplants.

Death-censored graft survival was 92.3% in DSA+ SLK and 76.9% in DSA+ KTA ($P = 0.39$) (Figure 1b). Five grafts were lost in the DSA+ KTA group (3 chronic glomerulopathy, 1 oxalate nephropathy, and 1 recurrent disease), and 1 in SLK (severe interstitial fibrosis/tubular atrophy) (Table 3).

Because graft loss may underestimate the prevalence of chronic injury, we evaluated the decline in renal function between 4 months and 5 years after transplantation. During this time period, the mean estimated glomerular filtration rate (eGFR) remained stable in the DSA+ SLK (56.1 ± 18.8 at 4 months, 56.9 ± 29.3 at 5 years) but declined by 44% in the DSA+ KTA (60 ± 21.3 at 4 months, 43.9 ± 24.6 at 5 years) (66.2% vs. 105.1%, $P = 0.0004$) (Figure 2, Table 3). We also examined a combined endpoint of graft loss or a >50% decline in GFR (4 months to 5 years). Only 1 DSA+ SLK patient reached this endpoint (the graft loss mentioned, due to fibrosis), whereas 7 reached this endpoint in the DSA+ KTA group (5 graft losses, plus 2 others with marked decline in function) ($P = 0.23$).

Histologic findings and the course of DSA. The cumulative incidence of Banff criteria acute T-cell–mediated rejection ([TCMR], clinical and subclinical) was lower in DSA+ SLK than in DSA+ KTA (7.1% vs. 46.4%; $P = 0.01$) (Table 4). In addition, at 2 and 5 years after transplant, no SLK kidney allograft biopsy showed chronic transplant glomerulopathy, whereas this lesion was common in DSA+ KTA recipients (37% at 2 years and 53.6% at 5 years; $P = 0.01$ at both time points). The incidence of peritubular capillaritis was not statistically different in DSA+ SLK versus DSA+ KTA recipients (28.6% in SLK vs. 46.4% in KTA; $P = 0.33$).

The incidence of TCMR (clinical and subclinical, 21.4% vs. 25%, $P = 1.0$) and subclinical inflammation (SCI) (i.e., cellular infiltrates on surveillance biopsy including those that do not fulfill criteria of TCMR) (14.3% vs. 32.1%; $P = 0.28$) were comparable in DSA+ SLK and DSA+ KTA recipients, respectively.

Persistence of high levels of pre-existing DSA in DSA+ SLK patients (6 of 14; SLK-9 through -14, Supplementary Table S1) was observed only in recipients who were documented to be noncompliant with their immunosuppressive medications (3 of 14; SLK-9, -10, and -13), or who had concurrent liver allograft dysfunction based on laboratory and liver biopsy findings (3 of 14; SLK-11, -12, and -14). Because liver dysfunction may be secondary to DSA-mediated injury, liver biopsies of these patients were rereviewed, and no evidence for such injury was found.

SLK versus KTA: conventional (DSA–) recipients

Patients. Of the 68 sequential SLK recipients who were censored for 1-year survival of both the liver and kidney allografts, 54 had no DSA or an MFI <2000 at the time of transplantation. These were matched 1:2 with 108 conventional (DSA–) KTA recipients based on transplant era, age, sex, and race. On average, there were more HLA mismatches in DSA– SLK (Table 2). Donor age and characteristics (e.g., extended criteria donor status) were similar in both groups. DSA– KTA