29 cases of late extra-hepatic biliary strictures, occurring 6 weeks to 3 years after transplantation, were identified by MRCP, ERCP or PTC in recipients of deceased donor liver transplants between 2002 and 2011 (n=286). Their preoperative sera were retrospectively examined for DSA using Luminex single bead assays. Donor cells were cross-matched using flow cytometry. 20 recipients with no evidence of biliary pathologies served as control. Acute rejection, hepatitis and demographic criteria were considered for matching the control group.

Cumulative class II MFI >500 and/or B-cell cross-match positivity was found to be strongly associated with the incidence of late extra-hepatic biliary strictures. Class I DSA did not reveal any association. The study group showed cumulative class II DSA >500 MFI in 24/29 patients (83%) and B-cell crossmatch positivity in 20/29 patients (69%). Using both criteria, 26/29 recipients (90%) could have been identified prior to transplantation for being at risk to develop late biliary strictures. Only 3/20 recipients (15%) of the control group showed B-cell cross-match positivity. None of them had a cumulative class II MFI >200. None of 4/20 controls (20%) with cumulative class II MFI >500 showed a positive B-cell cross-match.

This is the first evidence indicating that pre-transplant class II DSA and B-cell cross-match positivity are strongly associated with the risk of developing late extra-hepatic biliary strictures following liver transplantation. These data are suggestive for an immunological aetiology of non-vascular late biliary strictures.

Abstract# 447

Increased Incidence of Non Anastomotic Biliary Strictures in Case of Donation after Circulatory Death Versus Donation after Brain Death Liver Transplantation but Equivalent Graft and Patient Survival. N. Meurisse,[1] S. Vanden Bussche,[1] I. Jochmans,[1] V. Heedfeld,[1] R. Aerts,[1] W. Laleman,[2] S. Van der Merwe,[2] C. Verslype,[2] D. Cassiman,[2] W. Van Steenbergen,[2] F. Nevens,[2] J. Pirenne,[1] D. Monbaliu.[1] *[1]Abdominal Transplant Surgery Department, University Hospital Leuven, Leuven, Belgium; [2]Hepatology Department, University Hospital Leuven, Leuven, Belgium.*

Because of the concerns regarding short & long-term outcomes after Liver Transplantation (LTx) using Donation after Circulatory Death (DCD) compared to Donation after Brain Death (DBD) donors, we reviewed the results of DCD-LTx at our center. Between 2003 and 2010, 30 DCD-LTx and 385 DBD-LTx were performed. Demographics, LTx indications, post-LTx peak aspartate amino transaminase (AST peak), delayed graft function (DGF) (Olthoff criteria), biliary non-anastomotic strictures (NAS), early post-LTx kidney dysfunction (RIFLE criteria), re-transplantation rate and patient/graft survival were analyzed. Mean DCD donor warm ischemia (stop ventilation to cold perfusion) was 23+/-11'. Median cold ischemia was 6h54' for DCD compared to 8h40' for DBD-LTx; p=0.0001. Mean labMELD was similar for DCD and DBD-LTx (15 vs. 16; p=0.59). Median post-LTx AST peak was higher after DCD vs. DBD-LTx (1178 IU/L vs. 651 IU/L; p=0.005). DGF rate was similar between DCD and DBD-LTx (25 vs. 24%, p=0.8). The rate of NAS was higher after DCD vs. DBD-LTx (33% vs. 12%; p=0.001). Incidence of early post-LTx kidney dysfunction was not statistically different after DCD and DBD-LTx (37% vs. 23%, p=0.08). On the other hand, regardless the donor type, the AST peak - a surrogate of ischemia-reperfusion injury often used as an appropriate criterion for DGF evaluation - was associated with a higher rate of early post-LTX kidney dysfunction if greater than 2000 (28 vs. 10%, p=0.001) but not with NAS (12 vs. 15%, p=0.59). Re-transplantation rate within one year post-LTx was 3% after both DCD and DBD-LTx. The 1, 3, & 5-yr patient/graft survival were similar after DCD and DBD-LTx (93, 85, 85% vs. 88, 78 & 72%; p=0.3, and 90, 82, 82% vs. 85, 74 & 68%; p=0.5, respectively). Despite substantial ischemic injury, short& long-term patient/graft survival after DCD-LTx is comparable to DBD-LTx. Careful donor/recipient selection, rapid donor surgery and short ischemia times are key factors to optimize outcome after DCD-LTx. However, strategies to reduce ischemic injury and biliary complications remain warranted.

Abstract# 448

Late Versus Early Biliary Complications after Liver Transplantation. V. Gupta, N. Onaca, M. Saeed, A. Dabous, M. Asolati, R. Ruiz, P. Kim, G. Testa, R. Goldstein, G. Klintmalm. *Baylor Annette C. and Harold C. Simmons Transplant Institute, Dallas.*

Introduction

Biliary complications (BC) cause major morbidity and mortality after liver transplantation (LT). Literature is replete with articles on early BC (less than 1 year post LT); however, little is known about late BC.

Methods

We reviewed retrospectively our prospectively collected data for adult LTs from Jan 1997 to Dec 2007. Multiorgan transplants were excluded. Patients with BC more than a year after LT (late BC) were compared to patients with BC in the first year (early BC) and patients who never had BC. Fisher exact tests with post hoc Bonferroni test and Kruskal-Wallis analysis with post-hoc Dunn's test were used for comparisons. Univariate and multivariate Cox regression analysis was performed.

Results

1621 LTs were included, 92.4% primary and 7.6% re LTs. 29.3% patients had BC with 24.3% early BC (n=384) and 5% late BC (n=82). Late BC included anastomotic (53.6%) and nonanastomotic (21.9%) strictures, papillary stenosis (14.6%), stones (21.9%), biloma (10.9%) and tumors (1.2%). In the late BC group, 18.2% patients had surgical repair, 47.5% patients had resolution of BC, 9.7% had re LT and 32.9% patients died in follow-up. Main causes of death in late BC group were Hepatitis C (29%) and hepatic artery thrombosis (HAT) (14%). Late BC were associated with simultaneous acute cellular rejection (ACR) (21%), chronic rejection (7%) or recurrent primary sclerosing cholangitis (3.5%).

On stepwise multivariate Cox regression, use of T-tube (hazard ratio [HR] 2.0, 95% confidence interval [CI] =1.0-4.0), HAT (HR: 5.3, 95% CI=1.8-15.4), use of Cyclosporine (vs. Tacrolimus) (HR: 3.7; 95% CI=2.1-6.6) or steroids (vs. no use) at 4 weeks post LT (HR: 2.0; 95% CI=0.9-4.4), female donor gender (HR: 1.6; 95% CI=0.94-2.75) and black recipient race (HR: 1.9; 95% CI=0.8, 4.2) were predictors for late BC. Patients with early BC had longer ICU stay, higher rates of ACR, HAT and infections, higher recipient BMI and donor age, longer warm ischemia time and association with re LT.

Between the 3 groups there were no differences in regards to MELD score, cold ischemia time, intraoperative hepatic artery flow, intraoperative blood transfusion, donor BMI, B or T cell positive crossmatch and Sirolimus use at 3 months.

Conclusions

While early BC are related to perioperative events, late BC seem to be related to disease recurrence or an immunological event. Most late BC do not require surgical repair.

Concurrent Session 63: Kidney Issues in Liver Transplant Candidates and Recipients

Abstract# 449

Spectrum of Renal Pathology and Gene Expression Profiles of Kidney Biopsies in Patients with Cirrhosis Listed for Liver Transplantation. A. Gupta, A. Aws, J. Pullman, P. Gaglio, J. Reinus, E. Akalin, G. De Boccardo. *Transplantation, Montefiore Medical Center, Bronx, NY.*

Introduction: We previously demonstrated universal glomerular abnormalities in kidney biopsies after orthotopic liver transplantation (OLT). We hypothesize that these changes exist prior to OLT and may play an important role in the development of renal failure after OLT. We investigated the mechanism of kidney disease in patients listed for OLT by immunohistopathologic and genomic analysis of kidney biopsies (KB). **Methods**: Analysis of clinical and pathological data of 21 cirrhotic patients (pts) listed for OLT who underwent KB. The Gene expression profile of KB specimens was studied by Affymetric HuGene 1.0 ST expression assay and was compared with pre-implantation living donor KBs. **Results**: Etiology of liver disease: hepatitis C (71%), alcoholic hepatitis (24 %) and autoimmune hepatitis (5%). Mean MELD, serum creatinine, GFR and proteinuria were 17± 5, 1.9 ±0.7 mg/dl, 42±17 ml/min and 0.5±0.8 gm/day, respectively. Twelve pts had low complement levels. Mesangial proliferation was seen in 20 KBs by light microscopy. Five pts had nodular glomerulosclerosis (3 DM), 2 FSGS and 1 MPGN. Immunofluorescence staining showed mesangial, capillary wall or tubular basement-membrane deposition of IgG (16), IgM (18), IgA (10), C1Q (11) and C3 (12). Electron microscope in 16 pts showed effacement of podocytes (15) and duplication and widening of glomerular basement membranes (10). Gene expression profiles by Gene Ontology revealed significant up-regulation of genes implicated in immune response, including T-cell, leucocyte and platelet activation and differentiation. Pathogenesis-based transcripts revealed significantly increased expression of quantitative cytotoxic T-cell, quantitative macrophage, B-cell, natural killer cell, and endothelial cell associated transcripts, indicating an ongoing inflammatory immune response.

Conclusion: This study demonstrates the universal presence of glomerular abnormalities in KBs of cirrhotic patients. The majority had increases in mesangial matrix, podocyte effacement, and widening and duplication of glomerular basement membrane, as is also seen in patient's post-OLT. The increased gene expression profiles related to immune activity could indicate immune-mediated mechanisms in development of kidney disease in cirrhotic patients.

Abstract# 450

Superior Renal Function Sustained for 24 Months through Early Everolimus-Facilitated Reduction of Tacrolimus Versus Standard Tacrolimus in *De Novo* Liver Transplant Recipients: Results of a Randomized Trial. P. De Simone,[1] O. Detry,[1] G. Kintmalm,[1] J. Goss,[1] P. McCormick,[1] M. Rossi,[1] A. Moya,[1] P. Lopez,[2] G. Junge,[2] G. Dong,[3] D. Joseph,[3] C. Duvoux.[1] *[1]For the H2304 Study Group, Pisa, Italy; [2]Novartis Pharma AG, Basel, Switzerland; [3]Novartis Pharmaceuticals Corporation, New Jersey.*

mTOR inhibitors have the potential to reduce calcineurin inhibitor nephrotoxicity by minimizing or eliminating the need for their use. The 12 month (M) results of

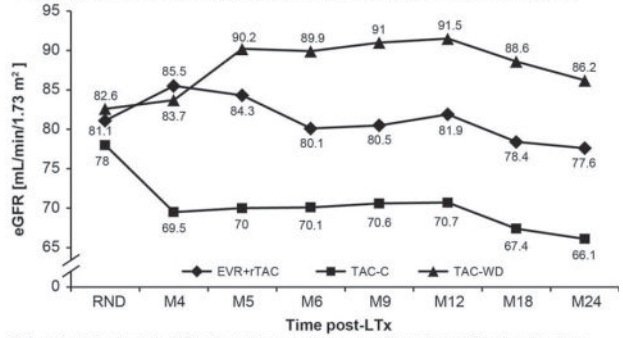
H2304 (NCT00622869) study demonstrated superior renal function with everolimus (EVR) plus reduced tacrolimus (rTAC) vs. standard TAC (TAC-C) in *de novo* liver transplant recipients (LTxR). Presented here are 24M renal function results.

For this 24M, multicenter, open-label study 719 *de novo* LTxR were randomized (1:1:1) after a 30-day (±5 days) run-in period with TAC (±mycophenolate mofetil), to receive either EVR (C0 3-8 ng/mL) with rTAC (C0 3-5 ng/mL; EVR+rTAC, N=245) or EVR (C0 6-10 ng/mL) with TAC withdrawal (TAC-WD; N=231) at M4 or TAC-C (C0 6-10 ng/mL; TAC-C, N=243); all patients received corticosteroids. Enrollment in TAC-WD arm was stopped early due to higher rejection rates. Main endpoints at M24 included composite efficacy failure rate of treated biopsy proven acute rejection, graft loss or death, and evolution of renal function from randomization (RND) to M24 measured as eGFR by MDRD4.

At M24, composite efficacy failure rate in EVR+rTAC arm was comparable to TAC-C (10.3% vs. 12.5%, p=0.452). Evolution of renal function from RND to M24 was superior for EVR+rTAC vs. TAC-C with an adjusted mean difference in eGFR change of 6.66 mL/min/1.73m^2 (p=0.0018; ITT population). Significantly higher eGFR with EVR+rTAC was achieved at M2 post-LTx and was maintained until M24. On-treatment data showed a decrease in mean eGFR from RND to M24 of 6.6 mL/min/1.73m^2 with EVR+rTAC vs. 13 mL/min/1.73m^2 with TAC-C and 2.5 mL/min/1.73m^2 gain with TAC-WD. Urinary protein:creatinine ratio (mg/g) at M24 was higher with EVR+rTAC vs. TAC-C (Mean±SD: 194±280 vs. 159±284, p=0.006).

Early introduction of EVR at 1M post-LTx with rTAC showed superior renal function sustained for 24M compared to TAC-C**,** without compromising efficacy in *de novo* LTxR.

Figure: Evolution of renal function from RND to M24 (on-treatment analysis)



RND, randomization; M, month; eGFR, estimated glomerular filtration rate; EVR, everolimus; rTAC, reduced tacrolimus; TAC-C, standard tacrolimus; TAC-WD, tacrolimus withdrawal; LTx, liver transplantation

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Abstract# 451

The Influence of Baseline Immunosuppresion on Renal Function and Clinical Outcomes in Liver Transplantation. A. Mardis,[1] D. Taber,[2] H. Meadows,[1] N. Pilch,[1] J. Fleming,[1] C. Jordan,[1] K. Morbitzer,[1] C. Makowski,[1] J. McGillicuddy,[2] C. Bratton,[2] K. Chavin,[2] P. Baliga.[2] *[1]Pharmacy, MUSC, Charleston, SC; [2]Surgery, MUSC, Charleston, SC.*

Background: Preserving renal function in liver transplantation has become paramount to improving long-term survival. However, there are limited definitive studies comparing different immunosuppression (IS) regimens in this capacity.

Methods: This was a large-scale longitudinal cohort study of all liver transplants at our institution from Jan 2000 - June 2011. Patients were excluded if they were <18 years old, multi-organ transplants, or experienced graft loss or death within the first month. Patients were divided into 4 groups based on baseline IS (CNI, IL2-RA+MMF+CNI, IL2-RA+CNI, CNI+MMF). Renal function was estimated using the MDRD equation; change in renal function from baseline was assessed by calculating the slope of MDRD. All patients received steroids in conjunction with IS regimens.

Results: 635 transplants occurred during this period; 532 were included in this analysis (mean follow-up 4.8 yrs). Baseline demographics and outcome data are in Table 1; the only differences at baseline were age, race, MDRD and MELD. Clinical outcomes demonstrated that the combination of IL2-RA+CNI +MMF was the only regimen that statistically significantly improved renal function with lower rates of acute rejection (Table 1). This was achieved through CNI minimization (see FK levels in Table 1). HCV recurrence was not influenced by baseline IS regimens. Death and graft loss were lowest in quadruple IS regimen. However, Cox Proportional Hazard Regression analysis demonstrated that only slope of MDRD influenced graft loss (HR 0.945, p=0.001 [95% CI 0.92-0.98]) in an independent fashion.

Conclusions: The results of this study suggest that quadruple IS regimens can safely and effectively preserve renal function and reduce acute rejection rates in liver transplant recipients without influencing HCV recurrence or graft survival.

Demographic/Outcome	CNI + CS (n=86)	IL2-RA+ MMF+CNI+CS (n=234)	IL2-RA+ CNI+CS (n=94)	MMF+CNI+CS (n=129)	p-value
Baseline Characteristics					
Recipient Age (yrs)	52.8±9.1	53.4±10.1	50.7±11.1	50.7±11.0	**0.04**
Recipient Male	58 (75.3%)	156 (66.7%)	60 (63.8%)	86 (66.7%)	0.42
Recipient Black	10 (13.2%)	29 (12.4%)	6 (6.4%)	25 (19.4%)	**0.04**
Baseline MDRD	65±22	52±21	51±27	68±26	**<0.001**
MELD at Txp	15.8±7.3	19.1±7.5	17.1±8.5	17.0±5.9	**0.001**
Hepatitis C Diagnosis	52 (60.5%)	138 (59.0%)	60 (63.8%)	74 (57.4%)	0.79
Outcomes					
Acute Rejection	23 (26.7%)	86 (36.8%)	47 (50.0%)	53 (41.1%)	**0.01**
Graft Survival Year 1	80%	92%	87%	93%	
Year 3	68%	87%	79%	84%	0.06
Year 5	66%	83%	72%	78%	
Death	22 (25.6%)	39 (16.7%)	21 (22.3%)	22 (17.1%)	0.24
Days to CNI Initiation	3.1±10.5	3.3±2.5	3.3±3.8	1.7±1.5	0.14
Avg FK during Year 1	7.1±1.8	6.4±2.0	7.6±2.0	6.8±2.1	**0.001**
Avg FK following Year 1	6.9±3.9	5.8±2.3	6.1±2.1	6.5±2.9	0.07
Receiving MMF at Month 3	14 (16.3%)	127 (54.3%)	22 (23.4%)	55 (42.6%)	**<0.001**
Receiving MMF at Year 1	16 (18.6%)	113 (48.3%)	30 (31.9%)	53 (41.1%)	**<0.001**
Receiving MMF at Year 3	14 (16.3%)	87 (37.2%)	22 (23.4%)	37 (28.7%)	**<0.001**
MDRD at Month 1	58±24	57±25	60±26	62±24	0.25
MDRD at Year 1	68±24	56±21	61±21	64±25	**0.001**
MDRD Slope at Year 1	0.7±29.7	4.4±24.6	-2.8±28.7	-4.1±28.0	**0.03**
MDRD Slope at Last Follow-Up	-3.6±14.4	0.7±11.6	-1.2±11.1	-4.5±12.9	**0.001**
Required Dialysis Post-transplant	7 (8.1%)	19 (8.1%)	5 (5.3%)	10 (7.8%)	0.84
Hepatitis C Recurrence	23 (26.7%)	66 (28.2%)	24 (25.5%)	36 (27.9%)	0.97

Abstract# 452

Liver Transplantation (LT) in Patients Receiving Renal Replacement Therapy (RRT): Predicting Renal Recovery and Post-Transplant Futility. V. Agopian,[1] J. Baber,[1] A. Dhillon,[2] H. Petrowsky,[1] A. Zarrinpar,[1] F. Kaldas,[1] H. Yersiz,[1] D. Farmer,[1] J. Hiatt,[1] R. Busuttil.[1] *[1]Surgery, UCLA, LA, CA; [2]Anesthesiology, UCLA, LA, CA.*

Background: The Model for End-Stage Liver Disease (MELD) system prioritizes liver allocation to patients in renal failure, increasing the number of simultaneous liver-kidney transplants (SLK). Identifying predictors of post-transplant futility (90-day or in-hospital mortality) and renal recovery could maximize utilization of these scarce resources.

Methods: Analysis of adult LT recipients on pre-transplant RRT from July 2004 to September 2012 at a single-institution using 33 recipient, donor, and operative variables. Multivariate logistic regression was used to identify predictors of futility and dialysis dependence at 3-months.

Results: Of 1546 LT recipients, 529 were on RRT (34%). The mean MELD score was 38. Compared to patients undergoing LT alone (LTA, n=407), SLK (n=94) patients were significantly older and more obese, diabetic, and hypertensive, but less likely hospitalized, on continuous RRT, ventilator-dependent, or on vasopressors. Despite kidney transplantation, 21% of SLK recipients were dialysis-dependent at 3-months, compared to 43% of LTA recipients (P<0.001). Of all futile LTs (n=94, 19%), only 4 patients (4%) became dialysis-independent prior to their death. Futile LT accounted for 43% and 75% of failures to achieve dialysis independence in LTA and SLK, respectively. Multivariate predictors of futility included coagulopathy requiring abdominal packing, pre-transplant length of RRT, mechanical ventilation, recipient and donor age, and hyperlipidemia. In non-futile patients, multivariate predictors of dialysis dependence included non-fulminant etiology, LTA, emergent intraoperative RRT, pre-transplant RRT > 7 days, metabolic syndrome, pre-transplant stay, and gender (Table).

Futility			**Dialysis Dependence at 3 mos**		
	Odds Ratio	P-value		Odds Ratio	P-value
Coagulopathy	4.4	<0.01	Non-fulminant etiology	9.6	0.003
Pre-tx RRT > 7 d	3.3	0.001	LTA	8.6	<0.001
Intubation	2.5	0.001	Intraop RRT	4.2	0.04
Recipient age > 55 yrs	2.4	0.002	Pre-tx RRT > 7 d	2.7	0.03
Hyperlipidemia	2.2	0.06	Metabolic Syndrome	2	0.056
Donor age > 45 yrs	2.0	0.01	Pre-transplant LOS > 2 wks	1.9	0.04
			Female	1.6	0.068

Conclusions: We report the largest single-institution experience of LT in patients on pre-transplant RRT. We identified important predictors of post-LT futility and renal recovery that may help to guide the allocation of kidneys in these challenging LT recipients.