Research Article

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Incidence and impact of rejection following simultaneous liver-kidney transplantation

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Background & Aims: Due to hepatic immunoregulation, simultaneous liver-kidney recipients are presumed to be reasonably protected from kidney rejection and typically receive less immunosuppression compared to kidney transplants alone. However, data to support these conclusions and practices are sparse.
Methods: We characterized the incidence and types of rejection, graft function, and graft and patient survival in a large population of simultaneous liver-kidney recipients (n = 140) with long-term follow-up at our centre (1998–2010).
Results: Acute cellular, antibody-mediated, and chronic kidney rejection was diagnosed in 9 (6.4%), 2 (1.4%), and 1 (0.7%) patient, respectively. Borderline acute kidney rejection was diagnosed in another 16 patients (11.4%). Acute cellular liver rejection occurred in 16 (11.4%) and chronic liver rejection in 4 (2.9%). One-, three-, and five-year patient survival was 86.4%, 78.0%, and 74.0%, respectively, and did not significantly differ by presence or absence of kidney or liver rejection. However, kidney rejection was associated with decreased renal function by lower serum GFR over time ($p = 0.003$).
Conclusions: Various forms of kidney rejection occurred in ~20% of our simultaneous liver-kidney recipients and were associated with deterioration in graft function, indicating that the liver may not confer complete protective allo-immunity. More stringent graft monitoring and management strategies, perhaps more akin to kidney transplant alone, should be prospectively studied in simultaneous liver-kidney recipients.

Introduction

The number of simultaneous liver-kidney transplants (SLK) has dramatically increased with the adoption of the model for end stage liver disease (MELD) scoring system for liver transplantation (LT), in which serum creatinine is heavily weighted [1,2]. As such, patients awaiting a kidney transplant alone (KTA) may be bypassed by those listed for SLK, given the uncertainty of predicting renal recovery post-LT [3]. As the demand for organs continues to outgrow the supply, clear data on patient and graft outcomes are necessary with the continued use of kidney organs for the LT population.

While most of the data in SLK has focused on refining pre-transplant selection, particularly concerning prediction of native renal recovery, little data exist on outcomes following SLK, including renal and liver graft rejection, function, and survival. The concept of the liver being immunologically "privileged" or "tolerant" has been well established [4]. Liver transplant alone (LTA) patients require less immunosuppression (IS) than other organs, have a lower incidence of acute and chronic cellular rejection, have better outcomes following rejection episodes, and are generally less susceptible to antibody-mediated rejection, compared to other solid organ recipients [4,5]. Spontaneous operational tolerance, defined by maintenance of normal graft function and the lack of graft rejection after withdrawal of IS, occurs in up to 20% of LTA patients [4,6,7].

Given this hepatic immunoregulation, immunosuppressive regimens for LTA differ from KTA, with the majority of centres minimizing maintenance therapy over time and not using initial induction of immunosuppressive therapy. For similar reasons, due to the presence of the parallel liver graft, SLK patients are thought to be reasonably protected against acute and chronic kidney rejection. As a result, immunosuppressive regimens for SLK are typically more similar to LTA than KTA. However, the assumption that the liver graft automatically confers full protective immunity toward other grafts is not well supported by literature. Clarity on the incidence, types, and impact of rejection in

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Abbreviations: SLK, simultaneous liver-kidney; MELD, model for end stage liver disease; UNOS, United Network for Organ Sharing; HRS, hepatorenal syndrome; LTA, liver transplant alone; KTA, kidney transplant alone; IS, immunosuppression; RRT, renal replacement therapy; DSA, donor-specific antibodies; IVIG, intravenous immunoglobulin; HCV, hepatitis C virus.

SLK are needed, given the increasing number of kidneys being utilized for SLK. As our institution is located in a high MELD region and performs a significant number of SLK procedures, we had the ability to report these SLK outcomes and test these assumptions.

Materials and methods

Adult patients ⩾18 years old who had undergone deceased donor SLK at our institution between January 1st, 1998 and June 1st, 2010 were included in this retrospective study, characterizing the incidence, types and outcomes of liver and kidney graft rejection. Exclusion criteria were as follows: (1) transplantation of ⩾3 organs; (2) prior organ transplant; (3) living donor transplantation; (4) transplant nephrectomy. The Institutional Review Board at the Northwestern University Feinberg School of Medicine approved this study.

Electronic medical records and pathology reports were utilized to obtain the data. As there are no universally accepted SLK indications, our decision to perform SLK was based on our multidisciplinary transplant (hepatology, nephrology, surgery) team's judgment that the renal dysfunction was unlikely to reverse following liver transplant alone. Variables considered in this decision included the following: (1) serum creatinine >2.0 mg/dl or estimated glomerular filtration rate (eGFR) by MDRD-4 <30 ml/min for >1 month; (2) risk factors for kidney disease such as diabetes mellitus (on anti-diabetic therapy, fasting glucose ⩾126 mg/dl, random glucose ⩾200 mg/dl, or glycated haemoglobin ⩾6.5%) and/or hypertension (systolic or diastolic blood pressure ⩾140/90 mmHg); (3) proteinuria >500 mg/24 h and/or haematuria (urine red blood cells >50 per high-power field on two separate urinalyses not from a urinary catheter); (4) renal replacement therapy (RRT) for >2 weeks.

Donor organs were matched by ABO compatibility only, as it is done for LTA. HLA cross matching was not performed. Our immunosuppression protocol for SLK was identical to our LTA recipients. No induction therapy was utilized. Patients were given 500 mg intravenous methylprednisolone intra-operatively, followed by an additional 500 mg immediately post-operatively. On post-operative day 1, patients received 250 mg IV methylprednisolone, and tacrolimus and mycophenolate mofetil were also started. On post-operative day 2, patients received 125 mg methylprednisolone, followed by prednisone 60 mg orally on post-operative day 3. Prednisone was rapidly tapered down to 20 mg daily by post-operative day 8 and over the next few months was gradually tapered off by six months after transplant. Patients were maintained on tacrolimus (trough goal 8–10 ng/ml for the first three months, then 5–8 ng/ml thereafter) and on mycophenolate mofetil (1–2 gm/day) when this became available in 2000. Other agents, including cyclosporine and sirolimus, were less commonly used at the discretion of the transplant providers as clinically appropriate.

An increase in serum aminotransferases or reduction in GFR from baseline prompted the performance of liver and kidney biopsies (for-cause biopsies). Protocol biopsies were not performed. Liver biopsies with evidence of rejection were stratified by acuity (acute *vs.* chronic) and severity by the Banff scoring system [8]. Renal biopsies with rejection were categorized as acute cellular rejection, antibody-mediated/humoral rejection, or chronic rejection, and those with acute cellular rejection were stratified by severity according to the Banff-07 score [9]. Biopsies that revealed borderline changes were counted formally as rejection episodes for statistical analysis. All biopsies performed prior to incorporation of the Banff-07 system were re-evaluated by a certified renal pathologist (N. Sustento-Reodica) and blindly scored according to the Banff criteria. In patients that had more than one episode of acute cellular rejection, only the most severe Banff score was used for analysis.

At the time of transplant, panel reactive antibodies (PRA) or donor-specific antibodies (DSA) were not performed. However, when available, donor-specific antibodies were used to confirm the presence of antibody-mediated rejection.

Treatment varied depending on the type of rejection. Acute liver rejection and mild or moderate acute kidney rejection were treated with high dose corticosteroids followed by taper. Severe acute kidney rejection was treated with intravenous thymoglobulin, and episodes of antibody-mediated rejection were initially treated with high dose corticosteroids pending biopsy results, followed by intravenous immunoglobulin (IVIG) and/or plasmapheresis when pathology results confirmed humoral rejection. Patients with rejection who had HCV were treated with steroids alone. Our institution's current practice is not to treat patients with pathology, showing only borderline changes, when found on routine protocol biopsies. However, in this study, only for-cause biopsies were performed due to clinical suspicion of rejection, and empiric corticosteroids were uniformly administered to patients who ultimately only had borderline changes, while awaiting final biopsy results.

Donor information when available was also collected, including donor age, gender, race, and warm/cold ischemia times.

Statistical analysis

All patients were followed for at least three years or longer until death, graft failure, or their last known visit. Graft failure was defined as re-transplantation of liver or kidney, death, or need for RRT (i.e. haemodialysis or peritoneal dialysis) for renal grafts. The immunosuppressive agents and trough levels were recorded within two weeks prior to rejection. Patients were then stratified by presence or absence of rejection of any type for either organ, and baseline demographics were compared among the groups. The impact of rejection episodes on patient survival, kidney graft survival, and liver graft survival were compared using the Kaplan-Meier method with log-rank test. Kidney graft function by MDRD-4 GFR was measured at the time of transplant and at months 1, 3, 6, 12, 24, and 36 post-SLK. An additional analysis was performed evaluating GFR over time according to the type of rejection. Categorical variables were analysed using the χ^2 test and Fisher's exact test; continuous variable were analysed using *t* tests (SAS 9.3 statistical software; Cary, NC).

Results

Patient and donor characteristics

A total of 179 patients underwent SLK transplantation at our institution between 1996 and 2010. Prior organ transplantation had occurred in 37 patients, who were then excluded from analysis. Two additional patients were excluded due to performance of transplant nephrectomy. A total of 140 SLK recipients were then included in the final analysis.

Baseline patient demographics and donor characteristics are displayed in Table 1. The main cause of renal disease was refractory hepatorenal syndrome (HRS), occurring in 50% of patients. Donor information was available for 93 (66%) of patients. Of this subset, only one patient received a liver graft with cold ischemia time greater than 12 h. No kidney cold ischemic time was greater than 20 h.

Incidence of liver and kidney rejection

Liver rejection (acute cellular or chronic) occurred in a total of 18 (12.9%) patients (Table 2). Acute rejection occurred in 16 patients (11.4%). Mild rejection occurred in nine (6.4%) patients, moderate in six (4.3%) and severe in one (0.7%). There were no cases of antibody-mediated liver rejection. Chronic liver rejection with ductopenia occurred in four patients (2.9%), of which two had had prior episodes of acute rejection.

Kidney rejection (excluding borderline changes) occurred in a total of 12 (8.6%) patients (Table 2). Acute cellular rejection occurred in nine (6.4%), of which 8 (5.7%) had Banff 1a rejection and one (0.7%) had moderate to severe rejection (Banff 2a); there were no (0) patients with Banff 1b or 2b scores. Antibody-mediated rejection occurred in two patients (1.4%) and chronic kidney rejection occurred in one (0.7%). An additional 16 patients (11.4%) had biopsies with borderline changes alone, and for statistical analysis these patients were included in the rejection group.

Patients with rejection of both organs were also evaluated for the temporal relationship between episodes. Kidney borderline changes preceded acute liver rejection within the next year in two patients. Another two patients had acute liver rejection followed by borderline changes within the following year. Two additional patients experienced both acute kidney rejection and