Kidney Rejection Following Simultaneous Liver-kidney Transplantation

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Background. Donor-specific antibodies are reported to increase the risk of rejection and reduce allograft survival following simultaneous liver-kidney transplantation. Optimal immunosuppression regimens to reduce this risk and to treat rejection episodes are underinvestigated. Methods. Cohort analysis of the first 27 simultaneous liver-kidney transplant recipients, between 2014 and 2018 at our unit, is performed under a new risk stratification policy. Those with donor-specific antibodies to class II HLA with a mean fluorescence intensity >10,000 are considered high risk for antibody-mediated rejection (AMR). These patients received immunosuppression, which consisted of induction therapy, tacrolimus, mycophenolate mofetil, and prednisolone. All other patients are considered low risk and received tacrolimus and prednisolone alone. Results. Three patients were high risk for rejection, and 2 of these patients developed AMR, which was treated with plasma exchange and intravenous immunoglobulin. At 1 y, their estimated glomerular filtration rate (eGFR) were 50 and 59 mL/min. Two other patients developed AMR, which was similarly treated, and their 1-y eGFR was 31 and 50 mL/min. The overall histologically proven acute rejection rate within the first year was 33%, and median eGFR, for the 27 patients, at 1 y was 52 mL/min and at 2 y was 49 mL/min. Conclusions. This study confirms that there is a risk of AMR following simultaneous liver-kidney transplantation despite increased immunosuppression. This can be effectively treated with plasma exchange and intravenous immunoglobulin.

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endothelial cell activation associated with the presence of preformed DSA in patients with HLA crossmatch positive SLK transplants compared with crossmatch positive kidney-alone transplants, though not completely reduced to the level of a crossmatch negative kidney-alone transplant, provide putative mechanistic explanations for the partial protection provided by the liver transplant.12,13

In our unit, we consider those for SLK transplantation if they have polycystic disease leading to massive hepatomegaly causing severe pain and malnutrition along with estimated glomerular filtration rate (eGFR) <30 mL/min or decompensated liver disease and chronic kidney disease with eGFR <30 mL/min or requiring renal replacement therapy. Although the majority of our SLK candidates are more stable than those with decompensated liver disease, to achieve preemptive kidney transplantation and to avoid the complications associated with malnutrition, it is not always possible to wait for an optimally HLA-matched donor. Therefore, in our view, it is appropriate to consider SLK transplantation despite a higher risk of rejection related to class II DSAs. However, optimal induction protocols and early immunosuppressive treatments for highly sensitized SLK recipients have not been established. Therefore, not surprisingly, in many transplant centers, SLKs are allocated based only on ABO compatibility without consideration of crossmatch results or level of HLA sensitization in the recipient and there is no change to the posttransplant care for patients with a positive crossmatch.9

This is an opportune time to focus on SLK outcomes in the United Kingdom as a national liver allocation scheme was implemented in 2018 and the impact on the number of SLK transplants performed is eagerly awaited. In the United States, SLK outcomes have become increasingly relevant because of the rising number of SLK procedures following the introduction of the model for end-stage liver disease for liver allocation.14

Following a case of AMR and renal graft loss after SLK transplantation related to DSA to class II HLA, in 2014, we modified our SLK program to include a flow crossmatch, increased immunosuppression with HLA surveillance for those with DSA to class II HLA with MFI of >10000. Retrospective studies have shown that induction therapy with antithymocyte globulin, muromonab-CD3, and interleukin 2 antagonists resulted in reduced renal allograft rejection, but this did not impact graft survival.9 To our knowledge, there are no published data on induction as well as maintenance immunosuppressive regimens and outcomes tailored for patients with preexisting DSA undertaking SLK transplantation. We report here on the renal rejection rates, graft, and patient outcomes following SLK transplantation since the implementation of this risk stratification protocol.

MATERIALS AND METHODS

In our unit, all patients considered for SLK are reviewed by a hepatologist, nephrologist, liver transplant, and kidney transplant surgeon often in joint clinics. The patients are discussed with a consultant clinical scientist who advises on the anti-HLA antibody profile of the recipient to understand the likelihood of being offered a donor to which the recipient has DSA to class II HLA.

Patients on the waiting list have 3 monthly blood samples for anti-HLA antibody monitoring. At the time of a transplant offer, the consultant clinical scientist advises on the likely virtual crossmatch result in the absence of any sensitizing events since the last anti-HLA antibody profile. If there has been a sensitizing event, a prospective flow crossmatch is performed using donor peripheral blood lymphocytes, but liver transplant surgery commences while the results are awaited. In addition, for all patients, a retrospective flow crossmatching is performed on both T and B cells. In our center, a positive result for either is defined as a relative median fluorescence of >2.29 times the negative control, once potential autoactivity has been accounted for. For those with DSAs to class II HLA with an MFI of >10000, or a positive prospective or retrospective crossmatch, induction therapy consisting of basiliximab 20 mg, after liver transplantation but before renal transplantation, is administered followed by a further 20 mg dose at day 4. Triple maintenance immunosuppression consisting of prednisone 20 mg tapered by 5 mg every 2 wk to 5 mg/d, mycophenolate mofetil (MMF), 500 mg BID, and tacrolimus adjusted to maintain a trough level of 8 to 10 µg/L is given. The patient is counseled for the risk attributed to the increased immunosuppression and increased risk of AMR. All other patients receive tacrolimus to maintain trough level of 3–7 µg/L and prednisolone.

Following SLK transplantation, for those with preexisting DSA, twice weekly anti-HLA antibody profiles are performed. A renal transplant biopsy is performed for patients with delayed graft function at day 7 posttransplant, for deteriorating renal function or if the graft function achieved is determined to be suboptimal based on the donor and recipient profile.

This is a cohort analysis of SLK transplant recipients between 2014 and 2018 at King’s College Hospital. We report the results of the first 27 SLK transplants performed under the new risk stratification policy. Descriptive statistics for characteristics and outcomes including rejection and graft and patient survival were used. Delayed graft function was defined as receiving dialysis after transplantation. eGFR was calculated using the Modification of Diet in Renal Disease formula.15 Antibody and T-cell–mediated rejection (TCMR) was diagnosed on the basis of histological examination of the kidney transplant and characterized according to the Banff classification.16

This study was exempt from approval from an ethics’ board.

RESULTS

Forthy-one percent of recipients were male with a median age of 55 y (range: 20–67). Thirty percent of SLK transplants were performed before dialysis therapy was initiated. The etiology of liver and kidney disease is listed in Table 1. Seventy percent had adult polycystic kidney and liver disease. Ninety-six percent received an SLK from a donor after brainstem death with a median age of 55 y (range: 30–68). Forty-eight percent of the donors were male. In this cohort, none of the patients received allografts from donors resulting in either a 000 or “favorable” HLA mismatch. Favorable mismatches include 100, 010, and 110 HLA mismatches. At the DR locus, 4% had 0, 37% had 1, and 59% had 2 mismatches.

Twenty-three patients received immunosuppression with tacrolimus and prednisolone only, as these patients had no preformed DSA to class II HLA with MFI of >10000. One
patient, receiving his second liver and kidney transplant, previously developed tacrolimus-related thrombotic microangiopathy and therefore, after multidisciplinary discussion, was prescribed basiliximab, ciclosporin, MMF, and prednisolone immunosuppressive therapy.

Three patients, A, B, and C, received basiliximab induction with tacrolimus, MMF, and prednisolone as they were known to have preformed DSA to class II HLA with MFI of >10,000. This was substantiated with the retrospective flow cytometric crossmatch results (B-cell–positive crossmatch with class II DSAs with MFIs of >10,000) in patients A and B. Patient C’s retrospective crossmatch was negative.

The median cold ischemic time for the kidney transplant was 13 h (range: 8–21). Delayed graft function rates were 63%. The median number of days of renal replacement therapy required was 3 (range: 0–34). A renal biopsy at the time of implantation was taken in 48% of patients, and the median Karpinski score was 3 (range: 2–5). At the time of transplantation, 5 patients underwent a right nephrectomy for space, infections, or other symptoms. The median length of stay in hospital after transplantation was 22 d (range: 10–136).

To date, renal graft survival and patient survival are 100%.

Renal Rejection

Eight patients experienced in total 9 episodes of acute rejection of the kidney graft during the first year after SLK transplantation (Table 2). Figure 1 shows the renal histological findings.

Patient A had preformed DSA to class I and II HLA. Immediately after transplantation, there was a reduction to all preformed DSA MFIs. However, by 1 wk, DSA to class I (predominantly B8 and B49) HLA MFIs had risen above pretransplant values and DSA to class II HLA has rebounded to similar MFIs as obtained pretransplantation. She was diagnosed with AMR (glomerulitis 1, peritubular capillaritis 2, C4d 3) at 1 wk after renal allograft biopsy was performed for delayed graft function (Tables 2 and 3). Patient A was successfully treated with 15 sessions of plasma exchange and intravenous immunoglobulin (PEXivG). Figure 2 shows the anti-DSA profile for patient A following treatment of AMR. DSA reduced significantly with PEXivG. At 1 y, her eGFR was 59 mL/min. The most recent HLA sample, 599 d after transplantation, does not demonstrate a DSA.

Patient C did not experience rejection.

For patient D, the retrospective flow crossmatch was T- and B-cell negative, but potential class I DSA to B8 (MFI 2091) and B35 (MFI 4401) were detected in pretransplant blood samples. As per our protocol, she received tacrolimus and prednisolone only. At day 11, a renal biopsy, for deteriorating eGFR from 49 to 30 mL/min, revealed borderline TCMR. In addition, she developed liver TCMR at day 13. In view of the liver rejection and the DSAs, MMF was commenced and tacrolimus concentrations were increased to 8–10 µg/L. At day 26, a further biopsy revealed AMR (glomerulitis 2, peritubular capillaritis 1, C4d 3), in association with rising DSA to class I HLA (B35), and a course of PEXivG was administered. Figure 2 shows the anti-DSA profile for patient D showing efficient decline in the DSAs. At 1 y, there is no DSA and she achieved a stable eGFR of 31 mL/min (Tables 2 and 3).

For patient E, DSA to class I HLA to A3 (MFI 2857), B7 (MFI 21176), and B35 (MFI 2548) were detected in pretransplant bloods leading to a positive retrospective T- and B-cell flow crossmatch. However, as per our protocol, she received tacrolimus and prednisolone immunosuppression. Initially,
DSA MFIs fell but were followed by an increase in preformed DSA to class I HLA (A3 and B7) as well as de novo DSA to class II HLA (DR53 and DP3). Of note, the MFIs were higher for DSA to class I compared with class II. At day 6, because of delayed graft function, a renal biopsy was undertaken, which showed acute tubular injury without microvascular inflammation and negative C4d staining. A further biopsy on day 12, performed for ongoing delayed graft function in the presence of rising DSA MFIs, confirmed the presence of AMR (glomerulitis 1, peritubular capillaritis 1, C4d 3), and she was treated successfully with 10 sessions of PEXivG. MMF was also commenced. The decrease in DSA is shown in Figure 2. At 1 y, patient E has an eGFR of 50 mL/min and continues to produce DSAs but at lower MFIs (Tables 2 and 3).

In general, treatment with PEXivG was well tolerated. However, patient A developed bleeding from her femoral artery, at the site of a previous arterial catheter insertion, which required surgical repair. For those receiving basiliximab induction with tacrolimus, MMF, and prednisolone, no increased adverse events were noted.

Four patients were diagnosed with cellular rejection after histological samples of the kidney transplant were examined. Patient F developed Banff 2A TCMR at day 11 and was treated with a 10-d course of antithymocyte globulin. Patient G acquired Banff 2A TCMR of the kidney allograft and TCMR of the liver allograft at day 13 after developing gastrointestinal bleeding requiring surgical resection of bowel and redo of the of jejunoojejunostomy. During this postoperative complication, his tacrolimus concentration reduced to 1.7 µg/L. He was treated with 500 mg of methylprednisolone on 3 consecutive days, and MMF was commenced. Patient H developed TCMR Banff 1A, at 2 wk after transplantation, and patient I developed 1A TCMR at 74 d after transplantation. Both were treated with methylprednisolone and introduction of MMF.

These results are summarized in Table 2 which also shows the eGFR at 1 y. The overall rejection rate in the first year was 33%.

After 1 y, there had been 1 further rejection episode in patient J. At 1 y, her eGFR was 32 mL. She then developed diarrhea and vomiting along with pseudomonas-related liver abscesses 556 d after transplantation. This was associated with acute kidney injury, and a renal biopsy demonstrated Banff 1B TCMR. In view of the sepsis, she was treated with 500 mg of methylprednisolone on 3 consecutive days only. Her eGFR at 2 y however remained stable at 30 mL/min.

Renal Transplant Function
All patients have completed 1 y since liver and kidney transplant surgery. At 1 year, the median eGFR was 52 mL/min (range: 30–98). At 2 y (n = 21), median eGFR was 49 mL/min (range: 30–90).

| TABLE 2. Renal rejection episodes in first y after transplantation |
|-------------------|-----------------|------------------|-----------------|-----------------|
| Patient | First rejection (Banff classification) | Time after transplant, d | Treatment | 1 y eGFR |
| A | AMR (7) | PEXivG | 50 |
| B | AMR (7) | PEXivG | 59 |
| D | AMR (11) | PEXivG | 31 |
| E | AMR (12) | PEXivG | 50 |
| F | 2A (11) | ATG | 43 |
| G | 2A (13) | Methylprednisolone, MMF 500 mg bd | 66 |
| H | 1A (15) | Methylprednisolone, MMF 500 mg bd | 55 |
| I | 1A (74) | Methylprednisolone, MMF 500 mg bd | 50 |

AMR, antibody-mediated rejection; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; PEXivG, plasma exchange and intravenous immunoglobulin.

| TABLE 3. Donor-specific antibodies |
|-------------------|------------------|-----------------|-----------------|-----------------|
| Patient (crossmatch result) | Pretransplant DSA (MFI) | Peak DSA during AMR (MFI) | DSA after PEXivG (MFI) | Posttransplant DSA at 1 y |
| A (T cell negative; B cell positive) | A1 (1452) | A1 (4044) | A1 (653) | A1 (581) |
| B (T cell negative; B cell positive) | Cw10 (7577) | Cw10 (3701) | Cw10 (3549) | No |
| D (T cell negative; B cell negative) | A1 (50) | A1 (3012) | A1 (807) | No |
| E (T cell positive; B cell positive) | A3 (2857) | A3 (11214) | A3 (409) | |
De Novo DSA

From our cohort of patients, 15% have developed de novo DSA. Four percent have class I, 7% have class II, and 4% have both class I and II of the overall cohort. The median MFI for class I is 2713 (range: 2120–3305) and for class II is 3285 (range: 1698–10 889). None of these patients have developed AMR.

Liver Outcomes

At 1 y, liver graft survival was 100%. Six patients were treated successfully for acute TCMR on histological samples with methylprednisolone at a median of 12 d (range: 9–15 d) after transplantation. Four of these patients did not develop kidney rejection. Patient D developed liver rejection at day 13 after SLK transplantation and, then at day 26, developed AMR in her kidney allograft. Patient G developed acute rejection of his liver transplant on day 13 as described previously. This was initially treated successfully, but unfortunately further rejection occurred in relation to noncompliance with his immunosuppressive therapy. This necessitated further liver transplantation 477 d after the first transplant surgery was performed. His kidney allograft continues to function.

DISCUSSION

This is a descriptive analysis of 27 patients undergoing SLK transplantation in our unit. Although this is an uncontrolled study, our results demonstrate some interesting findings that are of relevance to clinicians caring for patients undergoing SLK transplantation. Our data suggest that those with DSA to class II HLA with MFIs of >10 000, resulting in a positive crossmatch, are at increased risk of AMR despite increased immunosuppression. However, careful surveillance of HLA profiles along with timely kidney biopsy achieves early diagnosis of AMR and facilitates effective treatment with PEXivG.

Furthermore, our data suggest that class I DSAs may not be as innocuous as previously considered. Two of our patients had predominantly class I DSAs resulting in AMR. A recent case report demonstrated the deposition of both DSA to class I and class II HLA with strongly positive C4d staining in liver and kidney transplants demonstrating that the immunoprotective effect of the liver graft is not universal in the case of DSA to class I HLA. The authors suggest that very high MFIs of DSA to class I HLA may not be completely absorbed therefore by the liver and this was confirmed by their finding that although the crossmatch became negative 1 h after liver transplantation, it was positive again with the same MFIs for DSA to class I and II HLA at 6 h after liver transplantation. This patient received treatment with eculizumab and rituximab, but this did not prevent the occurrence of AMR. Single antigen bead analysis of kidney and liver allograft eluates demonstrated the deposition of both DSA to class I and II HLA in the allografts implying that AMR was as a consequence to DSA to both class I and II HLA. In our patient D, the MFIs of the DSAs to class I HLA were relatively low (<5000), but despite this AMR occurred. We were not able to confirm that DSAs

FIGURE 2. Donor-specific antibody (DSA) to class II HLA in simultaneous liver-kidney (SLK) recipients. A, Patient A. B, Patient B. C, Patient D. D, Patient E. MFI, mean fluorescence intensity.
to class I HLA were deposited in the kidney transplant, by a similar analysis, but in the absence of DSA to class II HLA in patient D, it seems very likely that the AMR was related to DSA to class I HLA. For patient E, DSAs to class I and II HLA were present and we suspect that this led to the development of AMR.

A further observation from our data is that AMR after SLK transplantation does not result in inferior graft function with increased graft loss as experienced by kidney transplant–alone recipients, who develop AMR as a result of de novo and preformed DSA.6,19-25 This is despite the observation that 50% of our patients experiencing AMR continued to produce DSAs at lower MFI in the longer term following treatment with PEXivG.

In kidney-alone transplantation, de novo DSA has been found to be more deleterious than preexisting DSA, but none of our patients who developed de novo DSA following SLK transplantation have experienced acute or chronic AMR.26,27 This may result from the relatively short duration of follow-up, but we plan to monitor this cohort and will report the long-term outcomes. It is therefore not appropriate to suggest improved HLA matching, particularly in younger patients who may require repeated transplantation, in SLK transplant programs.

In addition, our data demonstrate that the current standard of care for treating AMR using PEXivG to remove preformed DSAs in kidney transplantation is more successful in SLK recipients than in kidney-alone patients and perhaps, therefore, strategies to prevent DSA formation or remove DSA such as rituximab, bortezomib, eculizumab, and splenectomy are not warranted in this patient group.23

We therefore surmise that AMR may have a different phenotype in SLK recipients compared with kidney-alone recipients, possibly as a result of the effects of the liver allograft on DSA as previously described. This difference is not only on the risk of AMR with preexisting DSA but also on the historical severity of AMR and the response to treatment with superior graft outcome when compared with isolated kidney transplantation. It follows that de novo DSA formation may have a similarly less injurious effect in SLK recipients.

Several strategies can be undertaken to manage the increased risk attributed to preexisting DSAs as discussed in a recent article by Steggerda et al.22 We can transplant against donors resulting in a positive crossmatch, accepting the higher risk of AMR in the kidney allograft or we can decline these donors or we accept the liver transplant, which is likely to be life-saving and forgo the kidney transplant offer and consider future kidney transplantation with a donor resulting in a negative crossmatch. Retrospective observational data in SLK transplantation have shown that the presence of preexisting DSA is associated with inferior renal allograft outcomes and patient survival.1,8,11 This is perhaps not surprising as this was observational data. We suggest that with careful surveillance of DSA and early detection and treatment of AMR, this risk can be minimized. There is a significant risk of death while waiting for liver transplantation in the United Kingdom with data from NHS Blood and Transplant reporting a mean of 83% survival at 1 year after listing for liver transplantation, and therefore, declining organs may not be acceptable in the face of successful treatment strategies for AMR.30 Furthermore, not all patients with a positive crossmatch will develop AMR as in about a third of such cases, the DSA spontaneously is cleared.5

For those with liver failure and chronic kidney disease or persistent acute kidney injury, registry data suggest that SLK transplantation is associated with improved patient survival when compared with liver transplantation alone.31-33 Therefore, in our opinion, liver-alone transplantation should be reserved for patients with significant comorbidity such that the perioperative mortality risk justifies liver-alone surgery and for patients with decompensated liver disease, who cannot wait for both organs if an isolated liver transplant is offered.

It is increasingly important to consider immunosuppression regimens for SLK transplantation as the number of patients undergoing SLK transplantation rises along with the proportion of sensitized patients awaiting organ transplantation34 and yet there is a lack of studies comparing the outcomes with differing immunosuppressants. Analysis of the Scientific Registry of Transplant Recipients data showed that only a minority of patients undergoing SLK usually receive lymphocyte-depleting agents as induction (14%-19%), even among sensitized recipients.4 Several centers use only an interleukin 2 receptor antagonist for induction in SLK transplants.34,35 There are published case reports of administration of eculizumab with rituximab in highly sensitized recipients. But there is no clear evidence supporting any specific protocol. To our knowledge, most centers in the United Kingdom do not adjust immunosuppression on the basis of increased immunologic risk of renal rejection defined by preexisting DSA with the majority of recipients receiving immunosuppression protocols similar to those receiving liver transplantation alone. In our center, our immunosuppression protocol for SLK patients with DSA to class II HLA is similar to kidney-alone transplantation, and in this small cohort of patients, we report excellent outcomes despite AMR with such protocols in combination with posttransplant DSA surveillance and early treatment of AMR with PLEXvG. However, this small study cannot comment on the effect of lymphocyte-depleting agents on de novo DSA formation.

Twenty-two percent of our cohort experienced early liver allograft rejection. Four of these 6 patients did not experience renal allograft rejection. However, interestingly, in 2 patients, liver and renal transplant rejection occurred concurrently. For patient G, this may have been related to low concentrations of his immunosuppressive therapy. However, for patient D, the crossmatch was negative and therefore the risk of AMR of the kidney transplant was thought to be low. Given the temporal nature of the liver rejection followed by renal rejection, perhaps the dysfunction of the liver transplant resulted in circulating class I HLA antibodies, precipitating renal-related AMR. This hypothesis would need testing in future studies.

The main limitations of this study include the small number of patients in our cohort and the lack of a control group. It is therefore difficult to determine with certainty whether the increased immunosuppression or the early surveillance and treatment of AMR with PLEXvG is key to improving outcome. However, it seems inconceivable that it would now be considered acceptable not to treat histologically proven AMR in the kidney transplant. However, further investigation to consider immunologic risk stratification in SLK transplantation and optimal induction immunosuppression, by recruitment to a multicenter study, is warranted and should now be considered.
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