**Supplementary Appendix**

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**1. Factors associated with recipient viremia**

Supplementary Table 1 shows the recipient and donor characteristics of recipients with no viremia, detectable viremia <15 IU/mL and quantifiable viremia. The exact univariate p-value is shown for both ordinal (no viremia, <15 IU/mL, quantifiable) and dichotomous (viremic vs non-viremic) regression for each variable. The median donor HCV RNA level was associated with recipient viremia in a stepwise and dichotomous fashion. HCV genotype 3 was also associated with recipient viremia. To determine if these factors were independent, the factors were evaluated in a bivariate exact logistic regression model, which confirmed that both genotype 3 and donor viral load were associated with a higher likelihood of viremia in recipients. To illustrate that the factors are independent, Supplementary Figure 1 shows the donor viral load in genotype 3- and genotype non-3-infected donors in each category of recipient viremia.

**Supplementary Table 1. Factors associated with recipient peak viremia\***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|   |   |  **Peak Viremia in Recipients** | Ordinal Outcome | No viremia versus Viremia |
|   |   |  |   | N=9 versus N=21 |
|   |   | **No Viremia** | **Detectable < 15 IU/mL** | **Quantifiable viremia** | **Total** | **p-value (exact/exact ordinal)** | **p-value (exact)** |
|   |   | **N=9** | **N=11** | **N=10** | **N=30** |  |  |
| Recipient sex | male | 7 (30.4%) | 8 (34.8%) | 8 (34.8%) | 23 | 1.00 | 1.00 |
| female | 2 (28.2%) | 3 (42.9%) | 2 (28.2%) | 7 |  |  |
| Recipient Age (yr) | mean (SD) | 52 (18) | 55 (14) | 60 (16) | 56 (16) | 0.52 | 0.37 |
| Transplanted Organ | Lung | 4 (30.8%) | 5 (38.5%) | 4 (30.8%) | 13 | 0.51 | 0.72 |
| Heart | 1 (16.7%) | 4 (66.7%) | 1 (16.7%) | 6 |  |  |
| Kidney | 4 (40.0%) | 2 (20.0%) | 4 (40.0%) | 10 |  |  |
| Kidney-Pancreas |   |   | 1 (100%) | 1 |  |  |
| Donor Sex\* | male | 8 (32.0%) | 9 (36.0%) | 8 (32.0%) | 25 | 1.00 | 1.00 |
| female | 1 (20.0%) | 2 (40.0%) | 2 (40.0%) | 5 |  |  |
| Donor Age\* (yr) | mean (SD) | 37 (12) | 35 (9) | 36 (4)  | 36  | 0.90 | 0.69 |
| Donor HCV RNA (log IU/mL)\* | median (IQR) | 2.25 (1.18-4.93) | 4.93 (4.49-5.42) | 6.23 (4.73-6.66) | 4.93 (4.35-5.87) | **0.0012** | **0.0010** |
| Donor HCV Genotype\* | 1 | 6 (75%) | 4 (50%) | 3 (37.5%) | 8 | 0.13 | **0.042** |
| 2 | 1 (25.0%) | 2 (50.0%) | 1 (25.0%) | 4 |  |  |
| 3 |   | 4 (40.0%) | 6 (60.0%) | 10 |  |  |
| missing (excl) | 2 (66.7%) | 1 (33.3%) |   | 3 |  |  |
| Donor HCV Genotype\* | non genotype 3 | 7 (41.7%) | 6 (35.3%) | 4 (23.5%) | 17 | **0.049** / **0.045** | **0.026** |
| genotype 3 |   | 4 (40.0%) | 6 (60.0%) | 10 |  |  |

\* 30 recipients received organs from 18 donors

**Supplementary Table 2a**

|  |
| --- |
| **Exact logistic regression of factors associated with recipient viremia (Likelihood Ratio Test)** |
|   |   | **95% Wald** |   |
| **Effect** | **Odds Ratio** | **Confidence Limits** | **p-value** |
| Genotype 3 versus non 3 | 7.09 | 1.05 | 47.98 | 0.045 |
| Donor HCV RNA (log10IU/mL) | 5.27 | 1.74 | 15.90 | 0.0032 |
|  |  |  |  |  |
| **Proportional Odds Assumption accepted p=0.62** |

**Supplementary Table 2b**

|  |
| --- |
| **Logistic Regression of Peak Viremia in Recipients Viremic versus no Viremic**  |
| **with repeated structure to control for within donor effect** |  |  |
|   |   | **95% Wald** |   |
| **Effect** | **Odds Ratio** | **Confidence Limits** | **p-value** |
| genotype 3 versus non genotype 3 | inf \* |  |  |  |
| Donor HBV DNA (log IU/mL) Univariate effect | 5.56 | 2.33 | 13.29 | 0.0001 |

**Supplementary Figure 1. Donor HCV RNA by HCV genotype and peak recipient viremia**



**2. Adverse Events**

**Supplementary Table 3. Serious Adverse Events**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **SAE No.** | **Subject No.** | **Transplant type** | **Event** | **Timing****(days post-transplant)** | **Relationship to therapy** | **Outcome** |
| 1 | 1 | Lung | Atrial fibrillation | 12 | None | Resolution |
| 2 | 1 | Lung | Pulmonary Embolism | 84 | None |  |
| 3 | 2 | Lung | Death\*  | 49 | None | No resolution |
| 4 | 3 | Lung | Heart block | 13 | None | Resolution |
| 5 | 3 | Lung | Acute kidney injury (hospital admission) |  | None | Resolution |
| 6 | 5 | Lung | Chest Pain(hospital admission) | 20 | None | Resolution |
| 7 | 5 | Lung | Pulmonary Embolism | 37 | None | Resolution |
| 8 | 7 | Kidney-Pancreas | Extended recovery post-transplant surgery | 0 | None | Resolution |
| 9 | 7 | Kidney-Pancreas | Pancreatitis (hospital admission) | 184 | None | Resolution |
| 10 | 8 | Heart | Biopsy proven rejection | 85 | None | Resolution |
| 11 | 9 | Kidney | Subtotal thyroidectomy for tertiary hyperparathyroidectomy | 10 | None | Resolution |
| 12 | 9 | Kidney | Prostatitis (hospital admission) | 101 | None | Resolution |
| 13 | 11 | Kidney | Extended recovery post-transplant surgery | 0 | None | Resolution |
| 14 | 11 | Kidney | Diarrhea (hospital admission) | 37 | None | Resolution |
| 15 | 12 | Kidney | Perirenal collection | 16 | None | Resolution |
| 16 | 13 | Kidney | Extended recovery post-transplant surgery | 0 | None | Resolution |
| 17 | 14 | Heart | Biopsy proven rejection | 15 | None | Resolution |
| 18 | 15 | Kidney | High liver enzymes\* | 5 | Possible | Resolution |
| 19 | 17 | Lung | Extended recovery post-transplant surgery | 0 | None | Resolution |
| 20 | 17 | Lung | Death\* (subarachnoid hemorrhage)  | 109 | None | No resolution |
| 21 | 12 | Kidney | Pre-syncope (hospital admission) | 47 | None | Resolution |
| 22 | 19 | Lung | Stroke (TIA) | 28 | None | Resolution |
| 23 | 25 | Kidney | Renal graft hydronephrosis | 87 | None | Resolution |
| 24 | 26 | Lung | Hematuria and pleural effusion | 60 | None | Resolution |
| 25 | 26 | Lung | Fluid overload | 100 | None | Resolution |
| 26 | 27 | Heart | Syncope | 13 | None | Resolution |
| 27 | 27 | Heart | Acute cellular rejection | 19 | None | Resolution |
| 28 | 27 | Heart | Orthostatic hypotension | 39 | None | Resolution |
| 29 | 27 | Heart | Orthostatic hypotension | 59 | None | Resolution |
| 30 | 29 | Kidney | Hyperkalemia | 14 | None | Resolution |
| 31 | 28 | Heart | Hematoma | 53 | None | Resolution |
| 32 | 30 | Kidney | Febrile neutropenia | 64 | None | Resolution |

\* See details of deaths and liver enzyme elevations below

**3. Details of patient deaths**

Two lung transplant recipients died at days 49 and 109 after transplantation, respectively. Both received a left single lung transplantation. The first patient was a 65-year-old woman who was highly sensitized (panel of reactive antibodies >90%) and despite perioperative desensitization with plasmapheresis presented with refractory antibody-mediated rejection leading to prolonged mechanical ventilation, sepsis, and a protracted ICU course, at which point the family elected for withdrawal of life support therapy. The patient never had detectable HCV RNA after transplantation. The second patient was a 61-year-old man with interstitial pulmonary fibrosis and a remote history of stage III lung cancer treated with chemotherapy and radiation. He had a prolonged hospital stay, however during his rehabilitation on the regular ward he presented with a large spontaneous subarachnoid hemorrhage leading to brain death. The bleeding was likely associated with use of heparin for chronic atrial fibrillation (pre-transplant condition). HCV RNA below the limit of quantification was detected on day 1 and 2 after transplantation but remained undetectable after that.

**4. Laboratory Abnormality Grading**

Laboratory abnormalities were graded using the Common Terminology Criteria for Adverse Events. For ALT and CK, Grade 1: 1 to 5 x upper limit of normal (ULN), Grade 2: 5 to 10 x ULN, Grade 3: 10 to 20 x ULN and Grade 4: > 20 x ULN. For bilirubin, Grade 1: 1 to 1.5 x ULN, Grade 2: 1.5 to 3 x ULN, Grade 3: 3 to 10 x ULN and Grade 4: > 10 x ULN.

**5. Details of ALT and CK elevations**

Transaminase elevations occurred in 13 recipients (52%) within the dosing period of the study medications. The peak ALT observed was 1,333 U/L post-op day 1 after a kidney-pancreas transplant. Levels declined daily back to normal by post-op day 11. There was no associated change in bilirubin or INR and the elevation was attributed to shock liver related to a prolonged and difficult surgery. One grade 3 ALT elevation was also reported in a 54-year-old Hispanic man with pre-existing non-alcoholic fatty liver disease but normal ALT at screening. Pre-transplant ALT was 73 U/L, which increased to 105 U/L post-op day 1 and 262 U/L by post-op day 5. The ALT peaked at 650 U/L on post-op day 11 and then trended down to the normal range by post-op day 27. Peak total bilirubin was in the normal range at 19 µmol/L on post-op day 14 and there was no change in INR (1.0). Work-up for causes of acute hepatitis was unrevealing, including persistently undetectable HCV RNA, and the patient underwent a liver biopsy on post-op day 15, which showed a non-specific acute hepatitis with moderate steatosis but no steatohepatitis and no fibrosis.Two additional patients experienced grade 2 ALT elevations, one on day 7 post-transplant that resolved by day 9 post-transplant and the other on the day of transplant that resolved by day 4 post-transplant. No ALT elevations were associated with changes in bilirubin or INR and no patient developed signs or symptoms of liver failure. ALT elevations did not correlate with HCV RNA levels and were no more common in those with quantifiable viremia (5 of 9) or detectable but unquantifiable viremia (3 of 9) than in those with undetectable HCV RNA (5 of 7) throughout follow-up.

CK levels became transiently elevated during follow-up in 14 (56%) patients on therapy, with a peak value of 4,380 U/L in a recipient with post-operative hypotension. There was no reported symptomatic myopathy or myositis and no renal consequences attributed to rhabdomyolysis.

**6. Episodes of acute rejection**

At least one episode of rejection requiring treatment was observed in 3 of 4 heart transplant recipients. One patient who underwent re-do heart transplantation had 4 episodes of ISHLT Grade 2R rejection, and 2 other heart transplant recipients had a single episode of ISHLT Grade 2R rejection. Rejection occurred as early as 4 days post-transplant and was treated with pulse steroids and augmentation of immunosuppression with resolution. A single episode of rejection requiring therapy was documented in 3 lung transplant recipients, all of which responded to pulse steroids and increased immunosuppression. Rejection was not observed in kidney or kidney-pancreas recipients.