Pilot Study for the Use of Shortened Preemptive Therapy With Glecaprevir/Pibrentasvir (G/P) and Ezetimibe in Hepatitis C Seronegative Solid Organ Transplant Recipients (Kidney, Heart, Lung and/or Pancreas) of Hepatitis C Viremic Donors

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Bashar Aqel, Rolland C. Dickson, Hassan Khamash, D. Eric Steidley, and Adyr Moss.

Background: There is a shortage of solid organs for patients with end organ failure resulting in prolonged waiting times on kidney and heart recipient lists. Prolonged waiting times are associated with increased cost to the health care system, decreased quality of life and increased morbidity and mortality(1). Additional sources of organs are needed. The use of living donors and increased utilization of extended criteria donors have not completely bridged this gap, and these organs are associated with their own set of risks and complications as well. Donors who are seropositive for Hepatitis C Virus (HCV) represent a potential source of solid organ allografts. Stepanova et al. recently demonstrated that use of these grafts into HCV seropositive recipients has tripled over the past two decades. In 2013, 9.4% of HCV seropositive patients received an organ from an HCV seropositive donor. There were no differences in outcomes when compared to recipients of organs from HCV seronegative donors (2). However, as HCV treatment is now highly effective in patients with chronic hepatitis C, there are often not enough HCV positive patients to accept these grafts, resulting in higher rates of unsuccessful allocation and/or discards of grafts from HCV positive donors.

The primary concern with utilization of grafts from HCV viremic donors into seronegative recipients is transmission of HCV infection which could lead to complications of chronic HCV infection, liver disease, and graft failure. Highly effective direct acting oral antiviral drugs (DAA) are now available and widely utilized following LT. Cure rates (SVR) are over 95% and have minimal associated toxicity. These medications have importantly been shown to be effective in treating the most aggressive but rare form of post-solid organ transplant recurrence, fibrosing cholestatic hepatitis. Several regimens are approved by FDA for HCV treatment. Glecaprevir/Pibrentasvir (G/P) is a pan-genotypic regimen approved in August 2017 for treatment of all HCV genotypes. G/P was found to be highly effective in HCV treatment after LT with similar SVR rates in all genotypes (3). Furthermore, the regimen is well tolerated, has acceptable by a bioavailability when given through the nasogastric tube, and can be used in patients with advanced kidney disease including those who are on dialysis(4).

Our early work confirmed the safety and efficacy utilization of hepatitis C positive kidney allografts in hepatic C positive recipients. We showed the 1-year transplantation rate was 12.5% vs 67.9% (P = .0013) in those treated post transplantation favoring the practice of using those grafts and treating patients post transplantation. The median waitlist time in the posttransplant group was 122 (interquartile range [IQR] 21.5, 531.0) days, which were significantly shorter than the center's regional and national wait time. Pathologic review revealed no difference in allograft quality. Overall treatment related adverse events were minimal and patients tolerated treatment very well. Our strategy of post-transplant hepatitis C treatment increased access to transplant and reduced waitlist time. Delaying treatment until after transplant did not appear to adversely affect recipients' kidney allograft or overall survival (5).

With the help of a generous benefactor award, our team was able to complete Multicenter experience across the three Mayo Clinic sites evaluating outcomes of HCV seropositive donors to HCV-Seronegative recipients Liver Transplantation(6). We were able to show that using HCV-seropositive grafts to HCV-seronegative recipients resulted in acceptable short-term outcomes in our multicenter experience even with the use of DCD grafts and expansion into SLK or repeat LT. Anti-viral therapy was initiated post transplantation with 100% efficacy and minimal adverse events. This preliminary data supports continued use of HCV-seropositive grafts.

Our group was able to generalize this protocol to include all solid organ transplant recipients (so far close to 20 heart/lung transplants and 45 kidney transplants were done) utilizing HCV positive grafts in HCV negative recipients. This practice has proven to be successful and allowed the utilization of good quality grafts that would have been otherwise discarded. HCV infection was universal (100%) in recipients of HCV viremic grafts, and all patients required antiviral therapy post transplantation. Under the current protocol, hepatitis C treatment is initiated once active viremia is confirmed post transplantation. We generally wait for at least 2 consecutive positive viremias to initiate treatment authorization. Treatment outcomes so far have been excellent, and viral clearance was achieved in all recipients.

Our current practice, though successful, does have few challenges. Under our current protocol, HCV treatment, though effective, it continues to require a full treatment duration of 12 weeks. Furthermore, treatment regimens continue to be expensive. The authorization process for treatment approval varies significantly according to the patient health insurance and can take up to 24 weeks (7, 8). This can put the patients at the theoretical risk of an aggressive recurrence of hepatitis C in the absence of timely treatment. Our group was the first to report hepatitis C related membranous glomerulonephritis in a recipient of HCV positive liver graft (9). That complication could have been potentially prevented with earlier treatment initiation.

Preemptive therapy appears to be an excellent option especially in non-liver solid organ recipients (10, 11). Non-liver solid organ transplants differ from liver transplantation, because the heart, kidney and lungs are not reservoirs for HCV, and thus recipients of those solid organs would be exposed to a low hepatitis C viral load at the time of

transplantation. Therefore, a shorter duration of treatment than that used for patients with chronic HCV infection was hypothesized to be efficacious, since this type of solid organ transplant is analogous to post exposure prophylaxis, where a shorter treatment regimen is very effective. Woolley et al conducted a trial involving transplantation of hearts and lungs from donors who had hepatitis C viremia into HCV negative recipients. Sofosbuvir–velpatasvir, a pan-genotypic direct-acting antiviral regimen, was preemptively administered to the organ recipients for 4 weeks, beginning within a few hours after transplantation, to block viral replication. A total of 44 patients were enrolled: 36 received lung transplants and 8 received heart transplants. Of the first 35 patients enrolled who had completed 6 months of follow-up, all 35 patients (100%; 95% confidence interval, 90 to 100) were alive and had excellent graft function and an undetectable hepatitis C viral load at 6 months after transplantation. The study concluded that patients without HCV infection who received a heart or lung transplant from donors with hepatitis C viremia, treatment with an antiviral regimen for 4 weeks, initiated within a few hours after transplantation, prevented the establishment of HCV infection(11). Those studies clearly confirmed the efficacy and safety of preemptive HCV therapy, but yet continued to require treatment duration of 4-8 weeks.

In very small study, Zetia (ezetimibe), which is generally used as a lipid-lowering agent, was found to help blocking the cholesterol receptor used by the HCV virus for cell entry(12). The combination of this drug with DAA's can potentially be more effective in preventing the transmission of hepatitis C infection in recipients of solid organ transplants from donors with active viremia at time of procurement. During the Annual Meeting of the American Association for the Study of Liver Diseases in Boston (The Liver Meeting), Feld and his colleagues presented the data from a small pilot study utilizing preemptive therapy with a combination of direct-acting antivirals (DAAs) and the lipid lowering agent Zetia (ezetimibe). The recipients of transplanted organs from donors who had hepatitis C virus (HCV) either cleared or did not acquire the virus when they were treated with just eight days of a combination of direct-acting antivirals (DAAs) and the cholesterol medication Zetia (ezetimibe). The treatment was given hours prior to transplant and for seven days following transplantation. The study included 13 patients, and in those who had adequate follow-up, none of those patients developed infection post completion of the 8-days treatment course(13). The transplant community felt that larger study involving other solid organ transplants will be needed to confirm the efficacy of such a practice.

Mayo Clinic Arizona and Mayo Clinic Florida are considered two of the largest solid organ transplant centers in the country and we should be able to confirm the efficacy of this regimen using a larger cohort of patients. Confirming the findings of such a small pilot study will have a great impact on the utilization of HCV positive grafts. Such rapid treatment greatly lowers the cost of therapy, which typically runs for at least 8-12 weeks with a standard DAA regimen for those receiving HCV-infected organ transplants.

Our study proposes the implementation of this preemptive protocol for solid organ recipients (kidney, heart, lung, and/or pancreas). Patients who fail to respond to this

regimen will be treated using the standard of care protocol that's already in place for recipients of those organs.

Aim

To assess the efficacy of preemptive therapy with eight days of a combination of direct-acting antivirals (DAAs) (Mavyret) and the cholesterol medication Zetia (ezetimibe) in recipients of HCV viremic solid organ transplant (kidney or heart).

Inclusions

- Listed kidney, heart, lung, and/or pancreas patients who are negative for chronic hepatitis C infection
- Willing to accept and consent to accept hepatitis C positive graft

Exclusion

- Existing chronic liver disease (liver cirrhosis)
- Concomitant infection with HIV or Chronic hepatitis B
- Patient or any member of patient family or care giver team who does not understand or accept the risk of an acquired HCV infection.
- Pregnancy (Pregnant patients do not undergo solid organ transplants)

Methods

Patients who meet study criteria will be discussed in the Transplant Selection conference. All patients deemed to be good candidates will be offered enrollment in the study. We plan to enroll 300 patients as we continue to treat patients under the standard of care portion of the study. This will allow us to monitor patient outcomes post treatment. Interim analysis will be done after enrolling 10 patients to assess the rates of breakthrough infection. Our primary end points are 1. HCV RNA negative 12 weeks after completing anti-viral therapy and rate of viral breakthrough in patients completing 8 days of antiviral therapy. 2. Safety and tolerability of the treatment regimen in those patients' 3. Secondary end points will be short term graft and patient survival at 3 months, 6 months and 1 year.

Adult patients (18 years of age or older) who were on the waiting list for kidney, heart, lung and/or pancreas transplants will be eligible to participate in the trial if they were able to provide written informed consent to receive an HCV viremic organ. This consent process is already part of the standard of care across the transplant center. The consent form does outline that patients who become viremic after liver transplant, will need HCV treatment. The criteria for donor acceptance with respect to the quality of the donor organ, the geographic distance from the procurement center to the transplantation center, and procurement protocols will be determined by the transplant team. HCV-infected donors will be accepted for the trial before their HCV genotypes and quantitative hepatitis C viral loads were determined.

The study will enroll patients who are recipients of HCV viremic grafts. Per standard of care practice across the transplant center, patients will verbally consent for accepting HCV viremic organs once listed for transplant and the electronic medical record and the

United Network for organ Sharing (UNOS) national registry will reflect that. All patients who are listed and agree to accept HCV viremic grafts will be approached to enroll in this protocol and if they agree, a consent form will be singed. Per standard of care across the transplant center, those patients will sign a separate standard of care written consent form accepting those organs at time of the HCV viremic organ offer by the transplant team. For patients who agreed to participate in the study and will be receiving an HCV viremic graft, HCV pre-emptive will be initiated using Mavyret (Glecaprevir/ Pibrentasvir) and Zetia (ezetimibe) will be initiated. This is a pan-genotypic regimen with 98% sustained viral response and can be used in renal insufficiency and has a low side effect profile.

Preemptive treatment will be administered to the organ recipients for a total of 8 days, with the first dose administered upon call to the operative room. Treatment will be continued post transplantation on a daily basis for 7 days. Patient unable to take the pills by mouth, the pills will be crushed and introduced through the nasogastric tube. Bioavailability for this regimen when crushed and used through the nasogastric tube should be still acceptable. HCV RNA viral load will be checked on day 0, 1, 3, 7, and weekly for 13 weeks, and week 24 post-transplant, until two consecutive tests are positive. HCV antibody testing with reflex can be used on Day 0. Negative HCV antibody testing in that setting correlates with undetectable HCV RNA.

Labs will be recorded at Day 1, 3, 7, 14, 28 and week 6, 13, 28 and 1 year. Additionally, creatinine measurements will be documented at month 6. Immunosuppressant medications will be documented for both induction and maintenance for all transplants as well as primary and secondary diagnoses for transplant. Dates of cytomegalovirus (CMV) and/or polyomavirus hominis (BKV) will be documented on Month 3, 6 and year 1 if indicated as well as any rejections. Recipients and donor information will be collected on Day 0.

Table 1.0 Schedule of Events

	Day 0 Day of Transplant	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Week 2-13**	**Day 14, 28 and Week 6, 48**	**Week 13 / Month 3**	**Week 24 / Month 6**	**Year 1**
HCV antibody reflex lab (pre-transplant)	**X**												
HCV RNA lab	**X** + 1 day	**X** +/- 1 day		**X** +/- 1 day				**X** +/- 1 day	**X** +/- 3 days			**X** +/- 3 days	
Research Medication Pre-emptive treatment – study drug combination (8 days): MAVYRET and ZETIA	**X** **Pre-Op dose**	**X**	**X**	**X**	**X**	**X**	**X**	**X**					
Labs Creatinine, GFR, ALT, AST, Alkaline phosphatase, bilirubin		**X** +/- 1 day		**X** +/- 1 day				**X** +/- 1 day		**X** +/- 7 days	**X** +/- 15 days	**X** (creatinine only) +/- 15 days	**X** +/- 15 days

Secondary Endpoints Short term graft and patient survival checkpoint											**X** +/- 15 days	**X** +/- 15 days	**X** +/- 15 days

Patients who develop breakthrough viremia, defined as positive HCV RNA at least on two consecutive measurements after completion of 7 days of therapy, will be considered as failing the pre-emptive therapy intervention. Those patients will be treated per the standard of care protocol that already exists for patients with donor derived hepatitis C infection.

Secondary Use

The regimen within this protocol was adopted as standard of care based off of the interim results of the study. We plan to enroll 162 patients who have had this treatment clinically as standard of care. These participants who follow the schedule of activities in this protocol as clinical standard of care will have data from the schedule of activities added to a separate data repository from those who had this treatment performed as research. With the implementation of this treatment as standard of care the research consent for treatment is not required and patients whom have had consent collected clinically to the treatment identified in this protocol as standard of care will have a waiver of consent and an additional research consent will not be collected. No additional procedures outside of the clinical standard of care will be collected from these participants.

Plan of Recruitment

The option of accepting HCV viremic grafts will be discussed with patients during the transplant evaluation process. The selection committee, multi-disciplinary group, will review all patients undergoing transplant evaluation and will determine patient's candidacy for transplant.

Patients who are deemed candidates for transplant by the transplant selection committee and agree to accept HCV viremic grafts will be approached to participate in the study.

Interim Analysis

Interim analysis will be done after enrolling 10 patients. The interim analysis will assess the safety and tolerability of the treatment regimen and rate of breakthrough infection.

Publication Plan

The principal investigators hold primary responsibility for publication of the results of this study, and approval from the principal investigators must be obtained before any information can be used or passed on to a third party.

Safety Monitoring and Stopping Rules

The patients will be carefully monitored as per specific standard of care transplant protocol with labs and visits. The primary investigator will make the determination in regard to the clinical significance of abnormal lab results and whether it is related to study medications or study procedures. Any unexpected symptoms, lab abnormalities, or unexpected rise in HCV RNA levels will be brought directly to the attention of the primary investigators.

Throughout the course of the study, we will monitor adverse events and may suspend accrual if patients are experiencing a large number of adverse events. In particular, we will temporarily suspend accrual if at any time observed serious adverse events considered at least probably related to study treatment (i.e., an adverse event with attribute specified as possible, probable, or definite). AEs will be reported until 30 days after the last dose of IP. NOTE: Any death occurring greater than 30 days after the patient's last study treatment or procedure and deemed at least possibly related to that treatment or procedure will be reported

In addition, should discontinuation rate of the study drugs within their first week post transplantation exceeds 50%, we will temporarily suspend accrual to assess the reasons behind the discontinuation and the need for any modifications to help address this issue.

It should be noted that, if unexpected adverse event profiles are observed which do not meet any of the above criteria, but are nevertheless worrisome, we may still consider temporarily suspending accrual. Also, adverse event stopping rules may be modified if, during the course of the study, new information becomes available which suggests that such a modification is necessary, or if, after temporarily stopping accrual, the above rules are found to be overly conservative.

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