

JHM IRB - eForm A – Protocol

EXPANDER-1

Exploring renal transplants using hepatitis C infected donors for HCV-negative recipients

An open-label pilot study to determine the efficacy and tolerability of fixed-dose grazoprevir/elbasvir treatment in hepatitis C uninfected recipients of renal transplants from hepatitis C infected deceased donors

1. Abstract

Many individuals in need of a kidney transplant will die on the transplant waitlist before ever receiving a donor offer due to a national organ shortage crisis. At the same time, many high quality kidneys from hepatitis C infected (HCV+) donors are discarded every year because there is not a HCV+ candidate available to accept the organ. New HCV therapies are highly effective and well tolerated even in end stage renal disease with cure rates of nearly 100%. This is a single center open-label pilot interventional trial of hepatitis C therapy for 10 HCV-negative recipients of kidneys from HCV+-positive deceased donors at Johns Hopkins Hospital (JHH). Individuals who meet the inclusion criteria will be offered enrollment. Informed consent will be obtained by a physician on the study team and those who provide informed consent will be enrolled. All participants will be initiated on oral, once-daily, fixed-dose GZR-EBR starting at the time of transplant. Treatment adjustments will be made based on donor genotype information, as detailed below:

- Donor genotype 1a without NS5a resistance-associated variants (RAVs): GZR-EBR will be continued daily for 12 weeks
- Donor genotype 1a with NS5a RAVs at position 28, 30, 31 or 93: renally-dosed ribavirin will be added to GZR-EBV for 16 weeks from the day of treatment adjustment
- Donor genotype 2 or 3: Sofosbuvir (SOF) will be added for 12 weeks from the day of treatment adjustment

2. Objectives

Primary objective:

The objectives of this study are to evaluate the efficacy and tolerability of grazoprevir 100 mg/elbasvir 50 mg (GZR-EBR) treatment in HCV-uninfected transplant recipients (HCV R-) of a kidney from an HCV-infected deceased donor (HCV D+). GZR-EBR will be administered on-call to the operating room (OR) for the renal transplant procedure and continued for 12 weeks post-renal transplant. The primary efficacy outcome will be the proportion of HCV D+/R- renal transplant recipients with HCV plasma RNA less than the lower limit of quantification (< LLOQ) 12 weeks after end of treatment. The primary tolerability outcome will be the incidence of adverse events (AE) related to GZR-EBR.

Secondary objectives:

- Proportion of kidney transplant recipients who have HCV plasma RNA < LLOQ at 2, 4, 8 weeks after discontinuation of therapy.
- Proportion of kidney transplant recipients who become reactive for HCV antibodies following transplant
- Prevalence of NS5A resistance mutations in the HCV population from the deceased donors
- Measurement of interferon (IFN)-gamma inducible protein 10 (IP-10) a marker of acute hepatitis C infection.
- Kidney allograft function at 6 and 12 months following transplantation.

3. Background

Organ Shortage. Over 100,000 individuals are awaiting a life-saving kidney transplant in the United States, however due to a shortage of deceased donor organs, less than 17,000 kidney transplants are performed each year [1]. Depending on geography and patient characteristics, waiting times in the United States can be up to 10 years and more than half of individuals will die on the waiting list prior to receiving a kidney transplant.

Mortality on the Waitlist in Individuals Awaiting Transplantation. Overall mortality on the kidney transplant waiting list is on average 6 percent per year with significant variation depending on the region and patient characteristics. At Johns Hopkins in 2013, kidney transplant waitlist mortality for all individuals was 5% [1]. The death rate for older individuals or for individuals with diabetes is about 10% per year. Therefore, a patient > 60 years of age with an estimated wait list time of five years for a kidney has a 50% chance of dying before a kidney becomes available [2,3].

An Underutilized Source of Organs. Kidneys from hepatitis C-infected (HCV+) donors are currently underutilized. In 2013, 56% of kidneys from HCV+ deceased donors were discarded compared to 18% of kidneys from HCV-uninfected (HCV-) donors [1]. Many of these HCV+ organs are of excellent quality, but are frequently discarded due to a lack of HCV+ recipients [4].

Use of HCV+ Organs for HCV- Recipients. There was a small study performed in 2012 that provided kidneys from HCV+ deceased donors to elderly HCV- individuals on dialysis who had limited donor options. In this series, HCV donor to recipient transmission occurred in 7/13 (54%) of recipients. Of those who acquired HCV, elevations in transaminases occurred in 6/7 around month 3. There were no cases of acute fulminant hepatitis C. One HCV-related liver death occurred at 5 months post-transplant [5]. HCV treatment was not used in this study since only IFN-based treatments were available and IFN is contraindicated in kidney transplant recipients. Thus in the absence of any prophylactic HCV treatment, incident HCV infection occurred in about 50% of recipients of HCV+ kidneys and the majority did not have severe complications of the infection.

Currently Implemented Analogue: Infectious Risk Donors (IRDs). For individuals with high waitlist mortality, the lifesaving benefit of accepting an organ may outweigh the risk of acquiring an infection. In the past, standard donor screening used serology to detect infections such as HIV and HCV. Due to the biologic “window period” of approximately 6 weeks, where an infected individual will not have developed antibody, but can transmit infection, organs from donors who meet behavioral criteria, so-called “high risk” or infectious risk donors (IRDs), were discarded. This practice led to discarding more than 10% of deceased donor organs [4].

Our group at Johns Hopkins proposed screening IRDs with rapid nucleic acid testing screening to replace serologic screening for HIV and HCV in IRDs [5]. In addition, we designed a Markov decision model, to guide patients weighing the survival benefit against the potential risks of using an IRD [7]. This principle has been successfully put into practice and has safely provided organs

that would have otherwise been discarded to over 300 recipients of IRD kidneys at Johns Hopkins [8].

Direct Acting Antivirals as pre- and post-exposure treatment. The once daily fixed-dose combination of the NS3/4A protease inhibitor grazoprevir (GZR) and the NS5A inhibitor elbasvir (EBR) is highly safe and effective for the treatment of chronic HCV infection with sustained virologic response rates between 95-100% [9]. These drugs are not renally metabolized and therefore would be ideal in the early post-transplant period following a kidney transplant. We propose to use these medications as pre- and post-exposure treatment as a strategy to provide high quality HCV+ organs to HCV- recipients whose risk of dying on the transplant list is relatively high compared to their chance of receiving an HCV- organ.

4. Study Procedures

Screening phase: HCV- individuals on the kidney transplant waitlist at Johns Hopkins Hospital will be recruited and screened for eligibility. Individuals who are interested in the study will give informed consent. We will approach HCV- individuals on the deceased donor renal transplant wait list who meet the recipient inclusion criteria. Currently there are about 200 individuals meeting these criteria at JH. At JH approximately 50% of wait-list candidates currently will accept Infectious Risk Donors (IRDs). We anticipate a lower acceptance rate of HCV+ deceased donors and estimate a 10% participation rate. Therefore we estimate having a pool of at least 20 eligible screened participants. Once a patient signs a consent form, a unique baseline number will be assigned for identification purposes. The participant will be screened to identify if the participant is currently being prescribed any medications that are contraindicated to any of the study medication. If the patient is taking a medication that is contraindicated with the study medication or rescue therapies, the investigator will assess if the participant's medication can be safely discontinued or substituted prior to, or at the time of transplant. If the participant's prescribed medication cannot be safely discontinued or substituted then the participant will be removed from the study. Prior to transplantation, data on demographics (age, sex, race, etc), medical history, social history, and renal biopsy diagnosis will be collected.

HCV+ Donor Identification: Those who provide informed consent for the study, will have be listed in the United Network for Organ Sharing (UNOS) with a status of "willing to accept an HCV+ organ." The JHU transplant team will then receive HCV+ donor kidney offers for the study participant from Organ Procurement Organizations (OPO). If an HCV+ donor who meets the inclusion criteria is identified, the study participants will be offered the organ and if they accept, they will become an active treatment participant. A donor blood sample will also be obtained from the OPO for the purposes of this study. Currently, offering OPOs only perform a qualitative HCV RNA by nucleic acid testing – HCV quantification and genotyping are not performed on donors and no FDA approved assays exist for this indication in organ donors. Donor HCV RNA quantification and genotype will be performed in parallel with the transplantation and initiation of treatment. The OPO will ship a donor blood sample to Quest for HCV genotype using LiPA® assay HCV RNA quantification will be performed at JHH using COBAS AmpliPrep/COBAS TaqMan HCV v2.0 assays. Plasma will also be banked for future resistance testing if needed.

Active phase, transplant and treatment: At the time of transplant admission, kidney recipients will undergo the standard pre-operative work-up, including laboratory testing, chest X-ray, EKG, and urinalysis (if applicable). In addition, a sample for baseline HCV RNA quantification will be drawn. Donor and recipient crossmatch will be performed using T-cell and B-cell complement-dependent cytotoxicity crossmatch. In addition, quantitative assessment for the presence of donor specific antibody will be done by solid phase assay (Luminex) and confirmed to be below a flow positive level. Once a recipient and donor are deemed appropriate to undergo the kidney transplant and the

recipient is called to the OR, the initial dose of GZR-EBR will be administered (see treatment strategy below).

The deceased donor kidney transplant procedure will be performed in the standard manner under general anesthesia with appropriate monitoring lines. Intraoperative medications will include intravenous cefazolin, heparin, mannitol, and furosemide. Anesthetic medications including inhalational agents, muscle relaxant, narcotic pain medication, and other standard medications will be administered. Induction immunosuppression administered in the operating room will consist of intravenous Solumedrol (500 mg) and intravenous rabbit anti-thymocyte globulin (1.5 mg/kg) (Thymoglobulin, Genzyme). During the transplant operation a surgical drain(s), a ureteral stent, and a urinary catheter will be placed.

Postoperative care will be performed in the standard manner in a monitored step-down intensive care unit setting. Ongoing induction immunosuppression with daily Solumedrol and Thymoglobulin for three post-operative doses each will be administered. In addition, maintenance immunosuppressive therapy consisting of tacrolimus, mycophenolate mofetil, and prednisone will be initiated. Tacrolimus dosing will be adjusted to obtain a serum trough concentration between 7-10 ng/ml for the first three months postoperatively and then 6-8 ng/ml beyond three months. Mycophenolate mofetil will be administered in divided doses for a total dose of 1500-2000 mg daily. Prednisone will be initiated at a dose of 20 mg daily once the initial course of Solumedrol is completed and gradually tapered to 5 mg daily by 6-12 weeks.

Standard posttransplant prophylaxis strategies will be used in subjects for the prevention of opportunistic infections. These include trimethoprim-sulfamethoxazole (Bactrim) for pneumocystis pneumonia prophylaxis, valganciclovir for cytomegalovirus infection in cases of CMV seropositive donors and/or recipients, and clotrimazole for fungal prophylaxis.

Additional postoperative care will be performed in the standard manner and include intravenous fluids to replace urine output for the first 24 hours postoperatively. Early mobilization and ambulation will be encouraged. Diet advancement will start with clear liquids several hours after surgery and progress to a regular diet by approximately 24 hours after surgery. The urinary catheter will remain in place for 3 to 7 days after surgery depending on the condition of the patient's bladder at the time of the transplant operation. Surgical drain(s) placed at the time of the transplant procedure remain(s) in place until daily output is below 50 ml per day. The ureteral stent is removed by cystoscopy approximately 4 to 8 weeks after surgery.

Discharge from the hospital is typically between 7 and 10 days postoperatively-- once renal transplant function is established, the patient is tolerating a regular diet, having normal bowel and bladder function, and the subject has a satisfactory understanding of posttransplant care. During the hospitalization, teaching of transplant medications and planned follow-up will occur on several occasions. Included in this teaching will be the protocol medication and the follow-up labs and visits related to the study protocol.

Treatment strategy: The study participant will be admitted to the hospital and undergo standard recipient admission work-up. Once this is completed, crossmatch results are available, and relevant donor kidney information is available the first dose of GZR-EBR will be administered on call to the OR (typically 1-6 hours prior to the incision). Post-transplant, GZR-EBR will be continued daily at 10 AM to correspond with the inpatient daily dosing nurse medication administration. To ensure timely delivery daily at 10 AM, the first dose post-operatively may occur before but not after 24 hours. For example, if the participant received the first dose pre-transplant at 2:00 PM, the second dose will take place 20 hours later on post-operative day #1 at 10:00 AM. Most renal transplant

recipients are extubated in the operating room and able to take oral medications within eight hours after the transplant procedure. During the hospitalization GZR-EBR will be given once daily. If the subject requires hemodialysis in the post-transplant period due to delayed graft function, GZR-EBR will be given after dialysis on those days.

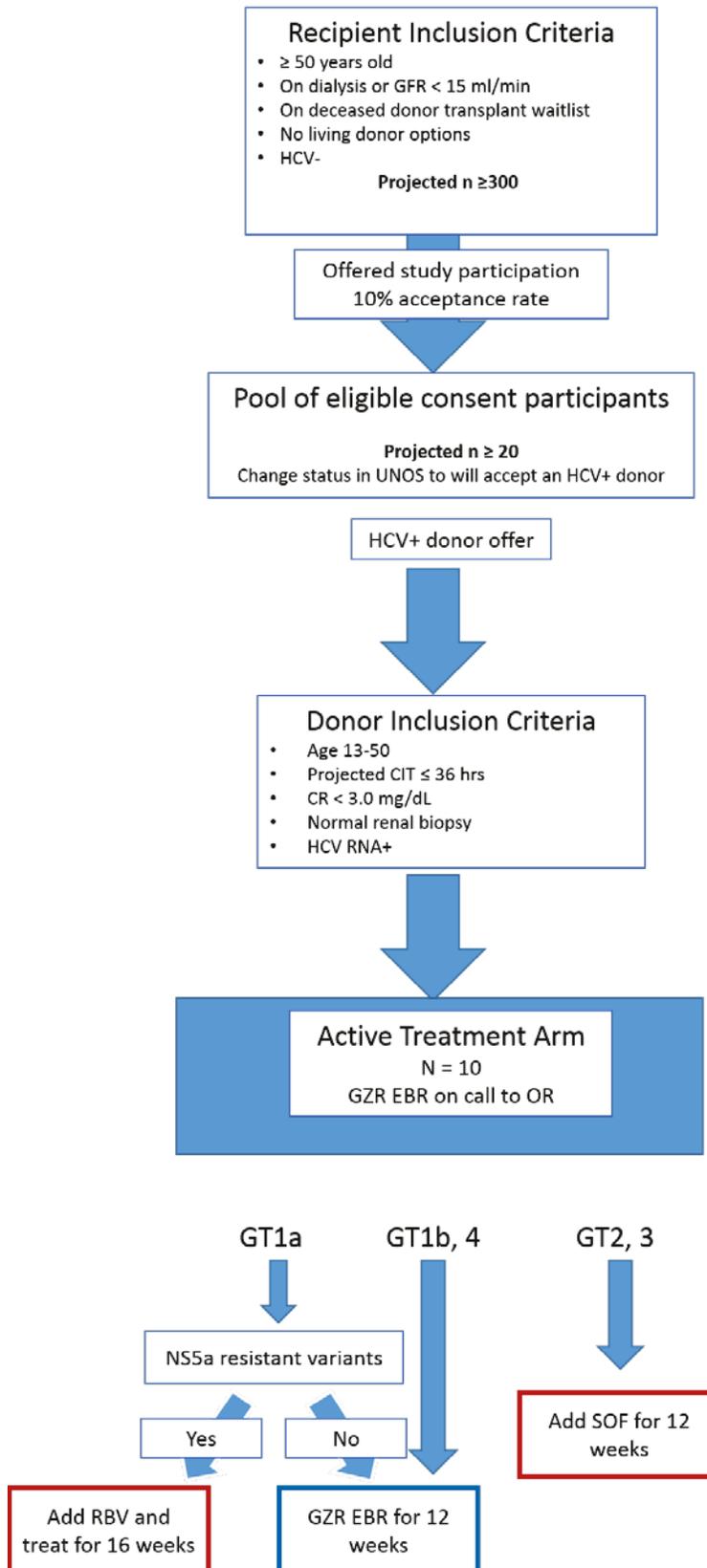
Treatment Adjustment: Donor HCV genotype will be performed by Quest Diagnostics. For HCV1a genotypes, Quest will reflexively perform an assay to identify NS5a resistant variants at positions 28, 30, 31 or 93. These assays are performed at least once weekly Tuesday through Saturday and the turnaround time is expected to be 4-7 days for genotype and between 7-14 days for resistance testing. We expect that the majority of HCV+ donors will have GT1 infection. For example, in the last 12 months for our liver transplant recipients, we used 12 HCV RNA+ donors. The donor HCV genotype is not tested by the United Network for Organ Sharing (UNOS). However, post-liver transplant, there is typically a genotype switch from recipient to donor; of these 12 transplants, the recipient genotype was 1a for 10 and 1b for 2 post-transplant, indicating that 100% of donors were genotype 1.

We have planned for treatment adjustment in the following scenarios i) the donor is found to have genotype 2 or 3 infection ii) the donor is found to have genotype 1a with NS5a resistant variants detected at positions 28, 30, 31 or 93 or iii) there is HCV viral breakthrough defined as an HCV RNA detected at > 100 IU/mL after previously being < LLOQ, confirmed on repeat testing. In these cases of donor genotype 2 or 3 or HCV breakthrough on treatment, sofosbuvir will be added to GZR/EBR and treatment will be extended to complete 12 weeks of triple therapy. SOF/GZR/EBR for 12 weeks has been shown to be an effective strategy in genotype 3 infection [10]. For cases where genotype 1a with RAVs at position 28, 30, 31 or 93 are identified, renally dose-adjusted ribavirin will be added and treatment will be for 16 weeks, starting from the day ribavirin was added.

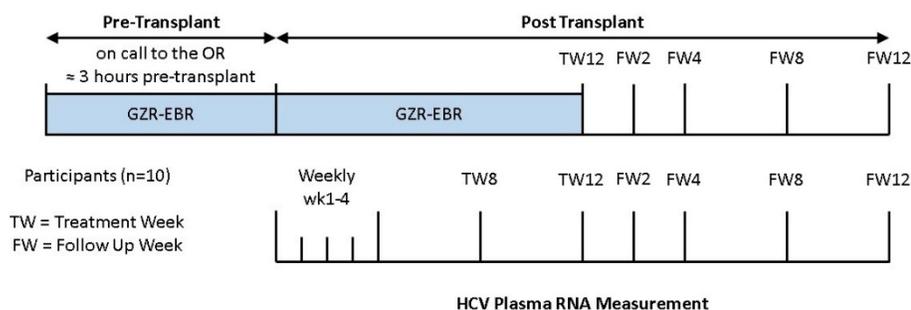
There may be instances where an HCV genotype may not be obtained. The most common reasons for failure to genotype are insufficient viral load, mutations in the viral genome at the assay priming sites, and presence of inhibitory substance in the sample. If a genotype cannot be obtained the participant will continue to be treated with GZR-EBR alone.

Study visits: Study visits will occur at day 0, POD1, 2, 3 and treatment weeks 1, 2, 3, 4, 8, 12, and follow up weeks (FW) 2, 4, 8, and 12. If treatment adjustments are required and treatment is extended beyond 12 weeks, the FW 2, 4, 8 and 12 will be moved up to correspond to week 2 off treatment, week 4 off treatment etc. Post-transplant data collection will include the laboratory data indicated in the Schedule of Events table, and we will also collect immunosuppression regimen, tacrolimus trough, creatinine level, acquisition of opportunistic infections, graft survival and patient survival. Allograft biopsies will be performed at any other point there is concern for rejection. Rejection will be classified by the Banff criteria.

Screening and enrollment



Treatment strategy



Schedule of events

	Baseline	POD 1	POD 2	POD 3	TW 1-4	TW 8	TW12	FW2	FW4	FW8	FW12
Donor HCV genotype ^a	X										
Donor HCV RNA ^b	X										
Recipient HCV RNA ^b	X	X			weekly	X	X	X	X	X	X
Recipient HCV Serology ^c	X										X
Recipient Hematology ^d	X	X			X	X	X	X	X	X	X
Recipient Chemistry ^e	X	X			X	X	X	X	X	X	X
Recipient Physical exam	X	X			X	X	X	X	X	X	X
Immunology Studies	X		X	X		X					

POD1 post operative day 1; TW treatment week; FW follow up week

^a HCV genotype and for genotype 1a specimens NS5A resistance variants will be determined using Quest Diagnostics LiPA® assay and NS5A subtype sequencing respectively. ^bHCV RNA will be measured using the Roche COBAS Ampliprep TaqMan HCV Test, v2.0

^cHCV antibody testing Advia Centaur (Siemens)

^dHematocrit, Hemoglobin, platelet count, red blood cell count, white blood cell count with differential – standard of care

^eAlanine aminotransferase, aspartate aminotransferase, albumin, alkaline phosphatase, creatinine, total bilirubin, glucose, lipase, potassium, sodium, and gamma-glutamyl transferase – standard of care

Outcome

The primary outcome will be the proportion of kidney transplant recipients with undetectable plasma HCV RNA at 12 weeks after stopping treatment. Secondary outcomes will include detection of HCV antibodies, allograft function at 6 and 12 months, measurement of IP10 levels to determine whether established infection occurred and was treated or whether this strategy prevented infection. If there are transplant recipients with detectable plasma HCV RNA after treatment or if there is viral breakthrough on treatment, we will measure prevalence of NS5A mutations in HCV from the donor plasma, which will be banked for this purpose.

Immunology Studies:

Antithymocyte globulin which is used as immunosuppression after kidney transplant may impact T cell responses irrespective of HCV donor status. In order to control for this, we will measure T cell responses to hepatitis C peptides at baseline and 8 weeks after kidney transplant in 5 HCV-uninfected patients who are undergoing standard kidney transplant from an HCV-uninfected donors. These responses will be used as a comparison for T cell responses pre- and post-kidney transplant with study participants from this study who have received an HCV+ kidney donor transplants.

Data Collection Mechanism. Data collection will be performed using REDCap. All data in REDCap will be de-identified. We will maintain a record of which subject corresponds to subject numbers assigned by REDCap, and this file will be password protected if electronic or kept in a locked location if in the subject binder.

Data monitoring: Upon enrollment of subjects, the REDCap database constructs a calendar of anticipated events, which includes completion of follow-up case report forms, with electronic reminders. Planning for a data and safety monitoring board and monitoring of the study for compliance with Good Clinical Practice and the study protocol. An independent Data and Safety Monitoring Board (DSMB), will review the protocol for study design and issues of Human Subjects protection prior to study implementation. The DSMB will conduct interim administrative, statistical, and safety reviews at least annually. Additional interim evaluations of accrual, safety, and/or endpoint data will be scheduled as necessary. We will provide study reports to the DSMB as requested.

Adverse Experience Reporting

Adverse experience reporting will follow the requirements outlined below. Adverse events will also be recorded and tracked in a safety monitoring database by the investigators. Serious adverse events will be reported to the Institutional Review Board at Johns Hopkins University according to IRB guidelines and to the sponsor.

Participants undergoing solid organ transplantation will be expected to have frequent adverse events (AEs) related to the organ transplant surgery and immunosuppressants which are not the subject of this protocol. This protocol focuses on the use of GZR-EBR. Grade 3 and Grade 4 AEs and SAEs related to the use of GZR-EBR will be collected.

All Grade 3 or 4 AEs and all SAEs will be reviewed by the principal investigator as they occur in a timely manner. All serious adverse events (SAEs) will be reported to the IRB. Grade 3 or higher AEs that are possibly or definitely related to GZR-EBR will be reported to the IRB.

In addition, we will report to the IRB any new HCV infection in the organ recipient within 1 week of identifying the new infection.

Adverse Event (AE) Definition

Any untoward or unfavorable medical occurrence associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Participants or Others and Adverse Events (1/15/07)" <http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2>)

For this study, an adverse event will include any untoward or unfavorable medical occurrence associated with, but not limited to:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study
- Intercurrent illnesses
- Infections
- Abnormal laboratory values (significant shifts from baseline within the range of normal that the investigator considers to be clinically important)
- Clinically significant abnormalities in physical examination, vital signs, weight, and/or tests and procedures
- Surgical complications

Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator it results in any of the following outcomes (21 CFR 312.32(a)):

1. Death.
2. A life-threatening event: An AE or SAR is considered “life-threatening” if, in the view of either the investigator, its occurrence places the participant at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Grading and Attribution of Adverse Events

AEs will be graded according to the criteria set forth in the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. This document (referred to herein as the NCI-CTCAE manual) provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all adverse events.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

- Grade 1 = mild adverse event.
- Grade 2 = moderate adverse event.
- Grade 3 = severe and undesirable adverse event.
- Grade 4 = life-threatening or disabling adverse event.
- Grade 5 = death.

Events grade 3 or higher that are possibly or definitely related to study procedures or intervention will be collected on AE case report.

Attribution Definitions

The relationship, or attribution, of an adverse event to the study intervention or study procedures will initially be determined by the investigator. For additional information and a printable version of the NCI-CTCAE manual, consult the NCI-CTCAE web site:

<http://ctep.cancer.gov/reporting/ctc.html>.

1. Unrelated: The adverse event is clearly not related: there is insufficient evidence to suggest a causal relationship.
2. Possibly related: The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
3. Definitely related: The adverse event is clearly related.

Collection and Recording of Adverse Events

Serious adverse events will be collected from the time of first dose of study medication until a participant completes study participation or until 30 days after he/she prematurely withdraws (without withdrawing consent) or is withdrawn from the study. Grade 3 or higher AEs will be reviewed by the investigator and will be reported if they are possibly or definitely related to the study medication.

Collecting Adverse Events

Adverse events (including SAEs) may be discovered through any of these methods:

- Observing the participant.
- Interviewing the participant [e.g., using a checklist, structured questioning, diary, etc.]
- Receiving an unsolicited complaint from the participant.
- In addition, an abnormal value or result from a clinical or laboratory evaluation can also indicate an adverse event, as defined in Section 12.3, Grading and Attribution of Adverse Events.

Recording Adverse Events

Throughout the study, the investigator will review all grade 3 or higher AEs and if potentially related to a study medication and will report them to the IRB. All SAEs will be reported to the IRB.

Once reported, an AE/SAE will be followed until it resolves with or without sequelae, or until the end of study participation, or until 30 days after the participant prematurely withdraws (without withdrawing consent)/or is withdrawn from the study, whichever occurs first.

Any AEs lower than grade 3 are exempt from Reporting

5. Inclusion Criteria

Recipient Inclusion Criteria

- Participants ≥ 50 years old
- On the deceased donor kidney waiting list at Johns Hopkins Hospital
- Awaiting a first kidney transplant
- No available living kidney donors
- On hemodialysis or peritoneal dialysis or stage 5 CKD defined as a glomerular filtration rate < 15 ml/min for the past 3 months
- HCV-uninfected (by both antibody and RNA PCR) and without any behavioral risk factors for contracting HCV other than being on hemodialysis.
- Calculated panel reactive anti-HLA antibody (cPRA) below 20 percent
- Female who is:
 - practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle)
 - sexually active with female partners only
 - not of childbearing potential, defined as:
 - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone (FSH) level indicating a postmenopausal state), or

- surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s);
- of childbearing potential and sexually active with male partner(s):
 - currently using at least one effective method of birth control at the time of screening and agree to practice two effective methods of birth control while receiving study drug (as outlined in the participant information and consent form starting with Study Day 1 and for 30 days after stopping study drug, or for 6 months after stopping study drug if receiving RBV (Note: Estrogen-containing hormonal contraceptives, including oral, injectable, implantable, patch and ring varieties, may not be used during study drug treatment).
- Males who are not surgically sterile and are sexually active with female partner(s) of childbearing potential must agree to practice two effective forms of birth control (as outlined in the participant information and consent form) throughout the course of the study, starting with starting with Study Day 1 and for 30 days after stopping study drug, or for 6 months after stopping study drug if receiving RBV.

Recipient Exclusion Criteria

- Plan to receive a multi-organ transplant
- Plan to receive a dual kidney transplant (including en bloc)
- Prior solid organ transplant
- Participating in another study that involves an intervention or investigational product
- Plan to receive a blood type incompatible kidney
- History of human immunodeficiency (HIV), hepatitis C (HCV), or active hepatitis B (HBV) infection defined as being on active antiviral treatment for HBV, a detectable hepatitis B surface Ag or detectable hepatitis B DNA
- Active or unresolved bacterial, viral, or fungal infection that is clinically significant
- History of cirrhosis or pre-existing liver disease such as non-alcoholic steatohepatitis
- History of illicit drug use or alcohol abuse within 12 months prior to screening
- Unable to safely substitute or discontinue a medication that is contraindicated with the study medication or rescue therapies.
- Psychiatric or physical illness that in the opinion of the investigator would make it unsafe to proceed with transplantation or interfere with the ability of the subject to participate in the study.

Donor Inclusion Criteria

- Donor age 13-50 years
- Donation after brain death or donation after cardiac death donor
- Projected cold ischemia time of 36 hours or less
- Terminal creatinine less than 3.0 mg/dL
- No evidence of significant chronic pathologic findings on pre-implantation biopsy
- HCV RNA PCR+

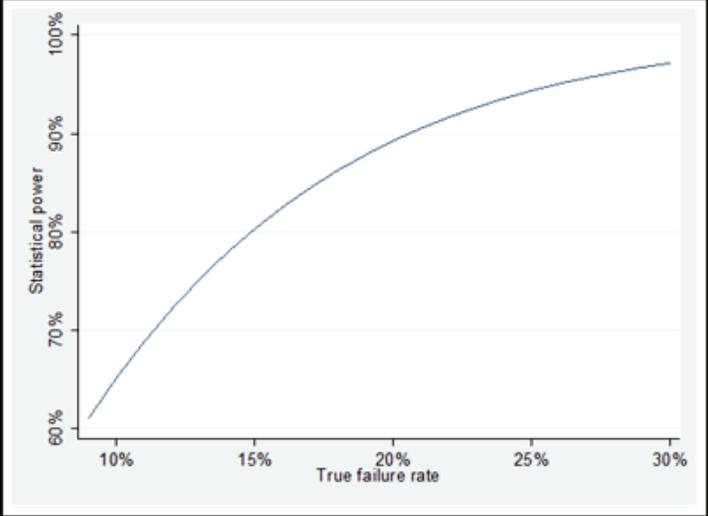
6. Drugs/ Substances/ Devices

Drug will be provided by Merck. The Johns Hopkins Research Pharmacy will have responsibility for filling and labeling individual patient containers. Grazoprevir/Elbasvir orally (100/50 mg) will be initiated on call to the operating room (OR) for kidney transplantation. Dosing will be continued every 24 hours post-operatively through 12 weeks after transplantation.

7. Study Statistics

We hypothesize that the treatment strategy will be 100% effective and that the HCV RNA < LLOQ in all 10 patients. Given that this is a pilot study with no comparison group, the power to detect a

difference depends on the true efficacy. For example if the true efficacy is 79%, then we will have at least one observed outcome 90.53% of the time ($1 - .79^{10}$). The figure demonstrates the relationship between the true efficacy and the power of the proposed study.



8. Risks

Although it has not been reported, due to acute infection with hepatitis C, there is a slight risk of acquiring hepatitis C, fulminant hepatitis, and death.

Grazoprevir and Elbasvir

The most common side effects with these study drugs are fatigue, headache, nausea, muscle weakness, diarrhea, joint pain, and insomnia. In rare cases, the study drugs have been associated with changes in the way the liver functions.

Ribavirin

The most common side effects when taking ribavirin are flu-like symptoms consisting of, body aches and pains, fever, chills, headache, rash, or an overall feeling of sickness. Other common side effects are anxiety, mood changes, depression and irritability. The most serious side effect seen with ribavirin is anemia (a decrease in the number of red blood cells in your body that carry oxygen). This may cause tiredness and lack of energy. Ribavirin can cause severe damage and even death of an embryo or fetus (see risks related to pregnancy).

9. Benefits

There may be no direct benefit to subjects in this study, but an understanding of this treatment regimen will be of benefit to transplant patients in the future. Subjects may benefit from the increased pathology testing in this study.

10. Payment and Remuneration

Subjects will be paid \$25 plus a parking vouchure for each study visit.

11. Costs

This study is funded by Merck Research Laboratories.

12. References

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