Partners Human Research Committee Detailed Protocol

Title: Pan-genotypic direct acting antiviral therapy in donor HCV-positive to recipient HCV-negative liver or simultaneous liver-kidney transplant

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I. Background and Significance

In the United States the prevalence of patients with end stage liver disease (ESLD) in need of transplantation has continued to rise, while the number of annual transplants performed has remained unchanged over the last decade. Donor liver availability continues to be the limiting factor. As this definite shortage of transplant viable organs in the U.S. continues, it is of paramount importance that available resources are handled efficiently; namely, that all transplantable organs are recognized for their enormous value as scarce resources and utilized to their maximum potential for the maximum benefit (the principle of Utility).

Hepatitis C virus (HCV)-positive organs have been used successfully for liver transplantation into HCV-positive recipients for years. In HCV-positive recipients, the outcome of HCV-positive liver transplantation is identical to transplantation using non-infected organs. An advantage of using HCV-positive organs is a potential decrease in wait time and waitlist mortality. In addition, as a result of the opioid epidemic currently plaguing the young demographic, the quality of HCV-positive donor organs is often better than other extended criteria organs, as many derive from youthful donors, age 18 to 35, following drug overdoses.

The use of HCV-positive organs is increasing in the era of safe, well tolerated, oral antiviral therapy with high cure rates. Previously, recurrent infection in the allograft, including fibrosing cholestatic HCV, with high viral loads and accelerated allograft damage were significant concerns. In addition, in the setting of immunosuppression, the potential for transplant recipients with HCV infection to experience an increase in opportunistic infections, new onset diabetes mellitus, post-transplant extra-hepatic neoplasia, and adverse effects of HCV on patient and graft survival also limited the number of HCV-donor organ transplants performed. However, these risks were determined prior to the current era of HCV treatment and were associated with untreated infection or interferon therapy. Now that HCV is largely curable following transplantation, we anticipate that many of these complications can be avoided with timely treatment.

Direct acting antiviral agents (DAAs) have dramatically improved treatment options and outcomes for patients with HCV in both the pre- and post-transplant setting. SOLAR-1 was a large, multicenter, randomized controlled trial of sofosbuvir/ledipasvir (SOF/LED) with weight-based ribavirin in 223 liver-transplant recipients infected with HCV genotypes 1 and 4, with a wide range of liver disease severity. The cure rate for 12 weeks of combination therapy was 96%. In patients with HCV without cirrhosis in the allograft, cure rates of many DAA regimens have been reported in the range of 95% or higher. The discontinuation rate for these medications is low and side effects rare. Importantly, the sofosbuvir-based regimens do not have major interactions with the commonly used post-transplant immunosuppressive regimens.

The daily, fixed-dose, of co-formulated sofosbuvir/velapatasvir (SOF/VEL) is similarly effective to its predecessor SOF/LED but has pan-genotypic activity. It is currently recommended as a first-line therapy for treatment-naïve, noncirrhotic HCV infection for genotypes 1-5. Reported cure rates in the non-transplant setting have been high in the 98-100% range. In the ASTRAL-1, ASTRAL-2 and ASTRAL-3

studies, more than 1,000 patients have been treated with SOF/VEL with an overall cure rate of 98%, without safety or tolerability concerns in the post-transplant setting.

In light of these recent advances in HCV therapy, we believe that DAAs have the potential to play an important role in curtailing the current discard rates for HCV-positive donor livers. In this study we plan to administer DAA therapy in donor HCV-positive to recipient HCV-negative liver transplantation. We plan for use of SOF/VEL in this study. The advantage of SOF/VEL as compared to other DAAs is that is has pan-genotypic activity. This avoids the need for rush donor genotyping, and prevents losing potential good-quality organs that are infected by a genotype not covered by the other antiviral drugs that lack pan-genotypic activity.

In the fall of 2017 an additional pan-genotypic regimen, glecaprevir/pibrentasvir (GLE/PIB), trade name Mavyret, was FDA approved. The Magellan-2 study demonstrated the safety and efficacy of GLE/PIB in liver transplant adults with chronic HCV infection. We updated our initial protocol to allow for inclusion of this additional pan-genotypic agent. SOF/VEL and GLE/PIB are both pan-genotypic regimens planned for use in this study.

A subset of patients awaiting liver transplant also require kidney transplant. The efficacy of DAAs in the treatment of donor derived HCV infection in kidney transplant has been documented in recent trials at the University of Pennsylvania and John's Hopkins Hospitals (THINKER and EXPANDER trials respectively). Given this recent data, patients requiring simultaneous liver-kidney transplant (SLKT) are also being considered for enrollment in this study.

II. Specific Aims

Primary Objective **-**
Aim 1a
Determine if preemptive administration of pan-genotypic direct-active antiviral (DAA) therapy in liver transplantation prevents the development of chronic hepatitis C virus (HCV) infection from a viremic HCV-positive donor liver to an HCV-negative recipient patient.
Aim 1b
Determine the rate of HCV transmission in patients receiving an HCV-antibody positive RNA-negative (non-viremic) donor liver, and evaluate the efficacy of DAA therapy when administered through a reactive approach, following viremia development.

Secondary Objectives **- Aim 2-3**
Aim 2
Evaluate the safety and tolerability of pan-genotypic DAA therapy in patients undergoing liver transplantation.
Aim 3
Determine the proportion of subjects with undetectable serum HCV RNA at study day 0, 1, 3, 7, 14, 28, 42, 56, 84, 112, 168, 252, and 365 in liver transplant recipients receiving pan-genotypic DAA therapy following transplant from an HCV infected donor.

Clinical hypotheses
Hypothesis 1.

We hypothesize that administration of pan-genotypic DAA therapy following liver transplantation will be well-tolerated and halt the development of chronic HCV infection in a transplant recipient as evidenced by a negative HCV viral RNA at 12 weeks post treatment.

Hypothesis 2.

We hypothesize that administration of pan-genotypic DAA therapy after HCV-positive donor liver transplantation will produce non-inferior survival results in recipient patients as compared to historical Scientific Registry of Transplant Recipients (SRTR), Organ Procurement and Transplantation (OPTN), and United Network for Organ Share (UNOS) data.

III. Subject Selection

- Cohort study (N=300)

This is a single center study for the donation of HCV-positive livers to HCV negative recipient patients, with interventional treatment to prevent the development of chronic HCV infection following transplantation. Up to 300 patients will be enrolled study wide, with 50 total patients receiving transplant and treatment with study drug. We plan to enroll all 300 subjects and perform all 50 transplants at MGH.

Patients will be selected based on the severity of their disease, overall prognosis, and diminished likelihood of receiving a liver from the waitlist. This will be determined in part through use of a patient's MELD score, listing status, and clinical judgment. Patients who are already being consented for extended criteria donor organs as part of their transplant evaluation will be considered for enrollment in this study; this will include patients with MELD scores greater than 20 or patients with significant morbidity associated with their end stage liver disease. To ensure maximal benefit for the recipient, only high quality donor livers will be accepted. Both in-person and remote written informed consent will be conducted in accordance with current Partners policy. Additionally, for this study, we (study staff) will implement the Mass General Brigham REDCap (Research Electronic Data Capture) eConsent as an option for obtaining and documenting remote written consent.

1. Donor Inclusion/Exclusion Criteria

1a. Donor Inclusion Criteria:

Donor is HCV antibody positive or has active HCV infection
Organ is otherwise acceptable for transplantation per usual evaluation

1b. Donor Exclusion Criteria:

Donor is known to have previously received HCV treatment (interferon, ribavirin or DAA)
Liver disease or signs of liver decompensation noted during recovery (splenomegaly, ascites, advanced fibrosis or cirrhosis)
Any standard contra-indication to donation noted in donor (significant malignancy, infection with human immunodeficiency virus (HIV), unusual infection, etc).

2. Recipient Inclusion/Exclusion Criteria

2a. Recipient Inclusion Criteria:

Recipient is Age ≥ 18 years and ≤ 70 years at time of enrollment
Met MGH transplant center criteria, listed for liver transplant

2b. Recipient Exclusion Criteria:

Any contra-indication to liver transplantation per center protocol
Pregnant or nursing (lactating) women

HIV positivity
For study patients in whom Mavyret™ therapy is being considered, exclusion criteria includes patients on the following medications who cannot stop therapy: carbamazepine, rifampin, St. John's wort, and ethinyl estradiol-containing oral contraceptives.

For any patient receiving pan-genotypic DAA therapy, the corresponding drug administration instructions will be followed as listed in the Mavyret™ package insert. This includes review of potentially significant drug interactions and discontinuation or alteration in dosages and monitoring as recommended. The Tables that will be followed can be found on the Mavyret™ package insert pg. 8 Table 5.

A subset of patients awaiting liver transplant also require kidney transplant. The efficacy of DAAs in the treatment of donor derived HCV infection in kidney transplant has been documented in recent trials at the University of Pennsylvania and John's Hopkins Hospitals. Given this recent data, patients requiring simultaneous liver-kidney transplant (SLKT) are being considered for enrollment in this study. If patients screened for enrollment meet inclusion criteria for liver transplant, they will ***not*** be excluded based on the need for SLKT. Their case will be discussed with the study's transplant nephrologist, and enrolled accordingly with plans to update UNET listing status for SLKT transplant. As far as DAA therapy is concerned, if a patient is already undergoing treatment based on receipt of an HCV-positive liver, there are no changes in Mavyret™ therapy duration that would be required if a kidney transplant is also performed. In patients receiving SLKT, a patient's renal function and potential for delayed graft function (DGF) will come into play when initiating DAA treatment..

Standard of care at Partners includes confirming that female patients are not pregnant at the time of organ transplantation. For women of childbearing potential, a urine pregnancy test will be performed as needed per standard of care prior to enrollment. A negative result will be required at the time of transplant and prior to continuing study treatment.

As part of standard transplant protocol, potential transplant recipients will be screened for Hepatitis B virus (HBV) infection and managed per guidelines. As part of standard protocol, donor livers will also be screened for hepatitis B virus (HBV) infection through HBV surface antigen, surface antibody, and core antibody testing. In patients who test positive for core antibody (anti-HBc), further close monitoring and/or treatment with HBV therapy will be initiated as per protocol algorithm. See protocol attachment algorithm 'HBV Monitoring'. In addition, for all patients who are core antibody positive, scheduled HBV viral load testing will occur alongside HCV viral load testing while on DAA therapy; additional draws will occur on an as needed basis.

IV. Subject Enrollment

This is a proof of concept, single center study for the donation of HCV-positive livers to HCV-negative recipients, with interventional treatment to prevent the development of chronic recipient HCV infection following transplantation.

A study clinician investigator (physician and/or nurse practitioner and/or physicians assistant) will obtain informed consent. The consent form and protocol will be reviewed with the potential subject and any questions will be answered. During in person informed consent, the subject may be seen in a private area located in the Hepatology or Transplant Clinic. Patients will have as much time as they feel necessary to review study consent. Subjects will have the option to take the consent form home with them to decide whether or not they wish to participate.

Ability to provide informed consent will be determined by the study investigator in discussion with the subjects treating physician. Encephalopathy occurs in patients with end stage liver disease and can limit a patient's ability to provide thorough informed consent. In cases where it is felt a patient cannot provide informed consent, surrogate consent for enrollment in this study will be obtained.

The PHRC preferred order of surrogates will be followed as outlined below, and the Investigator will document the relationship of the surrogate to the subject in the research records.

The following categories of surrogates (listed in general order of preference) may provide consent in writing on behalf of individuals incapable of providing informed consent:

i. court appointed guardian with specific authority to consent to participation in research or authority to make healthcare decisions for a class of diagnostic and therapeutic decisions inclusive of the proposed research
ii. health care proxy/person with durable power of attorney with specific authority for making health care decisions inclusive of the proposed research
iii. spouse, adult child, or other close family member who knows the subject well and has been involved in their care

Assent of subjects will be a requirement for participation in the research unless the subject is incapable of giving assent due to his/her medical condition. If the individual objects to participation, s/he should not be enrolled. When surrogate consent is relied upon, the Investigator must ensure that the surrogate understands that his or her decisions should be based on "substituted judgment." This means that the decision reflects a potential subject's own views when s/he had the capacity to express them. If a potential subject did not previously express a view on the matter, the surrogate should make the decision based on the potential subject's best interests.

V. Study Procedures

Prior to enrollment in the study, research staff will be working with patient insurance to confirm that the patient insurer will be covering the cost of HCV treatment. In the event that insurance does not agree to cover the cost of HCV DAA therapy, the cost of medication will be covered by pre-established hospital funds.

Day 0 is the day of transplantation. Detailed outline of information, studies, and labs obtained throughout enrollment is outlined in Appendix 1 (Schedule of Events) .

Full biochemical profiles of the patient will be performed at various stages throughout the study. On-treatment safety monitoring review of labs obtained as post-transplant standard of care, including baseline LFTs, BMP, and CBC.

Targeted physical assessment, vital sign measurements, emergence of treatment related adverse events and concomitant medication usage will be assessed throughout the study period and as needed at the time of any unscheduled contact during the 84 day study period and/or the 365 day post-dosing safety follow-up.

The **screening visit** will take place within an estimated 1-week to 6 months prior to liver transplantation. For all patients enrolled in the protocol, their transplant case will be reviewed on a weekly, bi-weekly, or monthly basis based on MELD and position on the waitlist as per usual active transplant waitlist patient management.

Day 0 represents the day of liver transplantation; study DAA treatment will be initiated within 7 days of liver transplant. After initiation of therapy, each subject will receive their study drug daily through 12-week course completion.

Patients will initially provide in person or remote written informed consent to be "waitlisted" for HCV-positive donor livers under this protocol. At the time a liver transplant becomes available, the "waitlisted" patients will be contacted and again sign informed consent for transplantation (standard of care surgical consent).

Upon receiving notification that an HCV-antibody (Ab) positive donor organ is available, we will review if the organ is nucleic acid testing (NAT) positive or negative. A pre-emptive treatment approach will be used in patients receiving NAT-positive donor organs, and a reactive treatment approach will be performed in patients receiving NAT-negative donor organs, as outlined below:

A study patient who receives an HCV NAT-negative donor liver (or liver and kidney) will be followed with HCV viral load (VL) testing per study protocol on study days 0, 1, 3, 7, 14, 28, 42, 56, 84, 112, 168, 252, and 365. Additional monitoring will be obtained if needed based on new LFT abnormalities.

- If the study patient does not develop a positive VL during this 365 day duration they will not undergo treatment with DAA therapy.
- If the study patient does demonstrate seroconversion with a newly positive HCV VL then we will initiate pan-genotypic therapy per study protocol.

Upon receiving notification that an HCV-positive donor organ is available with plans for transplantation, a patient's case will be reviewed and the appropriate DAA selected based on individual patient factorsthe study subject will be scheduled to receive treatment with the below pan-genotypic DAA:

- co-formulated glecaprevir (300mg)/pibrentasvir (120mg) (Mavyret™) given orally for a duration of 12 weeks post-transplantation.

Serum pregnancy tests (for all females of childbearing potential) will be conducted at screening and performed immediately prior to transplantation for all women of reproductive age as per transplant standard of care. Because the effect, if any, of Mavyret™ on an embryo or fetus (developing baby still in the womb) is not known, patients may not participate in this study if they are pregnant, breastfeeding, or planning to become pregnant. **Females** who are able to become pregnant must agree to use adequate birth control -throughout the duration of the study. For the purposes of this study, adequate birth control means one of the following:

1. Intrauterine device (IUD)
2. Condom with spermicide
3. Diaphragm with spermicide
4. Complete abstinence (not having sex at all)

Hormonal forms of birth control including birth control pills, vaginal rings (like NuvaRung), implants (like Implanon), or injections (like Depo-Provera) may not work during treatment with Mavyret™ and are not on the acceptable forms of birth control list. After patients have been off Mavyret™ for at least two weeks, they can again begin to use a hormonal form of birth control.

Men enrolled in the protocol must also agree to use adequate contraception while participating in this study. Adequate contraception is:

1. Condom with spermicide, and
2. Female partners must use an approved method of birth control as listed above

Men must also agree that they will not donate sperm during the entire study period.

Donor genotyping – HCV genotyping will be performed by MAYO sendout and/or by New England Donor Services. Because the treatment in this study is pan-genotypic, we do not need genotype results to return prior to medication administration; delays in HCV genotyping will not influence initiation of the study drug.

Drug to be used. As the DAA therapy used in this study may be given preemptively before donor genotype is known, the ideal medication would provide universal coverage of all potential genotypes. The two currently available, FDA approved pan-genotypic regimens are co-formulated sofosbuvir (400 mg)/velapatasvir (100 mg) (Epclusa®) and co-formulated glecaprevir (300mg)/pibrentasvir (120mg) (Mavyret™). For the purposes of this study, Mavyret will be utilized as the DAA of choice and once initiated, will be given orally for a duration of 12 weeks post-transplantation.

Achievement of Sustained Virologic Response (SVR). Patients who received an HCV-positive donor liver who have an undetectable viral load 12 weeks after completing therapy (SVR 12) are liver recipient patients in whom the use of DAA treatment has successfully prevented the development of chronic HCV infection. If during monitoring while on DAA therapy a positive viral load is detected, a plan may be made to extend the patient's course of Mavyret™ beyond 12 weeks. We may also add additional Hep C medications to increase the chance of curing HCV infection. If this happens, we will plan to review all of these details in person with the patient and determine, based on recent updates and clinical practice, the best regimen with which to treat the patient and achieve HCV cure.

The detailed protocol version of this study dated 3/13/2017 was reviewed by the food and drug administration (FDA). It was found that preemptive treatment with DAA therapy for donor HCV positive to recipient HCV negative liver transplant was determined to be IND exempt; this exemption letter has been uploaded to insight.

VI. Biostatistical Analysis

Variables/Time Points of Interest
The primary variable of interest will be HCV RNA at the multiple time-points assessed during and after treatment.

The primary efficacy outcome "prevention of HCV infection in liver recipient" will be determined by a negative HCV RNA test at 12 weeks following therapy completion (SVR 12).

The safety outcomes include summation of treatment related adverse events and transplant rejection or patient mortality. On treatment eGFR, proteinuria, hemoglobin, and liver function tests will be summarized to assess safety.

Statistical Methods
Patient characteristics for this cohort (N=50) will be presented with summary statistics for baseline demographics and clinical variables. The SVR12 rate will be presented and 95% CI constructed with the exact test. Mean and standard deviation for on-treatment laboratory values will be presented to analyze safety.

Power/Sample Size:
This is a pilot study. Up to 300 patients will be enrolled (consented for the possible receipt of an HCV-positive organ), the total number of patients eligible to receive transplant and study drug = 50.

VII. Risks and Discomforts

Psychological risk
Participation in research may result in undesired changes in thought process or emotion (episodes of depression, stress, guilt). Patients may experience discomfort when being asked questions about their medical history that they deem to be private.

Risks related to transplantation with an HCV-positive liver
Liver problems
While unlikely, it is possible that DAAs will not result in the same efficacy following liver transplant. If HCV is transmitted and not eradicated it is possible that HCV infection post-transplant could cause health problems, including liver injury. In the short term, infection with HCV can cause a flu-like illness that includes fatigue, nausea, fever, abdominal pain, vomiting, joint pain, and yellowing of the skin (jaundice). Although it is very rare, infection with HCV can cause severe inflammation of the liver or even liver failure, including a condition called fibrosing cholestatic hepatitis. The risk of this complication in patients without HCV who receive a transplant from a donor with HCV is unknown. This complication can be treated and cured in the majority of cases with the HCV medications.

Cirrhosis of the liver can cause someone to experience leg swelling, yellow skin, skin itching, abdominal bleeding, shortness of breath, and the abdomen to fill with fluid (ascites). Liver failure can also cause death. Based on the limited data available, it would be extremely rare for someone in the study to experience liver failure in the first few months after transplantation because the study will be giving HCV treatment right away.

In the unlikely event that the patient develops HCV infection despite DAA therapy, we will be prepared to offer 2nd line treatment and continue to reassess potential treatment options in the rapidly evolving field of HCV therapy. In the unlikely event that treatment fails, there may be continued inflammation and scarring of the liver that over many years lead to cirrhosis. If HCV causes cirrhosis, the patient is at increased risk of developing liver cancer, liver failure requiring a subsequent liver transplant, or death. Of note, we anticipate that with study drug treatment, or if necessary additional HCV therapies, we will be able to successfully eradicate HCV in our study population.

Additional risks of HCV:
HCV can cause other types of inflammation in the body, such as arthritis, rash, anemia, nerve pain and inflammation damage to your kidney. These problems are rare, and affect less than 2% of people who have HCV. These problems should respond to effective HCV treatment.

Risks Related to Study Medications

Risks of glecaprevir/pibrentasvir (Mavyret™)
Glecaprevir/pibrentasvir (Mavyret™) is an FDA approved pan-genotypic regimen for treating HCV infection. Thousands of patients have received this medication for HCV treatment.

The adverse reactions data for Mavyret™ in subjects without cirrhosis were derived from nine Phase 2 and 3 trials which evaluated approximately 2,300 subjects infected with HCV genotype 1, 2, 3, 4, 5, or 6 who received Mavyret™ for 8, 12 or 16 weeks. In patients receiving Mavyret™ the most common side effects were headache (13%), fatigue (11%), and nausea (8%). The overall proportion of

subjects who permanently discontinued treatment due to adverse reactions was 0.1% for subjects who received Mavyret™ for 8, 12 or 16 weeks.

The safety and tolerability of Mavyret™ after liver transplantation has not yet been extensively studied. It is possible that taking immunosuppressant medications needed after liver transplant may change the effectiveness or side effects of Mavyret™.

Risk of allergic reaction
As with any drug, an allergic reaction can occur. Allergic reactions can be mild or serious, and can even result in death in some cases. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If a patient develops an allergic response to study drug the medication will be discontinued and an alternative treatment initiated

Risks Related to Study Procedures

Risks of Blood Draws
The patient may have a bruise (a black-and-blue mark) or pain where researchers take the blood samples. There is also a small risk of feeling lightheaded, fainting, or infection.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant
Because the effect, if any, of Mavyret on an embryo or fetus is not known, the patient may not participate in this study if they are pregnant, breastfeeding, or planning to become pregnant. This is not a new requirement necessitated by this protocol, as patients on the liver transplant list must also agree to not become pregnant while awaiting and for a period of time post-transplantation.

VIII. Potential Benefits

Receipt of an organ
Participants may receive a high quality liver transplant because they are enrolled in this study. For some patients, they may have not received an organ at all if the severity of their disease would have otherwise led to death while awaiting organ transplant.

Shortened wait time
Participants may spend a significantly shorter duration on the transplant waitlist than they otherwise would have if they had not been a part of the research study.

Improved patient quality of life
A liver that would have otherwise gone to waste can potentially be used to prolong the life and significantly improve morbidity for an individual.

Cost Reduction
This procedure could also eliminate costs associated with the management of end stage liver disease and hospitalization.

Increase organ donor pool
This study could increase the number of viable livers for transplant and reduce the HCV-positive liver discard rate.

IX. Monitoring and Quality Assurance

An independent data safety monitoring board (DSMB) will not be used in this study as it is an open label study, will have low enrollment, and will only take place at 1 site.

Once a patient is enrolled (transplanted with an HCV Ab+ organ), Dr. Chung, Dr. Markmann, and Dr. Bethea will meet in person every three months to review any safety concerns. More frequent meetings will occur if needed.

Dr. Chung and Dr. Bethea will be regularly monitoring documents for accuracy and meeting with staff to review the status of the study. This protocol will be incorporated into the hepatology standard of care post-transplant protocol. A pool of hepatology and transplant attendings will be caring for the patients enrolled in this study. Dr. Chung will ultimately be responsible for protecting the rights, safety and welfare of all subjects enrolled in this study. In the case of Dr. Chung's absence, monitoring responsibilities will be delegated to one of the subinvestigators listed on the IRB protocol application.

Adverse events will be thoroughly assessed at each treatment visit. Adverse events will be reported to the HRC as per current guidelines. We plan to comply with the reporting of any IND safety reports or any other federal regulations. The research team will work with the physician investigators to process the report of these events as they happen.

Adverse events and unanticipated problems involving risks to subjects or others will be reported to the PHRC in accordance with PHRC adverse event and unanticipated problems reporting guidelines.

The study staff will ensure that all adverse events are reported according to the PHRC guidelines. The study staff will meet monthly to review the accuracy and completeness of case report form entries, source documents, informed consent, and all regulatory documents.

X. References

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