Protocol Title

Lung Transplantation in Chronic Hepatitis C Infection with Post Transplant EPCLUSA Treatment: A Pilot Feasibility and Efficacy Study

Purpose of the Study

Primary objectives

- Assess feasibility, safety and efficacy of Epclusa treatment after lung transplant in those with chronic Hepatitis C Virus infection.
- Establish Sustained Virologic Response (SVR)12 rates in HCV-infected lung transplant recipients treated with EPCLUSA. SVR 12 is the absence of detectable hepatitis C virus in the blood after 12 weeks of antiviral therapy. This is the standard outcome in studies evaluating therapies to treat hepatitis C virus.

Secondary Objective

- Evaluate impact of considering donors who are hepatitis C nucleic acid amplification test (NAT) positive in recipients with pre-existing hepatitis C viremia on wait times and post transplant survival.
  - Are wait times shortened by considering HCV NAT positive donors?

  Do HCV NAT positive donors otherwise meet criteria for lung donation?

Primary endpoints

- Sustained Virologic Response 12 weeks (SVR 12) in those treated with EPCLUSA
- Adverse events resulting in discontinuation of EPCLUSA
- Eligibility for EPCLUSA treatment within 12 months of lung transplant.
  - If subjects do not have adequate renal function or require medications with significant drug interactions with epclusa, they will not be eligible for treatment. Eligibility is an outcome because it is not known if these factors will limit utility of epclusa in this setting due to common complications associated with lung transplantation.

Secondary endpoints

- Serum HCV RNA levels at 12-, 24-, and 48-weeks after initiation of EPCLUSA
- Adverse events requiring temporary interruption in Epclusa therapy
- 90-day and 1-year post transplant patient survival
- 90-day and 1-year post transplant patient survival in recipients of HCV NAT positive donor organ

Exploratory outcomes

- Change in transient elastography score at 48-weeks post Epclusa treatment

- Acute rejection rates
- Primary graft dysfunction scores
- Infections requiring treatment
- Wait times associated with donor HCV status

Background & Significance

Nearly 150,000 deaths are attributed to end stage lung disease annually in the United States.[i] Lung transplantation remains the only effective therapy for end stage lung disease, yet just over 2000 were performed in the US in 2015 and hundreds of patients continue to die each year while awaiting a suitable organ.[ii] This is related to a limited donor pool as well as strict inclusion criteria. Active chronic hepatitis C infection in the recipient has been considered a contraindication to lung transplantation at most programs, however new highly effective direct-acting antiviral (DAA) treatment regimens have changed the landscape of hepatitis C and prompt reconsideration of this practice. More importantly, HCV is now a curable condition and these medications offer the promise of expanding the organ donor pool and increasing access to lung transplantation by utilizing HCV positive donors in HCV positive candidates.

A single center, retrospective review out of Canada comparing lung transplant recipients with detectable HCV RNA at time of transplant (n=14) with those who were HCV antibody positive (n=13) and those who were HCV antibody negative (n=443), demonstrated no difference in 1-, 3- and 5-year survival, in the absence of hepatitis-C directed treatment.[iii] A review of the U.S. national experience comparing outcomes between lung transplant recipients who were HCV antibody positive and those who were HCV antibody negative between 2000-2011 similarly did not reveal a difference in median survival (4.4 vs 5.4 years, P=0.10), although HCV RNA status was not captured in this highly selected cohort, so extrapolation of this data is limited.[iv]

In spite of this encouraging data, there is likely a negative long term impact from untreated HCV infection as demonstrated by 15% worse 10-year survival in kidney transplant recipients with chronic HCV infection compared with those who are HCV negative[v] as well as the overall mortality rates associated with HCV in the general population. Additionally, liver function is a legitimate concern given reports of acute worsening hepatic fibrosis in lung transplant recipients with HCV.[vi] [vii] DAA regimens to cure HCV result in improved liver function and survival in non-transplant populations and a retrospective study has demonstrated efficacy and safety of DAA regimens to treat HCV infection after renal transplantation.[viii] Presumably, viral clearance will optimize outcomes for these individuals post-transplant.

Given the promising initial reports, many renal transplant centers are now using HCV positive donors in order to minimize wait times for their HCV positive recipients, and then treating them with DAA regimens post-transplant to clear the HCV infection and preserve liver function. This strategy appears to be both safe and effective based on a single center retrospective review of 43

renal transplant recipients, 19 of whom received organs from HCV antibody positive donors who were treated with 4 different DAA regimens. 100% of the patients in this cohort achieved SVR 12, regardless of DAA regimen used, immunosuppressive induction agent or HCV status of donor. While wait times were significantly shorter in the HCV-positive donor cohort (median 485 days vs 969 days), there was no difference in allograft function or patient survival post-transplant.[ix]

Lung transplant recipients require the highest levels of maintenance immunosuppression for solid organ transplant; therefore, establishing efficacy in this population is critical for the solid organ transplant community as a whole. It is also an important and necessary step in working towards more widespread use of HCV positive donors. Again, this is particularly relevant in lung transplantation as lungs remain the least likely of the commonly transplanted organs to be utilized with only 17% of multi-organ donors providing lungs. HCV positive donors are routinely turned down due to published reports describing notably worse survival and major liver complications in HCV negative recipients receiving lungs from HCV positive donors,[x] however the potential to treat and make these lungs useful could revolutionize solid organ transplant and save thousands of lives.

Epclusa is a fixed-dose combination product containing sofosbuvir, an HCV NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor. It was approved by the FDA in June 2016 for the treatment of chronic HCV genotypes 1, 2, 3, 4, 5 and 6. The first antiviral approved to treat all major forms of HCV, it can be used in patients with compensated and uncompensated cirrhosis, as well as those without cirrhosis. Response rates, defined as a RCV RNA pcr less than the lower limit of quantification (<LLOQ) 12 weeks after completion of therapy (SVR12), in those without decompensated cirrhosis who were treated for 12 weeks range from 94-99%. It is recommended as first line therapy by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (ISDA) for treatment of chronic HCV infection with genotypes 1, 2, 3, 4, 5 and 6.

The goal of this study is to assess whether a strategy of performing lung transplant in individuals with end stage lung disease and chronic HCV infection, and then treating them post-transplant with Epclusa is feasible, safe and effective at curing HCV.

The reason to wait until after lung transplant to treat the hepatitis C virus is two-fold. First, it opens up the donor pool to include those with chronic hepatitis C. This can potentially shorten wait times and increase the number of lungs used for transplantation, which could increase access to a life-saving transplant and for those suffering with end stage lung disease and decrease deaths on the waiting list. The second reason to adopt this strategy is that it allows those with rapidly progressive lung disease to be transplanted prior to completing 12 weeks of antiviral

therapy, during which time their lung disease might progress to the point where they are too sick to survive a lung transplant.

As a first step, this study includes only lung transplant candidates with chronic HCV infection. For these candidates with chronic HCV infection, consideration would be given to organ offers from both HCV NAT positive and HCV NAT negative donors. Donors would be accepted based on quality and suitability, independent of HCV status. *There would be no intentional utilization of an HCV positive donor into an HCV negative recipient.*

Design & Procedures

Prospective, open-label study evaluating feasibility, safety and efficacy of Epclusa treatment in lung transplant recipients. Lung transplant recipients who are chronically infected with hepatitis C virus will be treated with Epclusa for 12 weeks and evaluated for evidence of hepatitis C virus in their blood at 12, 24 and 48 weeks after therapy initiation.

Individuals with chronic hepatitis C infection will be enrolled prior to transplant. Participation in this study will allow individuals with active chronic hepatitis C infection to be considered for candidacy for lung transplant, as chronic HCV infection has, until this study, been considered a contraindication for lung transplant at Duke.

Once the subject has undergone lung transplant, been discharged from the hospital and clinically stabilized (a process that can take weeks to months, depending on complications associated with this lung transplant), the subject will be referred for treatment screening. A regaining of functional status, increasing independence in activities of daily living, and a lack of significant or poorly controlled acute infections or need for hospitalization are markers of clinical stability which will be determined by the treating transplant pulmonologist.

If eligible, the subject will then be given study drug which will be taken for 12 weeks. Subject will be monitored throughout treatment course for adverse events. Upon completion of therapy, repeat testing will be performed to assess for clearance of the virus from the blood. Subjects will be followed for 48 weeks after initiation of study drug to monitor for recurrence and to evaluate change in degree of liver stiffness, as assessed by transient elastography.

<u>Regimen (drug/dose/frequency)</u>

Epclusa (sofosbuvir 400mg/velpatasvir 100mg) 1 tablet PO or VT daily x 12 weeks, taken with or without food.

<u>Projected duration of treatment</u>

12 weeks

Projected duration of enrollment
2 years

Study Details

- Treating pulmonologist will refer for treatment screening visit when clinically appropriate. Repeat HCV PCR and genotyping will be done prior to start of Epclusa treatment.as part of the treatment screen.
- Drug-drug interaction considerations: Many lung transplant recipients develop atrial fibrillation after lung transplant and may require treatment with amiodarone. Due to risk of bradycardia associated with concomitant use of epclusa and amiodarone, subjects must be off amiodarone for at least 60 days in order to be eligible for epclusa treatment.
- After 5 subjects complete 12 weeks of epclusa treatment, a preplanned analysis will be performed to assess safety and efficacy.
- HCV positive donors will have blood collected at time of procurement to be sent for genotyping and quantitative PCR.
- Because Epclusa is FDA-approved for all HCV genotypes, there is no anticipated safety risk associated with the organ donor having a different genotype than recipient.

Early discontinuation
If a subject decides to withdraw from the study prior to completion, the subject will be asked to return for a final visit for data collection.

Selection of Subjects
Inclusion criteria:

1. HCV RNA >= 10^3 IU/ml at screening
2. Chronic HCV infection, defined as positive HCV antibody and/or HCV RNA more than 6 months prior to screening
3. HCV Genotype 1, 2, 3, 4, 5 or 6
4. Otherwise eligible for lung transplant at study site

Exclusion criteria:

1. Age <18
2. Treatment with any of the following agents:
    - Amiodarone. Subjects previously treated with amiodarone must have stopped the amiodarone at least 60 days prior to day 1 SOF/VEL
    - Carbamazepine, phenytoin, phenobarbital, oxcarbazepine
    - Rifabutin, rifampin or rifapentine
    - HIV regimens containing tenofovir, tipranavir/ritonavir, or efavirenz
    - St John's wort
    - Modafinil

3. Have any serious or active medical or psychiatric illness which, in the opinion of the investigator, would interfere with subject treatment, assessment or compliance
4. Hepatitis B surface antigen positive (This is checked at the time of transplant evaluation.) . (
5. History of hepatic encephalopathy or variceal hemorrhage
6. Abnormal hematological and biochemical parameters, including:
    - Hemoglobin <8g/dL
    - Platelets <= 50,000/mm^3
    - ALT (alanine aminotransferase), AST (aspartase aminotransferase) or alkaline phosphatase >=10 times ULN
    - Total bilirubin >3mg/dL
    - Severe renal impairment, ie creatinine clearance (CrCl) <30mL/min
7. Pregnant women or women planning to become pregnant
8. Women who are breastfeeding
9. Active or recent history (<=1 year) of drug or alcohol abuse

Subject Recruitment and Compensation

10 subjects will be enrolled. Subjects will be identified during the transplant evaluation phase by the clinical team. The clinical team will assess subject's willingness to participate in the study prior to being approached by the research team. Due to active chronic HCV infection currently being considered a contraindication to transplant at Duke, declining to enroll in the study may impact the subject's candidacy for transplant. The suitability for transplant is ultimately made by the Lung Transplant Team, and dependent on multiple factors. Agreeing to participate in this study is not a guarantee for transplant. Subjects will not be compensated for participating in this study; however, subjects will receive study drug free of charge.

Consent Process – see Section 14 of the e-IRB submission form.

Risk/Benefit Assessment

The most common adverse reactions observed with treatment with EPCLUSA for 12 weeks are headache and fatigue. Bradycardia can occur when taken with amiodarone.

Hepatitis B virus reactivation: There have been case reports of hepatitis B reactivation with Epclusa treatment. All subjects will be screened for hepatitis B prior to enrollment.

Costs to the Subject

There will no additional costs to the subjects as a result of participating in this study. Every attempt will be made to coordinate study visits with routine clinical care.

Data Analysis & Statistical Considerations

This study is a small, pilot feasibility study and therefore not powered for comparative statistics. Descriptive and non-parametric statistics will be performed. A matched, case-control cohort will based on age and underlying lung disease from same center over same time period will be used to evaluate survival outcomes. An unadjusted Kaplan-Meier survival analysis for cumulative survival will be performed.

Data & Safety Monitoring

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research, all AE reports will be reported per the DUHS IRB policies.

Data collection, storage and confidentiality

- All data collected in the case report forms (CRF) will be by review of the subject's Duke medical record documentation or through patient interview. All subjects will be given a study ID in order to protect PHI. This will be stored on a secure study drive.
- The CRF will be built into a password protected REDCap database behind the Duke firewall.
- All paper forms will be stored in a locked cabinet in the research team's locked office.

Schedule of Assessments:

Screening Visit

Informed consent will be reviewed with the subject. After informed consent is signed, subjects will be assessed for eligibility for inclusion into the trial.

The following data will be collected from the subject's medical chart:

- Medical and medication history
- Liver biopsy results
- FibroScan results
- Laboratory results
- EKG results

Treatment Screening Visit

After the lung transplant subjects will have a treatment screening visit.

The following tests and procedures will be done at this visit as part of standard of care:

- Physical exam
- Vital Signs
- Routine blood tests will be collected (CBC, CMP, Mg, and PT/INR).
- Medical history will be reviewed.

The following tests and procedures will be done at this visit for research purposes:

- Female subjects of child-bearing potential will have serum beta HCG test

Female subjects are considered "of child-bearing potential" if they (a) are anatomically and physiologically capable of becoming pregnant and (b) they will be, or could possibly be, engaging in sexual activity with males while study interventions that pose the possibility of harm to a fetus are occurring. Sterilization (tubal ligation/cauterization or vasectomy of the male partner), while highly effective, does not perfectly prevent pregnancy. Women using these contraceptive methods are considered "of child-bearing potential."

Women are considered past the age of "child-bearing potential" if

- they are greater than 55 years of age, OR
  - they are at least 50 years of age AND
  - have not menstruated for at least **12** months, OR
  - have a documented Follicule Stimulating Hormone (FSH) level of greater than 40 mIU/mL.
- they are at least 45 years of age AND
  - have not menstruated for at least **18** months, OR
  - have a documented Follicule Stimulating Hormone (FSH) level of greater than 40 mIU/mL.
- A blood sample will be collected for HCV status.
- EKG
- If the subject is eligible to start Epclusa treatment a 6 week supply will be dispensed. A drug log will be provided to the subject for accountability purposes.
- Concomitant medications will be review
- Clinical data related to transplant and donor will be collected from subject's medical chart.

Treatment Initiation

Subjects will be started on EPCLUSA treatment. Treatment consists of 1 pill taken by mouth once a day, either with or without food. Treatment will last 12 weeks. This visit can be combined with the treatment screening visit if subjects are eligible at that time.

Week 4

The following tests and procedures will be done at this visit as part of standard of care:

- Physical exam
- Vital Signs

Routine blood tests will be collected (CBC, CMP, Mg, and PT/INR).The following will be done at this visit for research purposes:

- Dispense 6 weeks supply of Epclusa.
- Drug accountability review
- Adverse Events (AE) assessment
- Concomitant medications review

Week 8

The following tests and procedures will be done at this visit as part of standard of care:

- Physical exam
- Vital Signs
- Routine blood tests will be collected (CBC, CMP, Mg, and PT/INR).

The following will be done at this visit for research purposes:

- AE assessment
- Concomitant medications review

Week 12

The following tests and procedures will be done at this visit as part of standard of care:

- Physical exam
- Vital Signs
- Routine blood tests will be collected (CBC, CMP, Mg, and PT/INR).

The following test and procedures will be done at this visit for research purposes:

- A blood sample will be collected for HCV status.
- Drug accountability review
- AE assessment
- Concomitant medications review

Week 24

The following tests and procedures will be done at this visit as part of standard of care:

- Physical exam
- Vital Signs
- Routine blood tests will be collected (CBC, CMP, Mg, and PT/INR).

The following test and procedures will be done at this visit for research purposes:

- A blood sample will be collected for HCV status.
- AE assessment
- Concomitant medications review

Week 48

The following tests and procedures will be done at this visit as part of standard of care:

- Physical exam
- Vital Signs
- Routine blood tests will be collected (CBC, CMP, Mg, and PT/INR).

The following test and procedures will be done at this visit for research purposes:

- A blood sample will be collected for HCV status.
- AE assessment
- Concomitant medications review
- Transient Elastography

Schedule of Assessments

Study Week +/- 21 days	Lung transplant evaluation	Study Screening	Transplant	Treatment Screening Visit	Treatment initiation (can be combined with treatment screening)	Week 4	Week 8	Week 12	Week 24	Week 48
Study Informed consent		X								
Inclusion/Exlusion		X								
Demographics		X								
Medical history				X						
Physical exam	X			X		X	X	X	X	X
Vital Signs Height/Weight	X			X		X	X	X	X	X
Confirm treatment eligibility				X						
Serum HCG				X						
Liver biopsy	X									
Transient elastography	X									X
HCV PCR	X			X				X	X	X
HCV genotype	X			X						
Routine labs (CBC, CMP, Mg, PT/INR)	X			X		X	X	X	X	X
Drug and alcohol Screen	X									
Hepatitis B Screen	X									
EKG	X			X						
Dispense Drug					X (6 week supply)	X (6 week supply)				
Review Con Meds				X		X	X	X	X	X
Review for AEs						X	X	X	X	X
Donor HCV PCR/genotype (if donor HCV NAT positive)			X (At time of procurement)							
*All follow-up visits may occur inpatient or outpatient.										

*Boxes marked in red are part of standard of care for lung tx candidates/recipients.

Note: To ensure compliance with CMS guidelines, all studies involving patient care at Duke are required to have study protocol-specific EMR build for ordering, resulting and billing of protocol-related activities. This ensures SOC activities are billed to insurance and protocol-related activities are billed to the study. This is referred to as EPIC initiation. The EPIC build is specific to each protocol and will not be used for any future studies.

References

[i] http://www.cdc.gov/nchs/fastats/copd.htm

[ii] https://www.unos.org/about/annual-report/

[iii] Doucette KE[1], Halloran K[2], Kapasi A[2], Lien D[2], Weinkauf JG[2]. Outcomes of Lung Transplantation in Recipients with Hepatitis C Virus Infection. Am J Transplant. 2016 Mar 21 [Epub ahead of print].

[iv] Englum BR[1], Ganapathi AM[2], Speicher PJ[2], Gulack BC[2], Snyder LD[3], Duane Davis R[2], Hartwig MG[2]. Impact of donor and recipient hepatitis C status in lung transplantation. J Heart Lung Transplant. 2016 Feb;35(2):228-35

[v] J. Levitsky, K. Doucette. **AST Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation.** Am J Transplant, 13 (Suppl 4) (2013) 147-68.

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