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BRIEF REPORT

A Pilot Trial for Prevention of Hepatitis C Virus Transmission From Donor to Organ Transplant Recipient With Short-Course Glecaprevir/Pibrentasvir

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A 7-day course of glecaprevir/pibrentasvir started in the preoperative period prevented transmission of hepatitis C virus (HCV) from viremic donors to 10 HCV-negative recipients (2 heart, 1 lung, 6 kidney, 1 heart/kidney) with 100% sustained virological response at 12 weeks.

Keywords. DAA; direct-acting antiviral; donor-derived infection; glecaprevir/pibrentasvir; prophylaxis; HCV.

The opioid epidemic has led to a large increase in the number of hepatitis C virus (HCV)-infected organ donors. Many small studies demonstrate excellent short-term outcomes using HCV-viremic organs for transplantation into HCV-negative recipients with posttransplant 8- to 12-week course of direct-acting antivirals (DAAs) after infection transmission [1–4]. Long-term outcomes including allograft survival, rejection, and allograft vasculopathy are unclear. A single DAA treatment course can cost between $40 000 and $95 000 [5, 6]. Prevention of HCV transmission may be preferable; several studies demonstrate 82.5%–100% success in prevention of HCV transmission with 4 weeks sofosbuvir/velpatasvir (SOF/VEL), 8 weeks glecaprevir/pibrentasvir (GLE/PIB), 8 days of GLE/PIB with concomitant ezetimibe, and 4–7 days of SOF/VEL [2, 7–10]. Because a 7-day course of GLE/PIB alone has not been studied, the drug has manageable drug interactions (in particular, sofosbuvir interacts with amiodarone, which can be commonly used in the thoracic transplant setting), and the cost is low, we aimed to study prevention of HCV transmission with a 7-day course started in the preoperative period for nonliver transplant recipients.

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METHODS

Pilot Study Design

This was a single-arm, single-center, open-label, pilot clinical trial, enrolling patients that received an organ transplant from an HCV-viremic donor. The study was approved by the Institutional Review Board (IRB) of University of California San Diego ([UCSD] IRB Number 200895) and registered on ClinicalTrials.gov (NCT04596475), and each patient provided written consent.

Inclusion/Exclusion Criteria

Transplant candidates were as follows: adults aged >18 years who were listed for heart, lung, and/or kidney transplant and had consented to receive HCV-viremic organs. We excluded individuals with prior history of HCV infection regardless of treatment status, human immunodeficiency virus (HIV) infection, or hepatitis B virus (HBV) infection with detectable HBV surface antigenemia; patients receiving atazanavir and/or rifampin due to significant drug interactions with GLE/PIB; those unable to sign informed consent; those who had Child-Pugh B or C cirrhosis; or those who were listed for liver transplantation.

Deceased Donor

We included donors who tested positive via nucleic acid test (NAT) for HCV denoting viremia, and we excluded those with positive NAT for HIV and/or HBV infection or with positive HIV serology.

Study Intervention

The intervention consisted of a daily dose of 100/40 mg (3 tablets) GLE/PIB for 7 days. Dose 1 was administered within 8 hours before transplant surgery. The GLE/PIB was administered orally or crushed via a feeding tube when participants were unable to swallow by mouth in the immediate postoperative period.

Blood samples for HCV viral load (VL) were tested at the UCSD Center for Advanced Laboratory Medicine using Roche Cobas 6800. As noted in Figure 1, baseline HCV VL was drawn before surgery, on the third postoperative day

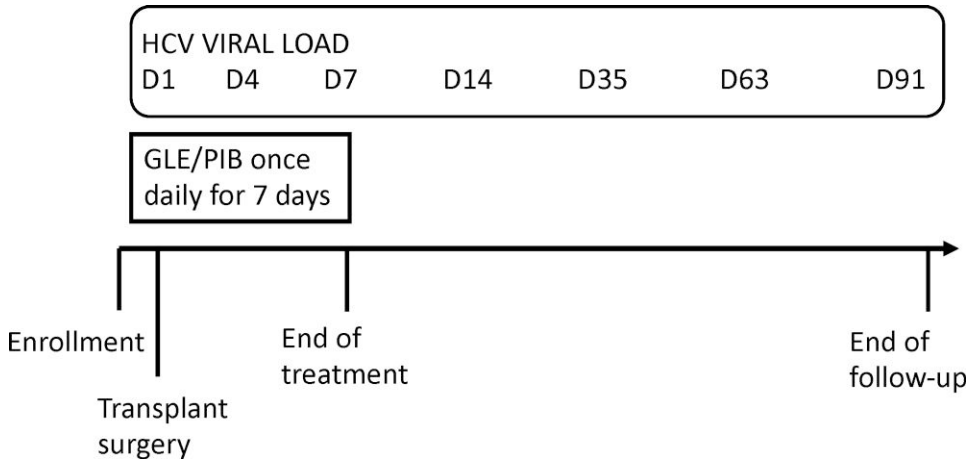

Figure 1. Study timeline schema; after study enrollment, the patient was started on glecaprevir/pibrentasvir (GLE/PIB) within 8 hours before transplant surgery and continued once daily for a 7-day treatment course. At the enrollment period, baseline assessment was performed and screened for the following: human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infection; HIV viral load (VL) and serology; HBV core antibody; HBV surface antigen; HBV polymerase chain reaction; HCV serology and HCV VL; complete medical history; physical examination; review of inclusion/exclusion criteria; and signed informed consent form. Blood samples for HCV VL were tested as per the schedule listed (day 1, 4, 7, 14, 35, 63, and 91). Day 91 measurement corresponded to sustained virological response at 12 weeks.

(day 4 of protocol), and days 8, 15, 35, 63, and 91. Participants had daily liver function tests and serum creatinine measurements while inpatient and weekly while outpatient during the study period.

Participant Clinical Care and Safety

Safety assessments occurred through medical record review, laboratory parameters, and open-ended questions at clinic visits. Organ rejection was determined by the transplant team.

Rescue Direct-Acting Antiviral

If participants were viremic from day 14 onwards, we planned to treat with a 12-week course of "rescue" DAA as per normal clinical care of HCV-viremic transplant recipients; drug choice would depend on the participant's medical insurance and HCV resistance testing. This timing of DAA initiation would be similar to routine clinical care for a transplant recipient with donor-derived HCV infection at our center where DAA is usually started 3–4 weeks after transplant [11]. Current international consensus document recommends that DAA be started within 90 days of transplant, and thus the current timeline for rescue DAA is within the standard of care timing of DAA initiation for donor-derived HCV infection [7].

Study End Points

The primary outcome was sustained virological response at 12 weeks (SVR12) after end of GLE/PIB course (day 91 per study timeline). The secondary outcomes were safety and tolerability of GLE/PIB and allograft rejection.

Sample Size

We planned to enroll 10 or more consecutive participants that fulfilled eligibility criteria in order to reach our goal of 10 participants who completed per-protocol analysis.

Analytic Cohorts

All participants who received the 7-day course of GLE/PIB started in the preoperative period, and completed day 91 follow-up was assessed for the primary outcome. All participants who received at least 1 dose of GLE/PIB were assessed for safety and adverse events as well as rejection.

Statistical Analyses

Baseline clinical characteristics, SVR12, secondary endpoints, and safety events were descriptive. The incidence of adverse events and abnormal clinical laboratory tests were summarized by severity, time to onset, duration, and by relationship to therapy.

RESULTS

We prospectively enrolled consecutive participants who were eligible to receive heart, lung, and/or kidney transplant from an HCV-viremic donor from May 2021 to November 2021. One patient received 1 preoperative dose of GLE/PIB but transplant surgery was canceled. One patient who received a kidney transplant completed a 7-day course of GLE/PIB but died on day 25. Ten additional patients completed the 7-day course of therapy and completed the study protocol follow-up and were eligible for assessment of the primary outcome. Baseline demographics for these 10 patients are detailed in Table 1.

Table 1. Baseline Characteristics of the 10 per Protocol Analysis Transplant Recipients Who Received an HCV-Viremic Organ

Patient Characteristics	*n* = 10
Recipient age in years, median (±IQR)	50 (42.5–60.75)
Recipient male sex, *n* (%)	6 (60)
Transplant Organ, *n* (%)	
Heart	2 (20)
Lung	1 (10)
Kidney	6 (60)
Heart/kidney	1 (10)
Cold ischemia time in minutes, median (±IQR)	883 (351.5–1114)
Induction Therapy, *n* (%)	
Antithymocyte globulin	7 (70)
Basiliximab	2 (20)
Hepatitis B core Ab positive, *n* (%)	0 (0)
Reason for Transplantation, *n* (%)	
End-stage renal disease	6 (60)
Heart failure	2 (20)
Interstitial lung disease	1 (10)
Coronary artery disease	1 (10)
Comorbid Conditions, *n* (%)	
Diabetes mellitus-2	4 (40)
Hypertension	6 (50)
Heart failure	4 (40)
Interstitial lung disease	1 (10)
Coronary artery disease	2 (20)
Chronic kidney disease	5 (50)
End-stage renal disease	6 (60)

Abbreviations: Ab, antibody; HCV, hepatitis C virus; IQR, interquartile range.

The SVR12 was achieved in all 10 (100%) patients who received a full 7-day course of GLE/PIB and completed day 91 follow-up. All 10 patients had undetectable HCV VL at every tested point (on days 1, 7, 14, 35, 63, and 91). The participant who died before completion of follow-up also had negative HCV VL on days 1, 7, and 14.

All patients who received at least 1 dose of GLE/PIB tolerated the drug well with no reported drug-related adverse event. There was 1 adverse event unrelated to the study drug (nonfatal cerebrovascular accident) during the follow-up period. One patient died before completion of follow up. The death was unrelated to the study and due to pulmonary embolism. There were no rejection events recorded during the study period.

DISCUSSION

According to the US Organ Procurement and Transplantation Network, a total of 3440 organs were HCV-positive in 2021, accounting for 7.7% of all organ donors. With the advent of DAAs, excellent outcomes have been reported with the treatment of HCV in organ recipients, and utilization of such organs has dramatically increased [12–15]. At our center, approximately 100 transplant recipients have received organs from HCV-viremic donors since April 2017 (S.A. unpublished data, 2022). All patients are treated with 8–12 weeks of DAA therapy, usually initiated in the outpatient setting, after documentation of infection transmission and insurance approval.

Given the costs of this approach and risk of HCV-related adverse events before DAA initiation, such as acute hepatitis, and unclear long-term outcomes, there is interest in prevention of donor-derived HCV transmission. In recent trials, researchers have investigated different approaches including 4 weeks [9], 8 days, [16], and even 4 days of DAA therapy [8]. We chose GLE/PIB because it is pan-genotypic, has less drug interactions, and is lower cost. The pan-genotypic SOF/VEL has been available as a generic since January 2019, costing $24 000 for a 1-month supply (https://www.gilead.com/news-and-press/press-room/press-releases/2018/9/gilead-subsidiary-to-launch-authorized-generics-of-epclusa-sofosbuvirvelpatasvir-and-harvoni-ledipasvirsofosbuvir-for-the-treatment-of-chronic, viewed September 13, 2022). The wholesale cost of GLE/PIB (https://www.mavyret.com/cost, viewed September 13, 2022) is $13 200 for a 1-month supply. One week of GLE/PIB costs approximately $3300, supporting overall cost saving for our medical system (although not assessed as part of this trial).

There is scant data regarding bioavailability of GLE/PIB. In a Phase 1 study, researchers assessed drug levels after different methods of tablet manipulation and found that grinding or crushing tablets resulted in lower GLE exposures (27%–61%) and higher PIB exposures (21%–83%) [17]. We started the drug in the preoperative period while the patient was able to take the drug orally so that appropriate drug levels would be present when the viremic organ was transplanted. We did not study GLE/PIB serum levels in our patients. Each preoperative dose was oral, and 4 patients received a median of 1 day (interquartile range, 1–3.25 days) of crushed tablets via the enteral route postoperatively.

The benefits of successful HCV prophylaxis include prevention of future HCV-related complications and significantly lowered drug cost compared with an 8- to 12-treatment course of established HCV infection. There may be future long-term benefits that we are not aware of yet. There were no drug-related adverse events, and, in general, GLE/PIB is well tolerated as reported in large-scale clinical trials [16, 19, 2 18]. It is notable that we excluded liver transplant recipients because the liver is the site of HCV infection and latency, thus a short course is not appropriate.

The limitations of this study include its single-center, open-label design and the small number of participants. However, HCV transmission without prophylaxis is 100%; therefore, zero transmission in the setting of prophylactic DAA is significant. Donor VL and genotype were not available (consistent with real-world situation), so we cannot assess whether successful HCV prophylaxis would depend on these factors or not. In addition, due to lack of serum drug levels, we cannot to assess whether drug levels were associated with successful outcome.

CONCLUSIONS

Our findings suggest that a 7-day prophylactic course of GLE/PIB started in the preoperative period can successfully prevent transmission of HCV from a viremic donor to an HCV-negative organ transplant recipient in the setting of heart, lung, and/or kidney transplantation; these findings will need to be verified in a larger clinical trial.

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