Multicenter Study to Transplant Hepatitis C–Infected Kidneys (MYTHIC): An Open-Label Study of Combined Glecaprevir and Pibrentasvir to Treat Recipients of Transplanted Kidneys from Deceased Donors with Hepatitis C Virus Infection

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ABSTRACT

Background Single-center trials and retrospective case series have reported promising outcomes using kidneys from donors with hepatitis C virus (HCV) infection. However, multicenter trials are needed to determine if those findings are generalizable.

Methods We conducted a prospective trial at seven centers to transplant 30 kidneys from deceased donors with HCV viremia into HCV-uninfected recipients, followed by 8 weeks of once-daily coformulated glecaprevir and pibrentasvir, targeted to start 3 days posttransplant. Key outcomes included sustained virologic response (undetectable HCV RNA 12 weeks after completing treatment with glecaprevir and pibrentasvir), adverse events, and allograft function.

Results We screened 76 patients and enrolled 63 patients, of whom 30 underwent kidney transplantation from an HCV-viremic deceased donor (median kidney donor profile index, 53%) in May 2019 through October 2019. The median time between consent and transplantation of a kidney from an HCV-viremic donor was 6.3 weeks. All 30 recipients achieved a sustained virologic response. One recipient died of complications of sepsis 4 months after achieving a sustained virologic response. No severe adverse events in any patient were deemed likely related to HCV infection or treatment with glecaprevir and pibrentasvir. Three recipients developed acute cellular rejection, which was borderline in one case. Three recipients developed polyomavirus (BK) viremia near or >10,000 copies/ml that resolved after reduction of immunosuppression. All recipients had good allograft function, with a median creatinine of 1.2 mg/dl and median eGFR of 57 ml/min per 1.73 m^2 at 6 months.

Conclusions Our multicenter trial demonstrated safety and efficacy of transplantation of 30 HCV-viremic kidneys into HCV-negative recipients, followed by early initiation of an 8-week regimen of glecaprevir and pibrentasvir.

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Nearly 95,000 people in the United States are waiting for a kidney transplant. Most waitlisted patients suffer progressive health deterioration,[1] and for some groups, such as patients >60 years, death is more likely than kidney transplant.[2] Given this substantial public health problem, the Department of Health and Human Services set a target of doubling

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the number of kidneys available for transplantation by 2030 as part of the Advancing American Kidney Health Initiative.[3] A key pathway to achieving this target is reducing the needless discard of viable kidneys, such as kidneys from donors with hepatitis C virus (HCV) infection. To date, single-center trials and retrospective case series describing transplantation of HCV-viremic kidneys into uninfected recipients have reported excellent HCV cure rates and good allograft function.[4–6] Multicenter trials with standardized protocols, and rigorous adjudication of outcomes and adverse events, are urgently needed to confirm these promising results and demonstrate their generalizability.[7]

Over the last 5 years, the opioid epidemic has driven a rapid rise in the number of deceased organ donors with HCV infection.[8,9] In 2016, only 396 HCV-viremic kidneys were transplanted in the United States. By 2018, 571 HCV-viremic kidneys were transplanted, but >350 kidneys from HCV-viremic donors were discarded and hundreds more were not recovered.[10] Kidneys from HCV-viremic deceased donors remain at elevated risk of discard for multiple reasons, including concerns about HCV-related allograft injury, lack of certainty by some centers about ability to provide timely antiviral treatment, and the potential for post-transplant complications such as fibrosing cholestatic hepatitis.[10] Notably, the kidney donor profile index (KDPI) assigns a substantial penalty to kidneys from HCV-seropositive donors. The KDPI is the main metric used to assess the quality of deceased donor kidneys in the United States, is integrated directly into kidney allocation, and influences organ acceptance decisions by centers.[11,12] As a result, the higher KDPI scores assigned on the basis of donor HCV-seropositivity may also lead centers to refuse offers for HCV-seropositive kidneys. Additionally, some studies involving transplantation of HCV-viremic into HCV-naïve recipients have reported high rates of complications including cytomegalovirus infection, polyoma virus (BK) infection, and several cases of fibrosing cholestatic hepatitis.[6,13]

Given the need for high-quality, prospectively collected data from a multicenter trial involving kidney transplants from HCV-viremic donors, we designed the MYTHIC trial (Multi-center Study to Transplant Hepatitis-C Infected Kidneys). MYTHIC was conducted at seven US transplant centers. The primary objective was to demonstrate the safety and efficacy (sustained virologic response at 12 weeks [SVR12]) of an 8-week ("shortened-course") treatment regimen of glecaprevir and pibrentasvir (G/P) initiated as early as 2 days after transplant of a study-eligible kidney from an HCV-viremic donor into a HCV-uninfected recipient. In this manuscript, we focus principally on outcomes for the 30 recipients of HCV-viremic kidney transplants, all of whom had sufficient follow-up to ascertain SVR12.

Significance Statement

Single-center trials and retrospective case series have reported promising outcomes transplanting kidneys from donors with hepatitis C virus (HCV) infection into HCV-negative recipients, although concerns remain about immunologic complications. In this first multicenter trial, 30 HCV-uninfected adults received a kidney from an HCV-viremic deceased donor and were cured of HCV with an 8-week regimen of coformulated glecaprevir and pibrentasvir initiated 2–5 days post-transplant. Three patients developed acute cellular rejection and three developed BK viremia near or >10,000 copies/ml that resolved after immunosupression reduction; none experienced severe adverse events associated with the antiviral treatment or HCV. Overall allograft function at 6 months was excellent. These findings demonstrate that HCV-viremic kidneys offer a valuable resource for transplantation and that donor-derived HCV can be effectively managed with early antiviral treatment.

METHODS

MYTHIC is an open-label interventional study. The trial protocol was approved by the institutional review boards at the clinical sites: Massachusetts General Hospital, University of Pennsylvania, University of Cincinnati, Johns Hopkins University, University of Michigan, Northwestern Medical Center, and Weil Cornell Medical Center. The trial was conducted in accordance with the protocol and followed the International Conference on Harmonization guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki. An external data safety and monitoring board reviewed study progress, adverse events, and outcomes. The trial was registered on ClinicalTrials.gov (NCT 03781726). All patients attended an informational session about HCV and kidney transplantation. A study investigator answered questions and obtained written, informed consent before any study-related procedures.

The protocol targeted the completion of 30 kidney transplants from HCV-viremic deceased donors, and all other consented subjects were categorized in the following subgroups: subjects who received a transplant from an HCV-antibody–positive/RNA-negative donor, subjects who received a transplant as per usual care at their transplant center, and subjects who remained on the transplant waitlist (Figure 1). The trial began enrolling in April of 2019 and this manuscript reports follow-up for the 30 recipients of HCV-viremic transplants meeting the trial donor criteria through April 20, 2020, when the 30th patient reached SVR12 (20 weeks post-transplant).

Supplemental Table 1 lists all inclusion and exclusion criteria. Eligible patients were ≥21 and ≤65 years of age at the time of consent, had an eGFR of <15 ml/min per 1.73 m^2 or were on dialysis, and had met each individual center's listing criteria for isolated kidney transplantation; eGFR was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) equation.[14] Patients with HIV, or active HCV or hepatitis B virus (HBV) infection, were excluded, as were patients who were pregnant, breastfeeding, or planning on becoming pregnant. To minimize risks of liver injury associated with donor-derived HCV infection, we excluded

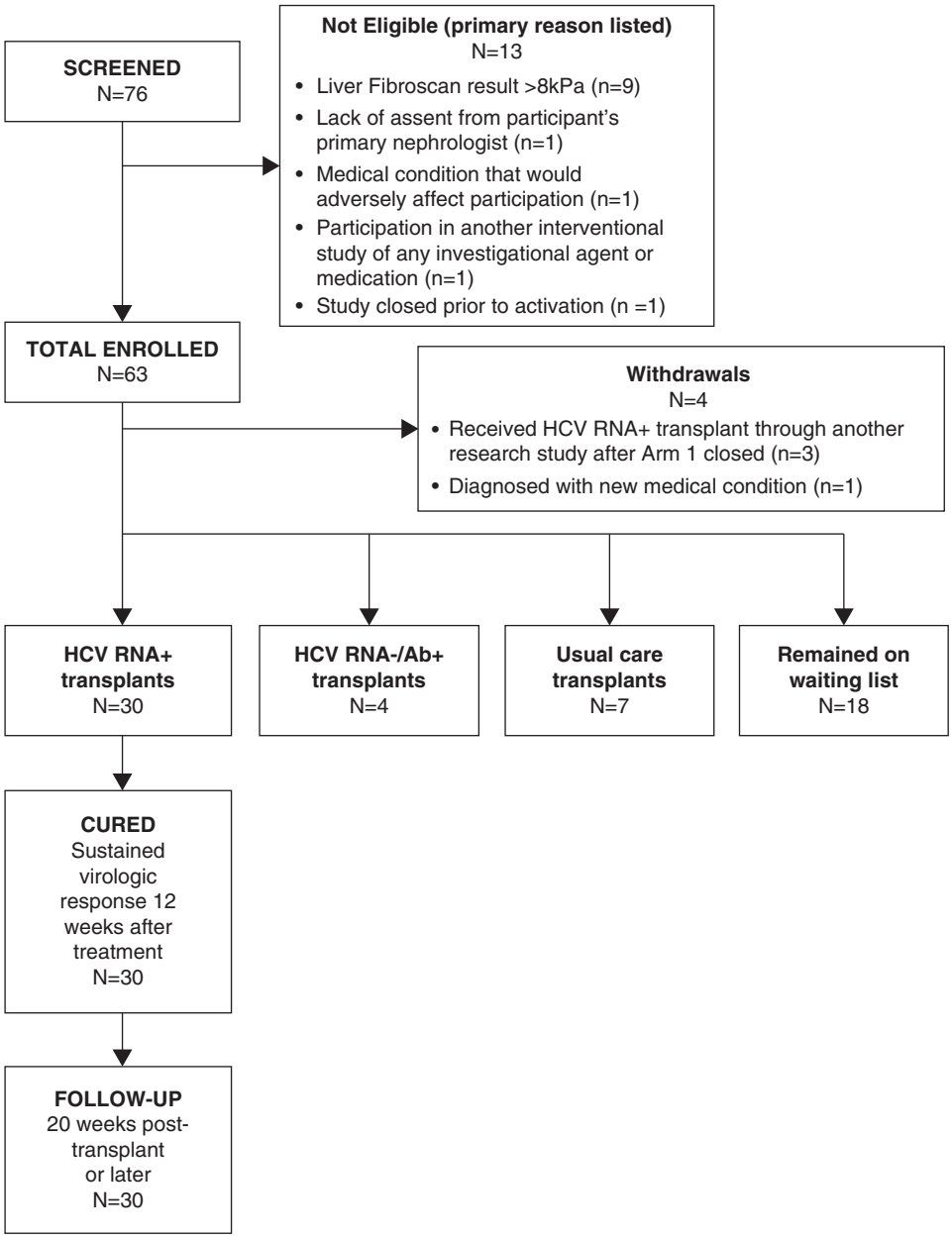

Figure 1. Consort diagram. The seven usual care transplants (six deceased donor and one living donor) involved donors that did not meet inclusion/exclusion donor criteria for MYTHIC.

patients with evidence of chronic liver disease as manifested by persistently elevated alanine aminotransferase (ALT) more than two times the upper limit of normal or a Fibroscan stiffness score >8 kPa. Participants with a calculated panel-reactive antibody >80% or those who planned to participate in a protocol to receive any desensitizing treatment for transplantation were excluded due to increased risk of graft loss from rejection, and likely need for additional immunosuppressive therapy beyond standard of care. Patients with primary FSGS or a disease process with very elevated risk of disease recurrence and graft failure as assessed by the transplant nephrologist and/or investigator team were excluded.

The MYTHIC protocol also included criteria for HCV-viremic donors; these deceased donors had a KDPI≤85% and did not have a known history of direct acting antiviral (DAA) treatment, nor a positive HIV RNA level, HBV surface antigen, or detectable HBV DNA.

Outcomes

The primary outcome was to assess the efficacy of an 8-week course of G/P, defined by undetectable HCV RNA at SVR12. Secondary outcomes were to determine: (*1*) time to transplant; (*2*) key clinical outcomes: patient survival, graft failure, acute allograft rejection, delayed graft function, eGFR,

Table 1. Demographic and clinical characteristics of eligible patients (n=63) and HCV-viremic kidney transplant recipients (n=30) in the MYTHIC trial

Characteristic	Eligible Subjects (n=63)	HCV-Viremic Kidney Transplant Recipients (n=30)
Age in yr at time of consent: median (IQR)	57 (51 to 62)	57 (51 to 60)
Women: count	24 (38.1%)	9 (30.0%)
Race/ethnicity: count		
White, not Hispanic	38 (60.3%)	19 (63.3%)
Hispanic	3 (4.8%)	1 (3.3%)
Black	16 (25.4%)	9 (30.0%)
Asian	2 (3.2%)	0
Other	4 (6.3%)	1 (3.3%)
ESKD cause: count		
Diabetes and/or hypertension	41 (65.1%)	20 (66.7%)
Polycystic kidney disease	5 (7.9%)	3 (10.0%)
IgA nephropathy	5 (7.9%)	3 (10.0%)
SLE	3 (4.8%)	0 (10.0%)
Congenital/genetic	5 (7.9%)	2 (6.7%)
Other GN	4 (6.3%)	2 (6.7%)
On dialysis at consent	55 (87.3%)	27 (90.0%)
BMI in kg/m^2: median (IQR)	30.0 (25.7 to 32.7)	29.5 (25.7 to 33.0)
History of diabetes: count	25 (39.7%)	11 (36.7%)
Weeks on waitlist before consent: median (IQR)	130.1 (57.0 to 208.3)	137.0 (95.1 to 219.0)
Weeks from consent to transplant: median (IQR)		6.3 (1.9 to 10.1)

proteinuria, and ALT elevation >5 times the upper limit of normal; and (*3*) safety as defined by serious adverse events (SAEs) and nonserious adverse events related to study participation (*i.e.*, related to HCV-viremia or G/P). Plasma HCV RNA levels were determined at each site. HCV viral kinetics were determined by analysis of HCV plasma RNA at the following time-points: day 3 post–kidney transplant, treatment week 1, treatment week 4, treatment week 8, and 12 and 24 weeks after completing G/P.

Treatment for HCV Infection

Recipients of HCV-infected kidney transplants received coformulated glecaprevir 300-mg and pibrentasvir 120-mg (G/P) tablets once daily for 8 weeks. G/P was started as early as postoperative day 2 (actual range was days 2–5 post-transplant) regardless of whether HCV viremia was detected in the recipient. The protocol also specified that any recipient who was not cured of HCV by the initial G/P regimen would receive a second DAA treatment provided for by the study.

Transplant-Related Treatment

Kidney transplant recipients received induction therapy, maintenance immunosuppression, and antiviral prophylaxis per each center's usual standard-of-care practice.

Study Visits

Supplemental Figure 1 and Supplemental Table 2 show the study arms and the visit schedule for study participants. The purpose of study visits was to ascertain clinical events, medication adherence, and adverse events, with an end-of-study visit 1 year after transplant.

Statistical Analyses

Patient characteristics are presented with summary statistics for baseline demographics and clinical variables of all eligible patients and all who underwent transplantation from an HCV-viremic donor. Median and interquartile range (IQR) were evaluated for laboratory values. For the purposes of computing the probability of receiving a kidney from an HCV-viremic donor, death and transplantation from a nonviremic donor were treated as competing risks using methods described by Lin.[15] For reporting of 6-month eGFR outcome, we used the MDRD equation to calculate eGFR (which has previously been validated as highly accurate in kidney transplant recipients),[16,17] and used the creatinine reported most closely in time to day 180 and collected a minimum of 20 weeks after transplantation.

RESULTS

A total of 76 kidney transplant candidates underwent the processes of informed consent and screening. Figure 1 shows that nine were excluded on the basis of abnormal liver Fibroscan and four were excluded for other reasons. Of the 63 eligible patients, 30 received a kidney transplant from an HCV-viremic donor between May 8, 2019 and October 31, 2019. By the end of follow-up on April 20, 2020, the status of the other 33 eligible patients was as follows: four underwent kidney transplant from an HCV-antibody–positive/RNA-negative donor, seven underwent a standard-of-care kidney transplant, 18 remained on the waitlist, and four became ineligible for the trial. Supplemental Figure 1 shows the

cumulative incidence of kidney transplant with HCV-viremic kidneys meeting study criteria versus other kidney transplants.

Table 1 shows the baseline demographics of the 63 eligible patients and of the 30 patients who received HCV-viremic kidney transplants. The median age of the 63 eligible patients was 57 (IQR, 51–62) years; 62% were men; and 60% were non-Hispanic white, 25% were black, 5% were Hispanic, 3% were Asian, and 6% were other/not recorded. The majority (87%) were on dialysis and had a median of 130 (IQR, 57–208) weeks of waitlist time at the time of consent. The median waiting time from consent to kidney transplantation with an HCV-viremic donor organ was 6.3 (IQR, 1.9–10.1) weeks, and these transplants took place at six different centers. As shown in Supplemental Table 3, the median KDPI score of the HCV-viremic kidneys was 53% (IQR, 41%–65%), the median donor age was 34 (IQR, 29–38) years, and the median donor terminal creatinine was 1.0 mg/dl (IQR, 0.7–1.5) for the 30 allografts. Death was categorized as anoxia (cause of death) caused by drug intoxication (mechanism of death) for 25 of 30 of these allografts. HCV genotype data were available from 15 viremic donors, including 13 infections with HCV genotype 1A, one with genotype 2, and one with genotype 4.

Twenty-nine (97%) recipients of HCV-viremic kidneys received thymoglobulin induction, one received thymoglobulin and also basiliximab, and one received no antibody induction therapy. Twenty-seven (90%) were discharged on oral immunosuppression regimens of tacrolimus, mycophenolate mofetil or mycophenolic acid, and prednisone.

SVR12 (Primary Outcome) and Early HCV RNA Kinetics after Transplantation with an HCV-Viremic Kidney

The 30 recipients had a median of 35.6 weeks of post-transplant follow-up (range, 24.6–49.7 weeks). G/P treatment was started between days 2 and 5 post-transplant in all 30 participants. A total of 23 of 29 patients tested at the start of therapy had detectable plasma HCV RNA viral load; the remainder of recipients were never viremic after transplant. Figure 2 reveals rapid decline in HCV RNA for all recipients. Median peak HCV RNA for the 20 recipients with quantifiable viremia was 2135 IU/ml (range, <15 IU/ml to 274,647 IU/ml). By week 1 of therapy, only 12 of 30 patients had detectable HCV RNA, and by week 4 of therapy, 0 of 28 patients had detectable viral load. All 30 recipients of kidneys from HCV-viremic donors (100%) achieved SVR12.

Secondary Clinical Outcomes and Adverse Events among Recipients of HCV-Viremic Kidney Transplants

Overall survival and graft survival was 97%. One of the 30 recipients of an HCV-viremic transplant through MYTHIC died after developing *Staphylococcus aureus* bacteremia and multiorgan failure at 9 months post-transplant and 7 months after completion of G/P, which was adjudicated as unlikely to be related to study participation.

Seven of 30 kidney recipients (23%) had delayed graft function. By the end of follow-up, seven recipients of HCV-viremic

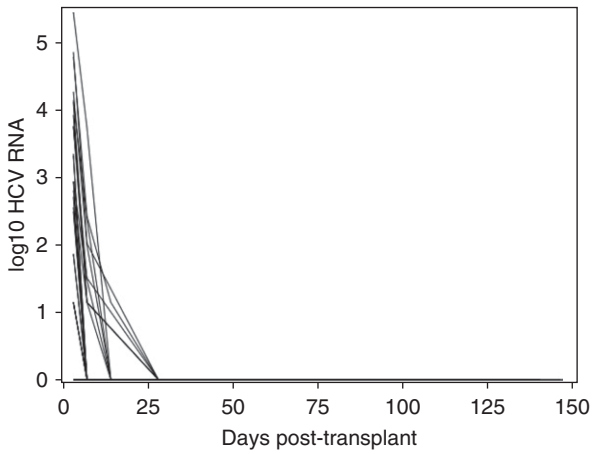

Figure 2. Change in log10 HCV viral load for 30 HCV-negative recipients of HCV-viremic kidneys. Detectable but unquantifiable HCV RNA is shown as 14 IU/ml as the lower limit of quantification for some assays was 15 IU/ml. Treatment with glecaprevir/pibrentasvir lasted 8 weeks. HCV, hepatitis C virus.

transplants had kidney biopsies; three biopsies revealed acute cellular rejection, one of which was borderline rejection (Supplemental Table 4 provides details). Per protocol, all recipients underwent surveillance for post-transplant proteinuria quantified using the ratio of urine protein to creatinine in a spot urine sample. Supplemental Table 5 shows that five recipients developed proteinuria estimated to be >1 g/d (range of urine protein-to-creatinine ratio, 1.03–1.79) at a time interval longer than 7 days post-transplant. For four of these recipients, estimated proteinuria had decreased to <300 mg/d at last evaluation, whereas the fifth recipient still had proteinuria estimated at 1.07 g/d at the last per-protocol evaluation. Two of the five had kidney biopsies, with the main indication for biopsy in both cases being elevated creatinine; one had acute tubular injury on biopsy whereas the other had pyelonephritis.

Six-month graft function was excellent; median creatinine was 1.2 (IQR, 1.06–1.50) mg/dl and median eGFR was 57 (IQR, 47–75) ml/min per 1.73 m^2. Figure 3 shows post-transplant trends in serum creatinine over time.

In general, G/P was well-tolerated in the post-transplant period. The most common adverse events during the treatment period were dizziness (n=7), hypertension (n=7), hyperglycemia (n=5), hyperkalemia (n=5), hypotension (n=5), nausea (n=5), and vomiting (n=5). In addition, 16 recipients of HCV-viremic kidney transplants experienced a total of 21 SAEs while on G/P. Supplemental Table 6 shows all SAEs. None of the SAEs were deemed by the study investigators to be related to either HCV viremia or G/P.

None of the 30 recipients of HCV-viremic kidneys experienced clinically significant hepatic enzyme elevations after transplant, defined per protocol as having ALT≥5 times the upper limit of normal. No patients developed clinical signs or symptoms of liver disease or required hospitalization or intervention for liver disease. Figure 4 displays trends in ALT at

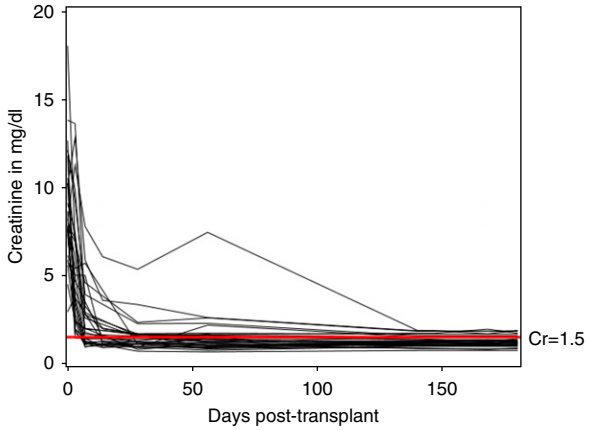

Figure 3. Post-transplant trends in serum creatinine in 30 HCV-negative recipients of HCV-viremic kidneys.

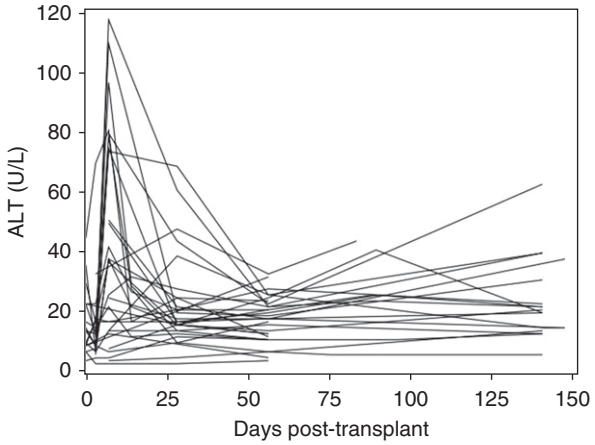

Figure 4. Post-transplant trends in serum ALT in 30 HCV-negative recipients of HCV-viremic kidneys. Glecaprevir/pibrentasvir (G/P) was started between days 2–5 in arm one recipients. Per protocol, ALT was measured peri-transplant, and at the following visits after transplant: day 3, day 1 of G/P treatment, week 1 treatment, week 4 treatment, and week 8 treatment.

study visits. Trends in aspartate aminotransferase and total bilirubin were similar (not shown).

BK Virus among Recipients of HCV-Viremic Kidney Transplants

All 30 recipients underwent PCR testing for the presence of BK virus in the blood and/or urine, with a median of 5 (IQR, 2–8) tests on different dates post-transplant. Five recipients ever had detectable BK virus in the blood. One had a peak BK level >10,000 copies/ml (the level often considered consistent with presumptive BK virus nephropathy), whereas two others had peak BK level between 9800 and 10,000 copies/ml. In four of those five patients, the oral immunosuppression dose was reduced. All five patients had undetectable or unquantifiable BK virus in the blood at last follow-up.

HCV Antibody Serostatus among Recipients of HCV-Viremic Kidney Transplants

Supplemental Figure 2 shows changes in serum HCV antibody status among the 30 recipients through week 4 of G/P treatment, among whom 28 (93%) had negative HCV antibody pretransplant whereas two (7%) had positive HCV antibody at the time of transplant. In the immediate post-transplant period, ten of the 28 with baseline negative result had a detectable HCV antibody. By G/P treatment week 4, seven of the 28 had a detectable HCV antibody, including two recipients who were HCV antibody negative initially post-transplant.

DISCUSSION

In the MYTHIC trial, all 30 HCV-negative recipients of HCV-infected kidney transplants were cured of HCV with an 8-week course of G/P. In this study, G/P treatment was initiated within 2–5 days of kidney transplant and, despite intense induction immunosuppression and a duration of therapy 4 weeks shorter than the Food and Drug Administration–approved treatment course for chronic HCV infection in kidney transplant recipients, patients had rapidly declining viral loads and all achieved SVR12.[18] In the context of an acute HCV infection and early initiation of DAA treatment, liver function test abnormalities were rare and low-grade. Once consented, participants who received an HCV-viremic organ waited a median of 6.3 weeks. A total of seven recipients had delayed graft function. G/P is not eliminated through the kidneys and, thus, is not expected to pose any additional safety concerns even in those with delayed graft function. Six-month allograft function was excellent, with a median creatinine of 1.2 mg/dl. The MYTHIC study should encourage more transplant centers to develop formal programs with rigorous patient education and informed consent to support the increased utilization of HCV-infected donors.[10,19]

The THINKER, EXPANDER, and NECKER trials demonstrated the potential safety and efficacy of transplanting kidneys from HCV-viremic donors into HCV-negative recipients.[4,5,20,21] However, all three studies used a 12-week course of grazoprevir and elbasvir, a non–pan-genotypic DAA regimen, as the backbone of therapy; this regimen is no longer recommended by the American Association for the Study of Liver Diseases.[22,4,21–23] Subsequent studies in kidney transplantation either used "ultra-short course" pan-genotypic therapy,[23,24] or used a "standard-of-care" approach with 12-week treatment duration but began therapy weeks to months after transplant.[6,13] Although both approaches are promising, one trial of "ultra-short course" therapy (2–4 days) was associated with treatment failures, including one patient who developed a highly resistant virus, whereas the delayed treatment approach has been associated with increased risks of cytomegalovirus and BK virus, and several cases of fibrosing cholestatic hepatitis.[6,13,23] The largest

clinical trial published to date of transplanting 44 HCV-viremic organs into HCV-negative recipients is in thoracic transplantation and at a single center, where sofosbuvir/velpatasvir started 6 hours after heart or lung transplant achieved 100% HCV cure rates.[25] This approach utilized a 4-week course of DAA treatment, yet application in routine practice would require that hospitals stock DAA therapy on formulary for immediate administration, and oral administration of the DAAs would need to be feasible without interruption.

In this context, the MYTHIC study is novel and provides a practical example that could be applied in real-world settings. First, our study enrolled a geographically and racially diverse group of patients from seven different transplant centers. Second, DAA therapy was initiated early within 2–5 days of transplant, which could be applied outside of a trial in the setting of expedited insurance approval of DAA therapy, although we acknowledge that an expedited pathway may not yet exist with many insurance plans.[26] Third, the use of a pan-genotypic regimen allowed for early deployment of DAA therapy without the need for prior identification of the HCV genotype. Finally, in MYTHIC, we utilized an 8-week treatment course of G/P, which is 4 weeks shorter than other regimens and achieved 100% SVR12. Shortened therapy would enhance the cost-effectiveness of the strategy of HCV-viremic to HCV-uninfected kidney transplant, which also depends on whether the strategy of accepting HCV-viremic transplantation reduces dialysis time.[27]

In the context of protocol-driven monitoring for adverse events with oversight from a data safety and monitoring board, we observed no SAEs adjudicated as likely related to HCV viremia or G/P treatment. Importantly, no recipient of a kidney from an HCV-viremic donor developed evidence of clinically meaningful liver disease. The ability of a multicenter consortium to achieve these results despite expected center-to-center variation in immunosuppression and post-transplant care practices should both provide substantial reassurance to future patients considering HCV-viremic organs and be a useful element of the informed consent process.

Prior studies of donor-derived HCV infection have also drawn attention to potential immunologic complications. Three recipients of HCV-viremic donor kidneys in MYTHIC developed acute cellular rejection between 3- and 6-months post-transplant, one of which was borderline rejection. A 10% cumulative prevalence of acute cellular rejection with median 9 months follow-up in a cohort treated predominantly with thymoglobulin induction and a maintenance regimen of tacrolimus, mycophenolate mofetil, and prednisone is slightly higher than observed in some other trials and cohorts.[28–30] However, the MYTHIC trial did not have a randomized comparator group, limiting inferences about whether HCV infection promotes rejection; this outcome should be examined in future, larger studies. One recipient developed BK viremia with >10,000 copies/ml, and two others had BK viremia close to 10,000 copies/ml, which is considered presumptive evidence of BK nephropathy by many experts.[31] All 30 MYTHIC recipients had no BK virus detectable at last surveillance, which is an encouraging outcome in light of concerns after publication of a 53-patient cohort by Molnar *et al.*[6] from Methodist University Hospital in Tennessee in which 34% of recipients of HCV-viremic kidneys developed BK viremia. Recipients in the Methodist cohort received DAA treatment a median of 76 days post-transplant. We hypothesize that the much lower rates of BK infection in MYTHIC and other studies are likely due to rapid DAA initiation; uncontrolled HCV infection after transplantation may reduce the immune system's ability to curb replication of other viruses.

We also acknowledge several important limitations. Because of the paucity of data about the risks of donor-derived, *de novo* HCV infection with transplant when MYTHIC was designed, we specified the inclusion and exclusion criteria with the main goal of minimizing risks. For example, all patients underwent Fibroscan elastography to exclude significant fibrosis. Therefore, it is unknown whether patients with more-advanced liver fibrosis could safely receive HCV-viremic kidney transplants. We also draw attention to the upper age limit of 65 years, which was implemented because of some evidence that older patients may be more susceptible to complications of acute viral infection.[32,33] Given the growing percentage of kidney transplant candidates >65 years of age, future trials may consider a higher age limit.[34] The excellent outcomes from MYTHIC may also be due to initiation of G/P treatment in the first few days after transplant, which is not generally feasible at many centers. On the other hand, transplant centers developing clinical programs to offer HCV-viremic organ transplants to their patients should work with hospital-based or payer-based mechanisms to support early HCV treatment. Furthermore, the small size and lack of a comparator group limit our ability to draw firm conclusions about the safety of this approach, although the 100% HCV cure rate is an important favorable outcome that requires no comparator group to evaluate. The success of this trial was also dependent on the excellent compliance of patients with their study treatment and follow-up visits; transplant centers must have adequate safety nets in place to provide DAA therapy as well as the ability and training to closely follow these patients. Finally, DAAs are costly. To address this cost issue, one transplant center has tested "ultra-short–course" DAA therapy that was administered immediately after transplant. However, this approach led to several treatment failures and one recipient who could not be cured of HCV.[23] We also note that kidney transplantation using HCV-infected kidneys and full-course DAAs is likely cost-effective if the approach reduces dialysis time.[27,35]

In summary, the MYTHIC trial enabled short waiting times from consent to kidney transplantation with HCV-viremic kidneys for 30 patients. Beginning antiviral therapy in the first several days after transplantation was associated with low postoperative HCV viral loads, which became either

undetectable or unquantifiable in all recipients of HCV-viremic kidneys by 4 weeks of treatment. Six-month allograft function was excellent, as expected for transplants with a median KDPI score of 53% and median donor age of 34 years. No SAEs were attributed to HCV or G/P therapy. Transplant centers should take note of these results and take advantage of the important opportunity to increase access to high-quality HCV-viremic organs, with the ultimate goal of increasing quality and quantity of life for patients waiting for kidney transplant.

DISCLOSURES

R. Alloway is an advisor and on the speakers' bureau for Genzyme/Sanofi and Veloxis. R. Brown has consulted personally for AbbVie, Gilead, and Merck & Co. N. Desai participated as an investigator on clinical trials funded by Merck and served as a consultant and speaker for Merck. C. Durrand serves on a grant review committee for Gilead sciences. R. Fontana provided consulting services to Sanofi. J. Friedewald is an equity owner of and consultant for Transplant Genomics, Inc., and is a member of Novartis, speakers' bureau, Novartis, Sanofi. J. Kort is an employee of AbbVie, may hold AbbVie stocks, and has a patent (US2017333428) issued to AbbVie, Inc. J. Levitsky served as a speaker for Gilead and Novartis, as a consultant for Novartis and Transplant Genomics, Inc., as a researcher for Novartis, and may own stock in Transplant Genomics, Inc. K.E. Sherman served as a consultant on the advisory board for Abbott Labs, Inovio, and UniQure, and served on the data safety and monitoring board for Inovio, MedPace, and Watermark. M. Sise has participated in scientific advisory board meetings for AbbVie, Gilead, and Merck W. Williams served as a consultant and investigator for Transplant Genomics, Inc., and on the external advisory board for Vertex Pharmaceuticals. All remaining authors have nothing to disclose.

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SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020050686/-/DCSupplemental.

Supplemental Table 1. Inclusion and exclusion criteria for the MYTHIC trial.

Supplemental Table 2. Summary of the visit schedule for recipients of HCV-viremic kidneys.

Supplemental Table 3. Characteristics of 30 HCV-viremic deceased donor kidneys.

Supplemental Table 4. Kidney biopsies in recipients of HCV-viremic kidneys.

Supplemental Table 5. Proteinuria among recipients of HCV-viremic kidneys.

Supplemental Table 6. Serious adverse events among 63 patients consented for MYTHIC.

Supplemental Figure 1. Cumulative incidence of kidney transplant in the MYTHIC trial.

Supplemental Figure 2. Changes in serum HCV antibody status among the 30 recipients of HCV-viremic deceased donor kidneys.

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