ORIGINAL ARTICLE

Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients

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ABSTRACT

BACKGROUND

Hearts and lungs from donors with hepatitis C viremia are typically not transplanted. The advent of direct-acting antiviral agents to treat hepatitis C virus (HCV) infection has raised the possibility of substantially increasing the donor organ pool by enabling the transplantation of hearts and lungs from HCV-infected donors into recipients who do not have HCV infection.

METHODS

We conducted a trial involving transplantation of hearts and lungs from donors who had hepatitis C viremia, irrespective of HCV genotype, to adults without HCV infection. Sofosbuvir–velpatasvir, a pangenotypic direct-acting antiviral regimen, was preemptively administered to the organ recipients for 4 weeks, beginning within a few hours after transplantation, to block viral replication. The primary outcome was a composite of a sustained virologic response at 12 weeks after completion of antiviral therapy for HCV infection and graft survival at 6 months after transplantation.

RESULTS

A total of 44 patients were enrolled: 36 received lung transplants and 8 received heart transplants. The median viral load in the HCV-infected donors was 890,000 IU per milliliter (interquartile range, 276,000 to 4.63 million). The HCV genotypes were genotype 1 (in 61% of the donors), genotype 2 (in 17%), genotype 3 (in 17%), and indeterminate (in 5%). A total of 42 of 44 recipients (95%) had a detectable hepatitis C viral load immediately after transplantation, with a median of 1800 IU per milliliter (interquartile range, 800 to 6180). Of the first 35 patients enrolled who had completed 6 months of follow-up, all 35 patients (100%; exact 95% confidence interval, 90 to 100) were alive and had excellent graft function and an undetectable hepatitis C viral load at 6 months after transplantation; the viral load became undetectable by approximately 2 weeks after transplantation, and it subsequently remained undetectable in all patients. No treatment-related serious adverse events were identified. More cases of acute cellular rejection for which treatment was indicated occurred in the HCV-infected lung-transplant recipients than in a cohort of patients who received lung transplants from donors who did not have HCV infection. This difference was not significant after adjustment for possible confounders.

CONCLUSIONS

In patients without HCV infection who received a heart or lung transplant from donors with hepatitis C viremia, treatment with an antiviral regimen for 4 weeks, initiated within a few hours after transplantation, prevented the establishment of HCV infection. (Funded by the Mendez National Institute of Transplantation Foundation and others; DONATE HCV ClinicalTrials.gov number, NCT03086044.)

A SHORTAGE OF AVAILABLE DONOR HEARTS and lungs limits transplantation in the United States, where approximately 1000 patients die each year while waiting for these organs.[1,2] Although organ transplantation has increased by 20% during the past 5 years — largely because of an increase in the number of available donors who have died from a drug overdose — many organs that are otherwise medically suitable for transplantation have not been used because of hepatitis C virus (HCV) infection in the donors.[3,4]

In the past, transplantation of organs from HCV-infected donors into uninfected recipients typically led to chronic HCV infection in the recipients, with HCV transmission to as many as 82% of the recipients.[5,6] Some studies have shown an increased mortality from liver disease and the development of accelerated graft damage due to graft vasculopathy among recipients of hearts from HCV-infected donors.[5,7,8]

The development of potent direct-acting antiviral agents to treat HCV infection has provided an opportunity to treat this infection in patients who acquire it through organ transplantation, although the use of organs from infected donors has been controversial.[9-13] Early data on patients who have received kidney and liver transplants suggest that treatment of HCV infection early after transplantation is feasible.[14-16] Therefore, given the need for organs in patients with advanced heart or lung failure, we conducted the Donors of Hepatitis C NAT [nucleic acid amplification test] Positive Thoracic Allografts for Transplantation Evaluation in Non-HCV Recipients (DONATE HCV) trial to determine whether organs from donors with hepatitis C viremia could be safely used in uninfected recipients. We hypothesized that by preventing transmission of HCV infection in recipients through a preemptive, shortened course of direct-acting antiviral therapy initiated hours after transplantation, hearts and lungs from HCV-positive donors might be safely transplanted into uninfected recipients.

METHODS

TRIAL POPULATION

We conducted this open-label pilot trial at Brigham and Women's Hospital in Boston to assess safety and efficacy. Patients were eligible for the trial if they were adults who had active status on the waiting list for heart or lung transplantation and were eligible to receive an organ from an increased-risk donor who had evidence of active HCV infection (i.e., positive results on an HCV NAT). According to the protocol (available with the full text of this article at NEJM.org), the trial was designed to include two complementary but independent groups according to the donor HCV status at the time of organ procurement (either HCV NAT–positive or HCV antibody–positive and HCV NAT–negative). The results in the HCV NAT–positive donor group met the scientific objectives of the protocol, so we are reporting these results.

A Quick Take is available at NEJM.org

TRIAL OVERSIGHT

The trial was approved by the institutional review board of Brigham and Women's Hospital and was conducted in collaboration with New England Donor Services. All patients provided written informed consent (details are provided in the Supplementary Appendix, available at NEJM.org). The trial was monitored by an independent data and safety monitoring board. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. No one who is not an author contributed to the writing of the manuscript.

INCLUSION AND EXCLUSION CRITERIA

Adult patients (18 years of age or older) who were on the waiting list for heart or lung transplants were eligible to participate in the trial if they were able to provide written informed consent to receive an organ from an increased-risk donor with a known transmissible HCV infection. The criteria for donor acceptance with respect to the quality of the donor organ, the geographic distance from the procurement center to the transplantation center, and procurement protocols were the same for HCV NAT–positive donors and donors who were not infected with HCV. HCV-infected donors were accepted for the trial before their HCV genotypes and quantitative hepatitis C viral loads were determined.

COMPOSITION, TIMING, AND DURATION OF DIRECT-ACTING ANTIVIRAL TREATMENT

The patients received a 4-week regimen of sofosbuvir (at a dose of 400 mg) plus velpatasvir (at a dose of 100 mg) once daily. The trial medication was provided by the hospital. No financial support or medication was received from the manufacturers of the medication used in the trial. This regimen was chosen because of its activity against all circulating HCV genotypes and its lack of drug

interactions with the immunosuppressive regimens used (see the Supplementary Appendix). The investigators assumed that the recipients would be exposed to a low hepatitis C viral load at the time of transplantation and initiation of direct-acting antiviral treatment. Therefore, a shorter duration of treatment than that used for patients with chronic HCV infection was hypothesized to be efficacious, since a short regimen is analogous to postexposure prophylaxis.[14] This type of transplantation differs from liver transplantation, because the heart and lungs are not reservoirs for HCV.[5] Preemptive treatment was administered to the organ recipients for 4 weeks, beginning on the day of transplantation, with the first dose administered a few hours after transplantation (Fig. 1A). An investigational new drug exemption for this treatment plan was obtained from the Food and Drug Administration.

Figure 1 (facing page). Trial Design and Patient Populations.

Panel A shows the trial design for treatment and monitoring tests after transplantation, and Panel B shows eligibility, screening, randomization, and transplantation in the trial patients. HBsAg denotes hepatitis B virus surface antigen, and NAT nucleic acid amplification test.

OUTCOMES

The primary outcome of the trial was the combination of a sustained virologic response at 12 weeks after completion of antiviral therapy for HCV infection (i.e., 16 weeks after transplantation) and graft survival at 6 months after transplantation. Secondary outcomes were the occurrence of irreversible adverse events of grade 3 or higher or severe adverse events that were deemed by the investigators and the data and safety monitoring board to be attributable to HCV infection; graft survival at 1 month and 12 months after transplantation; death at 1 month, 6 months, and 12 months after transplantation; a sustained virologic response 4 weeks and 24 weeks after completion of antiviral therapy; and the safety and side-effect profile of direct-acting antiviral regimens in the lung-transplant and heart-transplant recipients. The incidence of acute cellular rejection in the allograft for which treatment was indicated and mortality after transplantation were compared with these outcomes in all patients who received hearts and lungs during the same period from donors who did not have HCV infection.

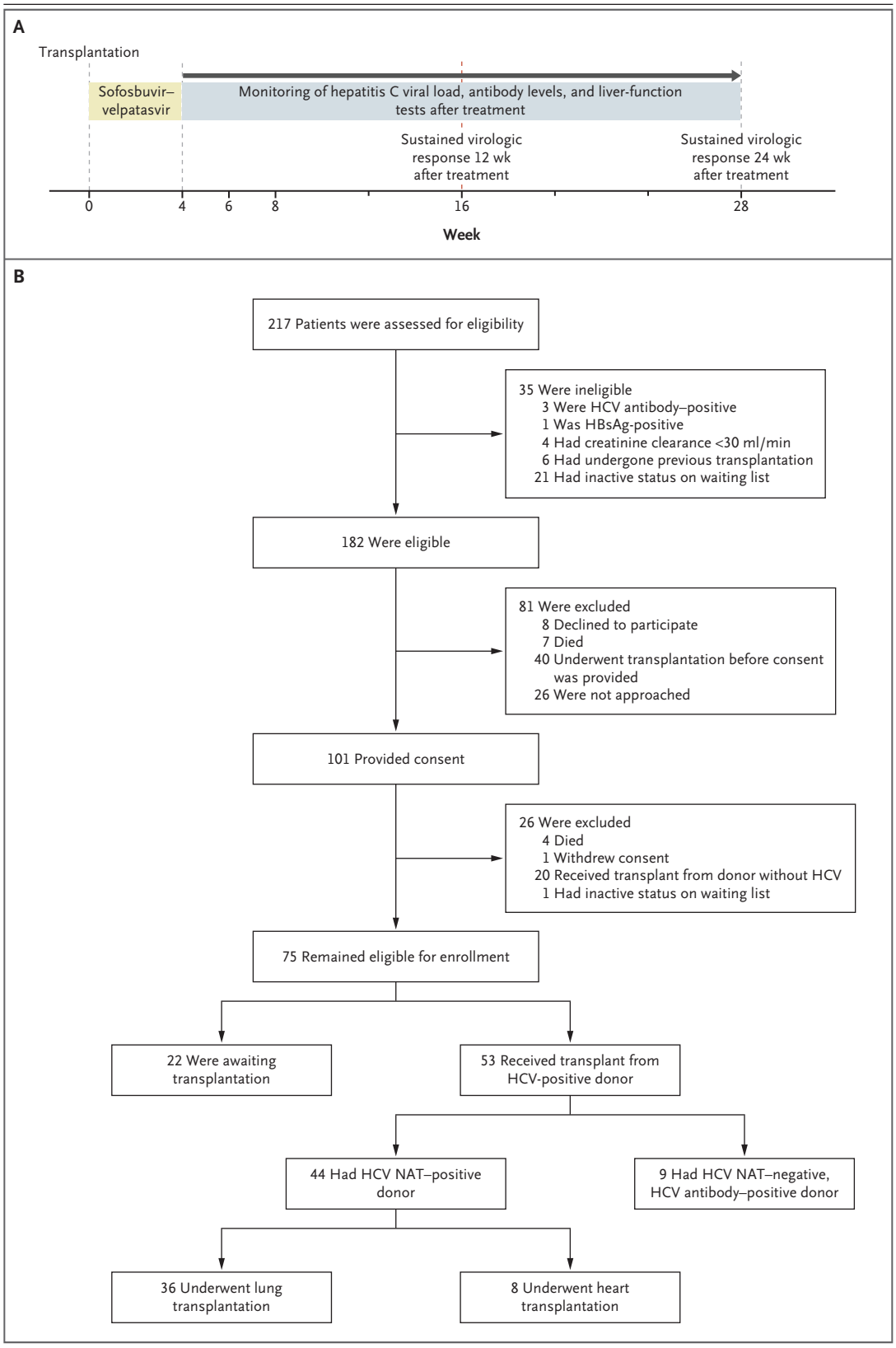
STATISTICAL ANALYSIS

The trial was initially designed as a two-stage, phase 2 trial according to the design described by Simon,[17] with a planned interim analysis after outcome data were available for 16 patients. Because of continuous safety monitoring, the sequential design for evaluating outcomes was amended in August 2017 to continuous monitoring of the sustained virologic response 12 weeks after completion of antiviral therapy and 6-month graft survival with the use of the sequential probability ratio test for a binomial distribution. After the amendment, continuous monitoring for a trial group began when the eighth patient had outcome data that could be evaluated, and the sequential probability ratio test boundaries were constructed so that the probability of crossing a boundary and declaring success was 0.81 if the probability of a successful outcome was 0.90. If the true probability of success was 0.75, the probability of crossing a lower boundary was 0.84. When a boundary was reached, the original analysis plan posited a test for efficacy based on a one-sided alpha of 0.05, by means of an exact binomial test of the null hypothesis that the probability of a sustained virologic response 12 weeks after completion of antiviral therapy and 6-month graft survival was 0.75.

The monitoring rule for adverse events was based on published monitoring plans.[18] The trial team and the data and safety monitoring board adjudicated whether adverse events were attributable to HCV infection.

In exploratory, post hoc analyses, possible differences in transplantation outcomes between the recipients of transplants from HCV-positive donors and the recipients of transplants from HCV-negative donors are shown with point estimates and unadjusted two-sided 95% confidence intervals. In the lung-transplant recipients, a post hoc logistic-regression analysis was used to explore the association between the safety outcome of acute cellular rejection for which treatment was indicated and HCV donor status after adjustment for possible confounders.

Baseline variables were compared between the HCV and non-HCV cohorts in the lung-transplant and heart-transplant groups with the use of either



a Wilcoxon rank-sum test (for continuous variables) or Fisher's exact test (for categorical variables). All statistical analyses were performed with the use of R software, version 3.5.1 (R Foundation for Statistical Computing).

RESULTS

TRIAL POPULATION

From March 1, 2017, to July 31, 2018, a total of 217 patients with active status on waiting lists for heart or lung transplantation were screened to participate in the trial and were assessed for eligibility. Eleven of those patients (5%) died while awaiting transplantation, and 35 patients (16%) were ineligible because they had an inactive status on the waiting list or they had positive test results for HCV antibodies or hepatitis B virus surface antigen (HBsAg), had a creatinine clearance of less than 30 ml per minute, or had had graft failure warranting a second transplant. Of 182 patients who were eligible, 101 patients provided written informed consent. Of these patients, 4 (4%) died before undergoing transplantation and 20 (20%) received a transplant from a donor who did not have HCV infection (Fig. 1B).

TRIAL PROGRESS AND THE PRIMARY OUTCOME

The stopping boundary for efficacy in the trial was crossed in February 2018, when the first 13 patients with 6 months of follow-up had a sustained virologic response 12 weeks after completion of antiviral therapy and 6-month graft survival ($P=0.02$ for the one-sided exact binomial test of the null hypothesis of 0.75 probability of success; exact one-sided 95% confidence interval [CI], 0.79 to 1.00). By February 2018, when the stopping boundary for efficacy had been met, 35 patients had been enrolled. The 6-month findings in those 35 patients are presented here. Given the successful outcomes, enrollment continued past February 2018 according to the trial design and in discussion with the data and safety monitoring board to allow the use of as many HCV-positive organs as possible and to better define the efficacy and safety.

As of July 31, 2018, a total of 44 patients were enrolled: 36 who underwent lung transplantation and 8 who underwent heart transplantation, with a total follow-up of 10,624 days and a median follow-up of 284 days (interquartile range, 171 to 365). Of the 44 enrolled patients, 35 patients had at least 6 months of follow-up, and 16 patients had at least 1 year of follow-up.

The primary outcome — a sustained virologic response 12 weeks after completion of antiviral therapy and graft survival at 6 months — was met in all 35 patients with at least 6 months of follow-up (exact two-sided 95% CI, 90 to 100). Of the 9 patients with follow-up of less than 24 weeks, data were available for 5 patients after week 8, and all 5 patients had had a sustained virologic response 4 weeks after completion of antiviral therapy (Fig. 2). Data for the remaining 4 patients were available between week 4 (completion of treatment for HCV infection) and week 8, and all these patients had an undetectable hepatitis C viral load.

The median viral load in the HCV-infected donors was 890,000 IU per milliliter (interquartile range, 276,000 to 4.63 million). The HCV genotypes were genotype 1 (in 61% of the donors, of whom 96% had genotype 1a), genotype 2 (in 17%), genotype 3 (in 17%), and indeterminate (in 5%). There were 41 donors for the 44 patients; both the heart and lungs were procured from 3 donors, whereas a single organ, either the heart or lungs, was procured from the other 38 donors. The initial hepatitis C viral load in the recipients was proportional to the viral load in the donor, with slightly higher viral loads in lung-transplant recipients than in heart-transplant recipients (Fig. 3A). A total of 42 of the 44 transplant recipients (95%) had a detectable hepatitis C viral load immediately after transplantation. The median initial viral load was 1800 IU per milliliter (interquartile range, 800 to 6180). All recipients had an undetectable hepatitis C viral load by approximately week 2, and the viral load subsequently remained undetectable (Fig. 3B).

KEY SECONDARY OUTCOMES

A total of 15 of the 16 organ recipients (94%) with data that could be evaluated 12 months after transplantation had graft survival at 12 months. One of the heart-transplant recipients died 8 months after transplantation from a disseminated bacterial infection, which the investigators and the data and safety monitoring board determined was not related to HCV infection. All 35 recipients who had completed at least 6 months of follow-up had a sustained virologic response 4 weeks after completion of antiviral therapy and a sustained virologic response 24 weeks after completion of anti-

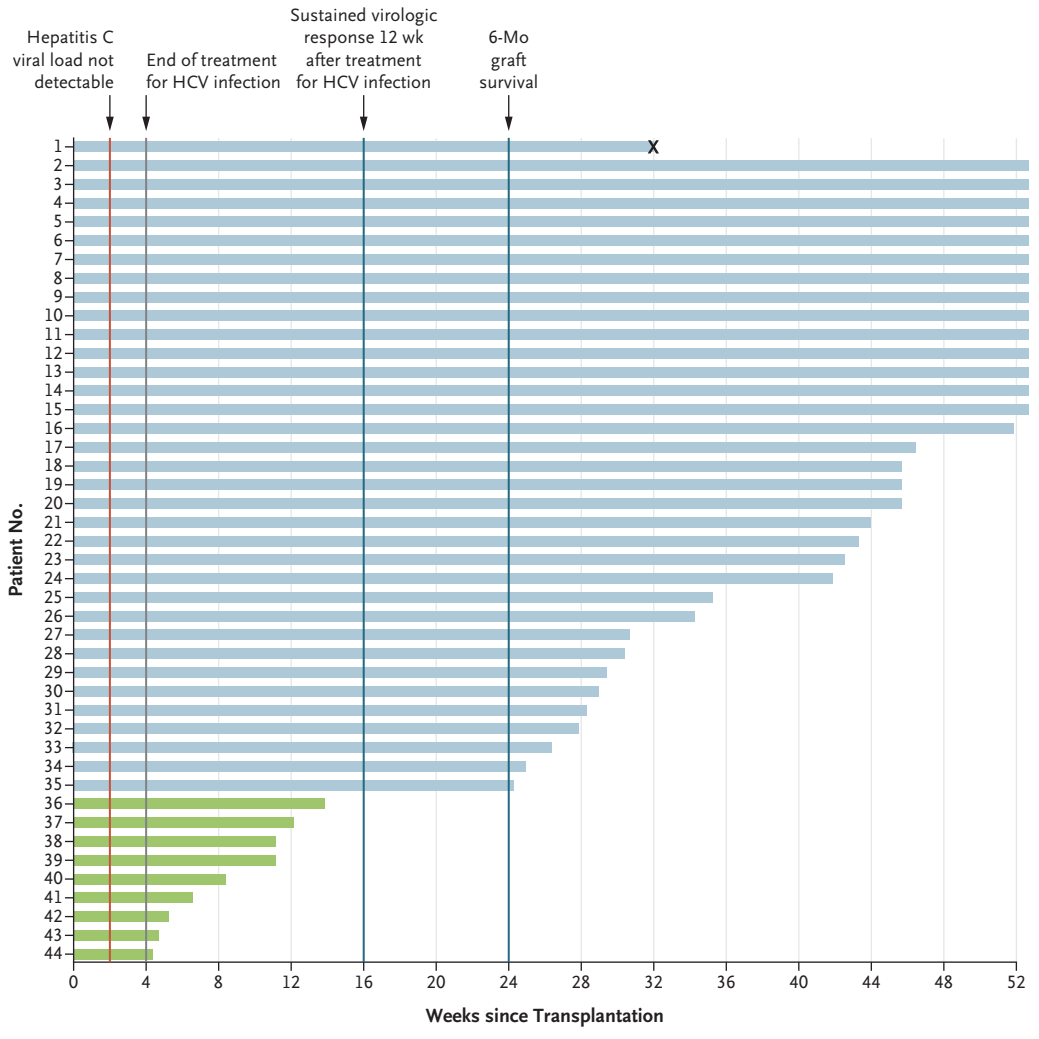


Figure 2. Results of Patient Follow-up after Transplantation.

The black X indicates that Patient 1 died at week 32. The green bars represent patients who had not completed 16 weeks of follow-up by July 31, 2018.

viral therapy. A total of 27 of the 35 recipients (77%) had positive HCV-antibody tests within 1 week after transplantation, and 17 of the 35 recipients (49%) continued to have positive HCV-antibody tests 6 months after transplantation.

RECIPIENTS OF ORGANS FROM DONORS WITH AND WITHOUT HCV INFECTION

Characteristics and outcomes in the trial population, including acute cellular rejection in the allograft for which treatment was required and mortality in the first year after transplantation, were compared with those in patients at our center during the same period who received hearts and lungs from donors who did not have HCV infection. During the trial, there were 77 transplantations of hearts and lungs from donors who did not have HCV infection; 20 of these recipients (26%) had provided consent to participate in this trial. A total of 53 patients received lung transplants and 24 received heart transplants, with a total follow-up of 20,956 days.

As of July 31, 2018, a total of 56 of the 77 patients who received transplants from donors without HCV infection had at least 6 months of follow-up, and 27 of the 77 patients had at least 1 year of

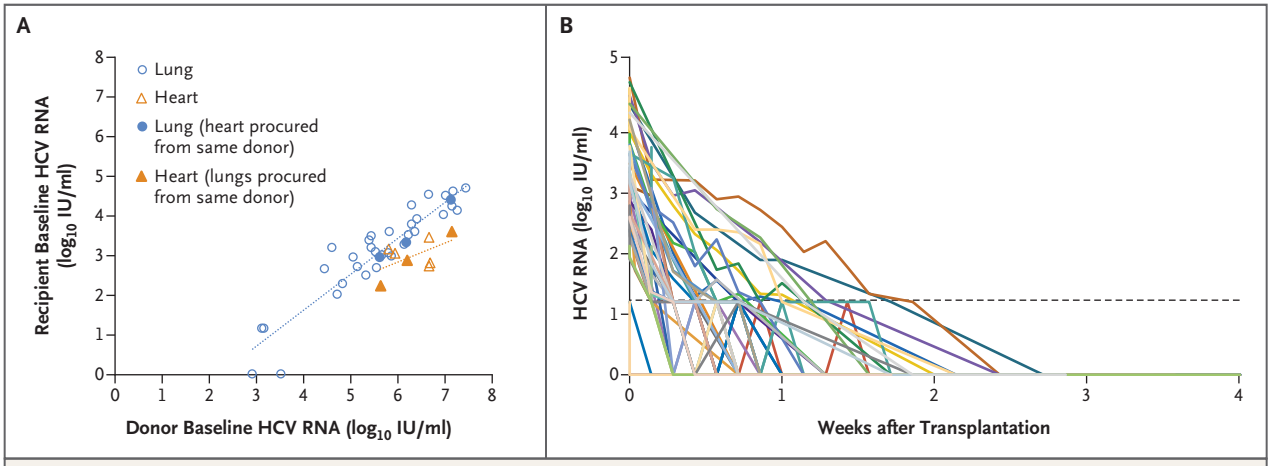


Figure 3. HCV RNA Levels.

Panel A shows the hepatitis C viral loads in the donors and recipients. Donor viral loads were measured at the time of organ procurement, and recipient viral loads were measured immediately after transplantation. There were 41 donors and 44 recipients; both the heart and lungs were procured from 3 donors, whereas a single organ, either the heart or lung, was procured from the other 38 donors. Panel B shows the decreases in the hepatitis C viral load in patients after transplantation. The viral load cleared in all recipients by approximately 2 weeks. The dashed line indicates the lower limit of quantification.

follow-up (Tables 1 and 2). The baseline characteristics of the recipients of lung transplants from donors with HCV infection and the recipients of lung transplants from donors without HCV infection differed significantly according to male sex (39% and 66%, respectively), median lung allocation score[19] (33.31 and 38.16; scores range from 0 to 100, with higher scores indicating a higher priority for a donor lung) (see the Supplementary Appendix), and the percentages of patients with restrictive lung disease (29% and 68%) and with obstructive lung disease (61% and 18%). The recipients who received a heart from a donor who did not have HCV infection had a higher Organ Procurement and Transplantation Network listing status[20] (100% had 1A status [see the Supplementary Appendix]) than the recipients who received a heart from an HCV-infected donor (most of whom had 1B status). Grades of pulmonary graft dysfunction at 72 hours after transplantation did not differ significantly between the two cohorts, although the mean donor ischemic time was significantly longer in the cohort of patients who received lungs from HCV-infected donors.

The outcomes between the two cohorts appear to be similar, but there are wide confidence intervals. The data suggest that the mean length of hospital stay after transplantation was shorter in the cohort of patients who received lungs from HCV-infected donors than in the cohort of patients who received lungs from donors without HCV infection, and fewer patients who received a heart from an HCV-infected donor stayed in a rehabilitation facility after transplantation than those who received a heart from a donor without HCV infection. The median time on the waiting list from consent to participate in the trial to transplantation was 22 days (range, 2 to 147) in the lung-transplant recipients and 78 days (range, 3 to 190) in the heart-transplant recipients.

SAFETY

All trial medication was administered to all patients without any interruptions or safety or side-effect issues related to the trial medication. A detailed list of the grade 3, grade 4, and serious adverse events is provided in Table S1 and Figure S1 in the Supplementary Appendix. No adverse events or serious adverse events were considered by the investigators and the data and safety monitoring board to be related to trial medication. No irreversible grade 3 or higher adverse events or serious adverse events were attributed by the investigators and the data and safety monitoring board to HCV infection. The adverse events in the first 30 days after transplantation and the 6-month sustained, irreversible adverse events in the patients who received organs from HCV-infected donors were similar to those in the patients who received

Table 1. Baseline Characteristics of the Transplant Recipients and Donors.*

Characteristic	Lung Transplantation		P Value†	Heart Transplantation		P Value†
	Organ from HCV NAT–Positive Donor (N=28)	Organ from Donor without HCV Infection (N=44)		Organ from HCV NAT–Positive Donor (N=7)	Organ from Donor without HCV Infection (N=12)	
Recipient						
Age — yr			0.92			1.00
Median	61	63		51	52	
Range	41–71	28–71		23–68	43–68	
Male sex — no. (%)	11 (39)	29 (66)	0.03	6 (86)	6 (50)	0.17
Race — no. (%)‡			1.00			
White	26 (93)	40 (91)		6 (86)	10 (83)	1.00
Other	2 (7)	4 (9)		1 (14)	2 (17)	
Median lung allocation score§	33.31	38.16	<0.001	NA	NA	
UNOS waiting-list status — no. (%)						<0.001
1A	NA	NA		1 (14)	12 (100)	
1B	NA	NA		5 (71)	0	
2	NA	NA		1 (14)	0	
Waiting-list time — days			0.05			0.30
Median	136	79		559	183	
Range	17–2616	3–2521		90–2366	3–1596	
Underlying disease — no. (%)			<0.001			0.52
Restrictive lung disease	8 (29)	30 (68)		NA	NA	
Obstructive lung disease	17 (61)	8 (18)		NA	NA	
Cystic fibrosis	3 (11)	6 (14)		NA	NA	
Ischemic cardiomyopathy	NA	NA		2 (29)	1 (8)	
Nonischemic cardiomyopathy	NA	NA		5 (71)	11 (92)	
Ventricular assist device — no. (%)	NA	NA		6 (86)	7 (58)	0.33
Bilateral transplantation — no. (%)	27 (96)	38 (86)	0.24	NA	NA	
Blood type — no. (%)			0.95			0.72
A	11 (39)	20 (45)		3 (43)	4 (33)	
B	3 (11)	3 (7)		2 (29)	1 (8)	
AB	1 (4)	2 (5)		0	1 (8)	
O	13 (46)	18 (41)		2 (29)	6 (50)	
Donor						
Age — yr			0.30			0.42
Median	32	33		27	31	
Range	21–53	14–64		24–42	20–53	
Increased risk — no. (%)¶	28 (100)	9 (20)	<0.001	7 (100)	3 (25)	0.003
Illicit drug use within 6 mo of death — no. (%)	20 (71)	22 (50)	0.09	5 (71)	5 (42)	0.35
History of cigarette use — no. (%)	6 (21)	3 (7)	0.14	0	2 (17)	0.51

* Data shown are from the analysis comparing the characteristics of the 35 patients who received organs from HCV-positive donors and had at least 6 months of follow-up with the characteristics of the 56 patients who received transplants from donors without HCV infection and had at least 6 months of follow-up. Percentages may not total 100 because of rounding. NA denotes not applicable, NAT nucleic acid amplification test, and UNOS United Network for Organ Sharing.

† All P values are two-sided and are based on Fisher's two-sided exact test (for categorical variables) or the Wilcoxon rank-sum test (for continuous variables).

‡ Race was reported by the patients.

§ Lung allocation scores range from 0 to 100, with higher scores indicating a higher priority for a donor lung when a compatible lung becomes available.

¶ According to the U.S. Public Health Service, an increased-risk donor has characteristics that could increase the risk of disease transmission (e.g., human immunodeficiency virus, hepatitis B virus, and HCV infection) to potential transplant recipients.

Table 2. Outcomes in the Transplant Recipients.*

Outcome	Lung Transplantation		Odds Ratio or Mean Difference (95% CI)†	Heart Transplantation		Odds Ratio or Mean Difference (95% CI)†
	Organ from HCV NAT–Positive Donor (N=28)	Organ from Donor without HCV Infection (N=44)		Organ from HCV NAT–Positive Donor (N=7)	Organ from Donor without HCV Infection (N=12)	
Mean donor ischemic time — min	327	281	46.65 (12.43 to 80.87)	269	236	33.64 (–20.50 to 87.78)
Mean cardiopulmonary-bypass time — min	185	199	–14.84 (–37.81 to 8.13)	167	170	–3.70 (–44.61 to 37.21)
Grade 3 pulmonary graft dysfunction at 72 hr — no. (%)	0	3 (7)	NE (0.26 to NE)	NA	NA	NA
Mean length of hospital stay after transplantation — days	14	21	–6.88 (–12.24 to –1.52)	49	72	–22.80 (–100.54 to 54.94)
Mean ICU stay after transplantation — days	6	10	–4.03 (–8.05 to –0.01)	38	36	2.12 (–77.28 to 81.52)
Patients with rehabilitation stay — no. (%)	13 (46)	17 (39)	0.73 (0.25 to 2.12)	0	7 (58)	NE (1.21 to NE)
Mean length of rehabilitation stay — days	31	32	–0.54 (–19.87 to 18.80)	NA	NA	
Patients with readmissions — no. (%)	22 (79)	36 (82)	1.22 (0.31 to 4.66)	3 (43)	9 (75)	3.69 (0.38 to 44.48)
Median readmissions — no.	2	2		1	2	
Patients with liver-function results >3 times upper limit of normal range — no. (%)‡						
<30 days after transplantation	2 (7)	5 (11)	1.66 (0.25 to 18.62)	3 (43)	8 (67)	2.53 (0.27 to 27.33)
≥30 days after transplantation	2 (7)	7 (16)	2.43 (0.42 to 25.83)	0	1 (8)	NE (0.10 to NE)
Stage 4 or 5 chronic kidney disease at 6 mo — no. (%)	8 (29)	9 (20)	0.65 (0.19 to 2.26)	2 (29)	4 (33)	1.24 (0.12 to 18.58)
Dialysis at 6 mo — no. (%)	1 (4)§	1 (2)	0.63 (0.01 to 51.10)	1 (14)	2 (17)	1.19 (0.05 to 82.40)
Respiratory failure at 6 mo — no. (%)	0	4 (9)	NE (0.43 to NE)	1 (14)	3 (25)	1.93 (0.12 to 122.13)
Acute cellular rejection for which treatment was indicated — no. of patients (%)	15 (54)	13 (30)	0.37 (0.12 to 1.09)	3 (43)	4 (33)	0.68 (0.07 to 7.06)
Graft survival — no. (%)						
1 mo	28 (100)	43 (98)	0 (0 to 61.23)	7 (100)	11 (92)	0 (0 to 66.79)
6 mo	28 (100)	43 (98)	0 (0 to 61.23)	7 (100)	10 (83)	0 (0 to 9.25)
Overall survival at 6 mo — no. (%)	28 (100)	43 (98)	0 (0 to 61.23)	7 (100)	10 (83)	0 (0 to 9.25)

* Data shown are from the analysis comparing the outcomes in the 35 patients who received organs from HCV-positive donors and had at least 6 months of follow-up with the outcomes in the 56 patients who received transplants from donors without HCV infection and had at least 6 months of follow-up. ICU denotes intensive care unit, NA not applicable, and NE could not be estimated.

† Estimates for categorical data are unadjusted odds ratios, and 95% confidence intervals are two-sided and were calculated with the use of Fisher's exact test. Estimates for continuous data are mean differences, and 95% confidence intervals were calculated with the use of t tests. The widths of the confidence intervals are not adjusted for multiple comparisons and should not be used to infer definitive differences between groups.

‡ The liver-function tests were measurements of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase.

§ This patient began dialysis on day 9 after transplantation, and sofosbuvir–velpatasvir treatment was continued without any adverse events.

organs from donors without HCV infection. None of the recipients died in the first 6 months. One of the patients who received a heart transplant died at 8 months.

Although none of the recipients of a lung transplant from an HCV-infected donor had worsening pulmonary graft dysfunction at 72 hours after transplantation, low-grade acute cellular rejection for which treatment was indicated was noted in the first 6 months in more recipients of an organ from an HCV-positive donor than in recipients of an organ from an HCV-negative donor. No high-grade cellular rejection was seen in the recipients of a lung transplant from an HCV-infected donor, and only one patient (4%) had antibody-mediated rejection, as compared with five patients (15%) among recipients of a lung transplant from donors without HCV infection during the trial period. All the lung-transplant recipients with acute cellular rejection had a response to the initial treatment of pulse-dosed glucocorticoids. The incidence of acute cellular rejection was similar in recipients of a heart transplant from an HCV-positive donor and recipients of a heart transplant from an HCV-negative donor.

The odds of acute cellular rejection for which treatment was indicated were smaller among recipients of lung transplants from donors without HCV infection than among recipients of lung transplants from HCV-infected donors (odds ratio, 0.37; 95% CI, 0.12 to 1.09). The adjusted odds ratio was 0.65 (95% CI, 0.12 to 3.58) in a logistic-regression analysis that incorporated the lung allocation score, donor ischemic time, the increased-risk status of the donor, and underlying pulmonary disease in the recipients. The recipient's initial hepatitis C viral load was not significantly associated with the occurrence of acute cellular rejection for which treatment was indicated (odds ratio, 1.35 per $\log_{10}$ viral load [IU per milliliter]; 95% CI, 0.70 to 2.59).

DISCUSSION

These data show that hearts and lungs from donors with hepatitis C viremia can be used for transplantation, despite evidence of transmission of HCV in nearly all recipients. A 4-week course of a pangenotypic antiviral agent blocked ongoing HCV replication. The hepatitis C viremia was cleared in all recipients by approximately 2 weeks, and HCV remained undetectable thereafter. This regimen was effective irrespective of the baseline viral loads.

This regimen was not associated with any identifiable toxic effects, and 100% adherence to the treatment was achieved. This short 4-week course of treatment was probably successful because this situation is analogous to postexposure prophylaxis rather than treatment of established infection (in which 8 to 12 weeks of treatment are administered in patients with typically higher viral loads). These data build on trials of kidney and liver transplantation and a case series in heart transplantation[15,16,21]; however, there are key differences in our trial. For instance, we used a short course of therapy, HCV genotyping before transplantation was not required because of the pangenotypic regimen, the antiviral agent was administered preemptively, and our approach was used in heart and lung transplantations. This streamlined approach is easily scalable for adoption by other centers.

The emergence of HCV antibodies in many of the recipients was an unexpected finding, but it was probably related to the passive transfer of donor antibodies in a clinical setting involving ultrasensitive antibody-detection methods or the transfer of passenger lymphocytes in the transplanted grafts. We think these are the most likely explanations, since the antibodies were detected very early after transplantation, before the recipients' adaptive immune response could develop, especially in patients who were receiving induction immunotherapy. In addition, limited HCV antigen delivery probably occurred at the time of transplantation, and levels of HCV antibodies decreased over time and were no longer detectable in one third of the patients in follow-up. Studies are under way to better characterize the source of the HCV antibodies.

Safety was shown but cannot be fully assessed given the small numbers of patients in the trial and the inherent complexity of heart and lung transplantation. Acute cellular rejection for which treatment was indicated occurred in more recipients of lung transplants from HCV-positive donors than in recipients of lung transplants from donors who did not have HCV infection; this is possibly explained by differences between the patient groups that were compared in this open-label trial. Organs obtained from increased-risk donors with a history of intravenous drug use may contain excipient deposits in the donor lung

(which complicates the diagnosis of rejection on surveillance biopsies) or the presence of HCV antigen may result in inflammation and contribute to stimulation of the immune response and consequent rejection. Alternatively, this finding may be due to chance. The pulmonary graft dysfunction score at 72 hours after transplantation, the low grade of rejection observed, the lack of increased rejection in the patients with longer follow-up, and the lack of increased rejection in the heart-transplant recipients are all reassuring. The 6-to-12-month follow-up period is insufficient to assess the potential effect of the higher incidence of acute cellular rejection on the incidence of chronic lung-allograft dysfunction. In addition, the 5% mortality among patients on the transplant waiting list during the trial period should not be overlooked. Further follow-up is needed so that the full potential risk–benefit profile of this intervention can be better characterized.

This is a small trial; thus, conclusions based on these data should be made with caution. The limitations of this trial include its single-center nature, the small numbers of various HCV genotypes studied, and the limited follow-up time, which does not allow for the long-term assessment of chronic lung-allograft dysfunction or cardiac allograft vasculopathy. The direct-acting antiviral regimen used to treat HCV infection warrants further study in patients with clinically significant renal dysfunction (creatinine clearance <30 ml per minute). This was an open-label trial because randomization was not deemed to be possible. The results show that this can be a successful strategy, and the comparisons with the recipients of heart and lung transplants during the same period who received organs from donors who were not infected with HCV are encouraging. Since this approach is preemptive, which probably prevents the hepatic phase of established lytic infection, it is unclear how much therapy is required after clearance of HCV in the bloodstream. On the basis of our data, it is unclear whether treatment for 4 weeks is required or whether even shorter courses may be equally effective.

In our trial, hearts and lungs from HCV-infected donors were transplanted safely with excellent graft function at 6 and 12 months. However, longer-term data are needed to fully define the risk–benefit profile.

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