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Transplanting Hepatitis C Virus–Infected Versus Uninfected Kidneys Into Hepatitis C Virus–Infected Recipients

A Cost-Effectiveness Analysis

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Background: Direct-acting antiviral agents are now available to treat chronic hepatitis C virus (HCV) infection in patients with end-stage renal disease (ESRD).

Objective: To examine whether it is more cost-effective to transplant HCV-infected or HCV-uninfected kidneys into HCV-infected patients.

Design: Markov state-transition decision model.

Data Sources: MEDLINE searches and bibliographies from relevant English-language articles.

Target Population: HCV-infected patients with ESRD receiving hemodialysis in the United States.

Time Horizon: Lifetime.

Perspective: Health care system.

Intervention: Transplant of an HCV-infected kidney followed by HCV treatment versus transplant of an HCV-uninfected kidney preceded by HCV treatment.

Outcome Measures: Effectiveness, measured in quality-adjusted life-years (QALYs), and costs, measured in 2017 U.S. dollars.

Results of Base-Case Analysis: Transplant of an HCV-infected kidney followed by HCV treatment was more effective and less costly than transplant of an HCV-uninfected kidney preceded by HCV treatment, largely because of longer wait times for uninfected kidneys. A typical 57.8-year-old patient receiving hemodialysis would gain an average of 0.50 QALY at a lifetime cost savings of $41 591.

Results of Sensitivity Analysis: Transplant of an HCV-infected kidney followed by HCV treatment continued to be preferred in sensitivity analyses of many model parameters. Transplant of an HCV-uninfected kidney preceded by HCV treatment was not preferred unless the additional wait time for an uninfected kidney was less than 161 days.

Limitation: The study did not consider the benefit of decreased HCV transmission from treating HCV-infected patients.

Conclusion: Transplanting HCV-infected kidneys into HCV-infected patients increased quality-adjusted life expectancy and reduced costs compared with transplanting HCV-uninfected kidneys into HCV-infected patients.

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An estimated 110 000 U.S. patients start dialysis each year. In 2016, approximately 500 000 patients received dialysis for end-stage renal disease (ESRD), of whom 19 060 (3.8%) received kidney transplants. Because of limited organ availability, hemodialysis is the final treatment for most patients with ESRD. The scarcity of kidneys for transplant and high mortality rate while awaiting the procedure have led some physicians and patients to consider transplanting organs that otherwise might not be considered. For example, between 10% and 15% of U.S. patients receiving dialysis are seropositive for hepatitis C virus (HCV) (1). Some of these patients are willing to accept HCV-infected kidneys from deceased donors (2), in part because wait times for such kidneys are shorter than those for HCV-uninfected kidneys (average, 469 vs. 856 days [3]). Because the yearly mortality rate for patients receiving hemodialysis is 4% to 16% (4, 5), reducing the time to kidney transplant can have a dramatic effect on overall survival and quality of life. Moreover, the U.S. Food and Drug Administration approved elbasvir–grazoprevir in January 2016 and glecaprevir–pibrentasvir in August 2017 for treating chronic HCV infection in patients with ESRD (6, 7). The availability of these drugs has created opportunities for transplanting HCV-infected kidneys into patients who already have HCV infection, but it has also introduced an interesting dilemma. Should patients with chronic HCV infection receive an HCV-uninfected kidney, which means that they would be treated for HCV infection before the transplant and would have to wait longer for the procedure? Alternatively, should they receive an HCV-infected kidney, with treatment for HCV infection after the transplant and a shorter wait time? We developed a decision analytic model to estimate the comparative effectiveness and cost-effectiveness of these 2 options.

See also:

Editorial comment 1
Summary for Patients 2

Web-Only
Supplement

METHODS

Review of Data

Patient Characteristics

The demographic characteristics of patients with ESRD differ between those with and without HCV. Patients with HCV are younger (mean age, 57.8 vs. 65.3 years), and a larger proportion are African American (54.0% vs. 36.4%) (8). Data describing HCV genotypes are biased by clinical trial designs that frequently oversample particular genotypes. In the general U.S. population, approximately 70% of patients with HCV are infected with genotypes 1a and 1b, 15% to 20% with genotype 2, 10% to 12% with genotype 3, and 1% with genotype 4. Infection with genotypes 5 and 6 is rare (9, 10).

Natural History of Liver Disease Progression

We used a computer simulation of natural history that is based on a previously published model of disease progression and outcomes with chronic HCV infection (11). Progression of fibrosis is based on a series of meta-regressions using the METAVIR scoring system (12) and data from 111 studies involving more than 33 000 persons with chronic HCV infection (13). Fibrosis proceeds until cirrhosis develops (METAVIR stage F4). Once patients have developed compensated cirrhosis, they can progress to decompensated cirrhosis and hepatocellular carcinoma. Patients may receive liver transplants for either decompensated cirrhosis or hepatocellular carcinoma (14–17).

Natural History of ESRD

In a large retrospective cohort study using registry data from the United Network for Organ Sharing of 1814 patients with chronic HCV infection, median wait times were 231 days for HCV-infected kidneys versus 771 days for HCV-uninfected kidneys (18). In addition, patients receiving infected kidneys had a shorter mean duration of dialysis (2.7 vs. 4.7 years). Recipients of HCV-infected kidneys have higher mortality rates during the first month after transplant than recipients of HCV-uninfected kidneys (1.5% vs. 0.85%) (19). Other studies have described similar findings (3, 20). In addition, data from the United States Renal Data System have shown that among patients on transplant waiting lists who are receiving dialysis, annual mortality rates increase with longer dialysis duration (4). Annual adjusted all-cause mortality for patients receiving hemodialysis has improved over the past 2 decades but is still almost 17% (4). However, those on transplant waiting lists have roughly half the annual risk for death (5), whereas annual excess mortality after a first deceased-donor transplant is 2% (4, 5).

Treatment of Chronic HCV Infection

Treatment of chronic HCV infection has evolved rapidly with the availability of new direct-acting antivirals and interferon-free regimens. The 21 September 2017 update to guidelines from the American Association for the Study of Liver Diseases and Infectious Diseases Society of America recommends testing for NS5A resistance-associated substitutions in patients with genotype 1a infection (21). Once-daily elbasvir (50 mg) combined with grazoprevir (100 mg) is a first-line treatment that can be used for patients with ESRD and genotype 1a infection. Patients with resistance-associated substitutions receive 16 weeks of elbasvir–grazoprevir and a weight-based dose of ribavirin, whereas those without resistance-associated substitutions receive 12 weeks without ribavirin. A 12-week course of elbasvir–grazoprevir is also a first-line treatment of ESRD for patients infected with genotypes 1b and 4. In a trial of previously untreated patients, those with genotype 1a infection and NS5A resistance-associated substitutions had a sustained virologic response rate of 82% (22). In a separate study, sustained virologic response rates for treatment-naive patients were 98.5% for those with genotype 1a infection and no resistance-associated substitutions, 99.2% for those with genotype 1b infection, and 100% for those with genotype 4 infection (10).

Three once-daily tablets of glecaprevir (100 mg) combined with pibrentasvir (40 mg) is a new pangenotypic direct-acting antiviral that can be used in patients with ESRD. Treatment lasts 8 weeks for patients without cirrhosis and 12 weeks for those with compensated cirrhosis. In the EXPEDITION-4 (Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients With Renal Impairment and Chronic Hepatitis C Virus Genotype 1-6 Infection) trial, 98% of HCV-infected patients with stage 4 or 5 chronic kidney disease achieved sustained virologic response (7, 23). We used this regimen in our decision model for patients with genotype 2 or 3 infection before kidney transplant. Patients being treated after kidney transplant received a 12-week course regardless of genotype or presence of compensated cirrhosis.

Description of Simulation Model

We used a computer program to develop a 75-state Markov transition model, analyze decision trees, and perform sensitivity analyses, using a lifetime horizon (24). We considered 2 strategies (**Supplement Figures 1** and **2**, available at Annals.org), transplant of an HCV-uninfected kidney preceded by HCV treatment versus transplant of an HCV-infected kidney followed by HCV treatment. Treatment was based on genotype-appropriate regimens, as recommended by current guidelines (21).

The model considers a population of men and women of various races based on demographics described by the United States Renal Data System of HCV-infected patients who are receiving dialysis. They are an average age of 57.8 years, and have just been waitlisted for kidneys from deceased donors (8). Patients are assumed to be HCV treatment–naive. At the time the simulation begins, patients awaiting HCV-uninfected kidneys have been receiving dialysis for almost 2.6 years, compared with roughly 2.1 years for those awaiting infected kidneys, which reflects actual wait times (18). Before entering the Markov simulation section of our model, patients are divided into clinical subgroups based on sex,

race, HCV genotype, and the presence or absence of NS5A resistance-associated substitutions (among those with genotype 1a infection). Patients enter the simulation distributed across the 5 fibrosis stages described among HCV-infected patients awaiting a kidney transplant (25). We did not consider patients with decompensated cirrhosis in our model, although antiviral therapy, when administered by experienced clinicians, may be appropriate for these patients. However, they may be candidates for both liver and kidney transplant, which could be either simultaneous or sequential—our model does not address this further complexity. With each 1-month cycle in the Markov simulation, patients move from 1 health state to another depending on chance events based on real-world probabilities.

Patients who receive an HCV-uninfected kidney are treated before kidney transplant and receive a course of genotype-guided therapy for 8, 12, or 16 weeks, as appropriate. The small proportion of patients in whom treatment fails return to the natural history model, where they may progress to further stages of fibrosis and develop hepatocellular carcinoma or decompensated cirrhosis. Successfully treated patients remain on the transplant waiting list until they receive an HCV-uninfected kidney. A small proportion of patients die during the first month after kidney transplant (19). Patients die or survive based on the U.S. population mortality tables matched for age, sex, and race plus the excess mortality among kidney transplant recipients (4, 5).

Patients who receive an HCV-infected kidney and treatment of HCV infection after transplant may die, remain in their current stage of fibrosis, or progress to the next stage. Once cirrhosis develops, patients may die of causes based on the U.S. population mortality tables matched for age, sex, and race; die of compensated cirrhosis; develop hepatocellular carcinoma; progress to decompensated cirrhosis; or remain in their current stage. Patients who develop hepatocellular carcinoma or progress to decompensated cirrhosis may be considered for liver transplant (26, 27). Those having a liver transplant may die within the first 30 days. Patients who have developed decompensated cirrhosis or hepatocellular carcinoma and have not had a transplant face the same possible events as those with compensated cirrhosis, although with different outcome probabilities. After a liver transplant, the model considers only survival and not repeated liver or kidney transplants. Patients remain on the waiting list for an HCV-infected kidney and may die during the first month after transplant. In this strategy, patients are not treated for chronic HCV infection until 6 months after the transplant. Because of complex drug interactions between immunosuppressive therapies and direct-acting antivirals, these patients all receive a 12-week course of glecaprevir–pibrentasvir (21). Subsequent events are similar to those described for patients receiving HCV-uninfected kidneys and treatment before transplant.

Costs

The analysis was done from the health care system perspective and does not include indirect costs, such as those associated with time lost from work. Costs are expressed in 2017 U.S. dollars. Details of the microcosting models are described in Table 1 and the Supplement (available at Annals.org). Future costs and effectiveness were discounted at 3% per year.

Quality of Life

Numerous studies have examined the effect of HCV infection on health-related quality of life (28–30, 42, 43). We based quality-of-life estimates on standard gamble utility assessments, which were calculated in a meta-regression of HCV-infected patients who had had a liver transplant or had "moderate disease," compensated cirrhosis, or decompensated cirrhosis (29). Because the meta-regression did not include utilities for patients with hepatocellular carcinoma, we used standard gamble assessments from another study of 193 outpatients with chronic HCV for this outcome (28). Utilities for HCV health states were consistent across studies (28, 29, 43). We used separate utilities for patients with ESRD receiving hemodialysis and for patients after a kidney transplant (31–33). Utilities for more than 1 health state were combined in a multiplicative fashion.

Sensitivity Analysis

We did both deterministic and probabilistic sensitivity analyses to examine the effects of uncertainty in parameter estimates and population-level variation in parameters. We used second-order Monte Carlo simulation for probabilistic sensitivity analyses, although we did not assign distributions to all parameters (44). We used β and logit distributions for probabilities and log-normal distributions for relative risks, hazard ratios, rates, and costs (Table 1). Deterministic sensitivity analyses were done by systematically varying the values of 1 or more parameters over clinically relevant ranges.

Role of the Funding Source

The funding sources had no role in the study design, data collection or analysis, or manuscript preparation. Merck Sharp & Dohme was given the opportunity to review the manuscript for intellectual property considerations.

RESULTS

Transplanting an HCV-infected kidney followed by HCV treatment decreased quality-adjusted life-years (QALYs) by increasing the lifetime probability of dying of end-stage liver disease and related causes to 5%, compared with 3.4% for transplanting an HCV-uninfected kidney preceded by HCV treatment. However, transplanting an uninfected kidney preceded by treatment decreased QALYs by increasing the duration of dialysis while waiting for a kidney and thus increasing the lifetime probability of dying of chronic kidney disease to 34.5%, compared with 29% for patients receiving HCV-infected kidneys followed

Table 1. Data Required in the Analysis: Probabilities, Rates, Costs, and Quality of Life

Variable	Value	Reference	Distribution Type
Characteristics of patients with ESRD awaiting transplant			
Mean age, *y*	57.8	8	–
Men, %	57.6	8	–
Race, %			
Caucasian	39.3	8	–
African American	54.0	8	–
Hispanic	6.7	8	–
HCV genotype (95% CI), %			
1a	39 (28–50)	9	Logit
NS5A RAS–positive	12 (7–17)	10	β
1b	31 (22–41)	9	Logit
2	17 (15–20)	9	Logit
3	12 (10–12)	9	Logit
4	1	9	–
Natural history			
Liver disease			
Fibrosis stage at the time of the decision, %			
F0	19	25	–
F1	27	25	–
F2	22	25	–
F3	8	25	–
F4	24	25	–
Kidney disease			
Average wait time for deceased-donor kidney (95% CI), *y*			
HCV-uninfected	2.11 (0.91–3.6)	18	Log-normal
HCV-infected	0.63 (0.21–1.52)	18	Log-normal
Additional wait time for an HCV-uninfected kidney (95% CI), *y*	1.48 (0.70–2.11)	–	Log-normal
30-d mortality after kidney transplant (95% CI), %			
HCV-infected kidney	1.5 (0.9–2.0)	19	β
HCV-uninfected kidney	0.85 (0.2–1.7)	19	β
Mortality†			
Annual excess mortality rate in patients with ESRD receiving hemodialysis (95% CI), %	7.4 (7.3–7.5)	4, 5	β
Relative risk for dialysis-related mortality			
<2 y of dialysis	0.59	4	–
2–4 y of dialysis	1.0	4	–
≥5 y of dialysis	1.5	4	–
Annual excess mortality rate after kidney transplant (95% CI), %	2 (1.9–2.1)	4	β
Sustained virologic response related to HCV treatment (95% CI), %‡			
Elbasvir–grazoprevir			
16-wk course plus weight-based ribavirin for NS5A RAS–positive patients with genotype 1a infection	82 (70–95)	22	β
12-wk course for NS5A RAS–negative patients with genotype 1a infection	98.5 (96.4–100)	10	β
12-wk course for patients with genotype 1b infection	99.2 (97.8–100)	10	β
12-wk course for patients with genotype 4 infection	100	10	–
Glecaprevir–pibrentasvir			
8-wk course for patients with genotype 2 or 3 infection without cirrhosis	98 (95.6–100)	7, 23	β
12-wk course for patients with genotype 2 or 3 infection with compensated cirrhosis	98 (95.6–100)	7, 23	β
12-wk course for all genotypes with or without compensated cirrhosis after kidney transplant	98 (95.6–100)	7, 23	β
	Cost (SD), *2017 USD*		
Disease state			
Annual cost for chronic HCV§			
No liver disease	4402 (167)	34	Log-normal
Compensated cirrhosis	4402 (167)	–	Log-normal
Decompensated cirrhosis	33 893 (1028)	34	Log-normal
Hepatocellular carcinoma	54 073 (2756)	34	Log-normal
Annual cost for liver transplant			
First year	214 622 (7974)	34	Log-normal
Subsequent years	48 858 (4044)	34	Log-normal
Annual cost for hemodialysis‖	93 019	4	–
Kidney transplant‖			
1-time cost of procedure	106 981	4	–
Subsequent years	35 077	4	–

Continued on following page

Table 1–Continued

Variable	Cost per Month Clinically Plausible Range), *2017 USD*	Reference	Distribution Type
Drugs			
Ribavirin for NS5A RAS–positive patients with genotype 1a infection¶	188 (99–277)	35	Log-normal
Elbasvir, 50 mg, and grazoprevir, 100 mg, once daily	17 377 (17 012–17 742)	35	Log-normal
Glecaprevir, 100 mg, and pibrentasvir, 40 mg, 3 times daily	9830 (7260–12 400)	35	Log-normal
Laboratory testing and office visits			
HCV antibody enzyme immunoassay (CPT code 86803)	19.57	36	–
Probe amplification assay for HCV RNA (CPT code 87521)	48.14	36	–
HCV RNA quantification assay (CPT code 87522)	58.76	36	–
HCV genotype assay (CPT code 87902)	353.15	36	–
NS5A resistance-associated variant testing	563.00	37	–
Uric acid testing (CPT code 84550)	6.20	36	–
Triglyceride testing (CPT code 84478)	7.88	36	–
Hepatic function panel (CPT code 80076)	11.21	36	–
Complete blood count (CPT code 85025)	10.66	36	–
Renal panel (CPT code 80069)	11.91	36	–
Thyroid-stimulating hormone testing (CPT code 84443)	23.05	36	–
Urine pregnancy test (CPT code 81025)	8.67	36	–
Office outpatient visit for an established patient			
Level-1 visit (CPT code 99211)	20.46	38	–
Level-2 visit (CPT code 99212)	44.14	38	–
Level-3 visit (CPT code 99213)	73.93	38	–
Level-4 visit (CPT code 99214)	108.74	38	–
Ultrasonography of the abdomen (CPT code 76705)	93.31	38	–
Ultrasound-guided needle biopsy of the liver with pathologic examination**	926.29	38	–
	Value		
Quality of life			
Well without HCV infection	1.0	29	–
Chronic HCV infection			
Without cirrhosis	0.79	29	–
With compensated cirrhosis	0.79	29	–
With decompensated cirrhosis	0.72	29	–
After liver transplant	0.75	29	–
With hepatocellular carcinoma	0.72	28	–
Chronic kidney disease			
Receiving hemodialysis (95% CI)	0.53 (0.23–0.85)	31, 32	Logit
After kidney transplant (95% CI)	0.84 (0.80–0.88)	33	Logit
Treatment			
Ribavirin	0.99	30	–
Direct-acting antiviral agents	0.96	39, 40	–

CPT = Current Procedural Terminology; ESRD = end-stage renal disease; HCV = hepatitis C virus; RAS = resistance-associated substitution; USD = U.S. dollars.
* Values are from base-case analyses.
† Calculated by adjusting United States Renal Data System all-cause mortality rates using relative survival at 10 y based on an age-matched U.S. population sample (41).
‡ Assuming that patients were treatment-naive.
§ 2009 USD were inflated to 2017 USD using the medical care component of the Consumer Price Index (see the **Supplement**, available at Annals.org). Excludes costs of antiviral therapy.
‖ 2014 USD were inflated to 2017 USD using the medical care component of the Consumer Price Index.
¶ Dosing was weight-based. A dose of 1200 mg was administered for patients weighing >75 kg.
** Includes ultrasound guidance for biopsy (CPT code 76942; $61.37), needle biopsy of the liver (CPT code 47000; $312.23), pathologic examination (CPT code 88307; $269.88), and special pathologic stains (original magnification × 4) (CPT code 88313; $282.80).

by HCV treatment (Supplement Figures 3 and 4, available at Annals.org). The net benefit of transplanting an infected kidney followed by HCV treatment was a survival gain of 0.50 QALY at a lifetime cost savings of $41 591 compared with transplant of an HCV-uninfected kidney preceded by HCV treatment (Table 2).

Deterministic Sensitivity Analysis

Using an HCV-infected kidney and deferring treatment was more effective and less costly than using an HCV-uninfected kidney preceded by HCV treatment in sensitivity analyses within clinically plausible ranges or 95% CIs for most model parameters.

Some model parameters were more sensitive to variations in other parameter values. Additional wait time to receive an HCV-uninfected kidney may vary substantially from center to center and patient to patient. Figure 1 (*top*) explores variations in this wait time between 0 and 1.6 years compared with the average wait time to receive an HCV-infected kidney. In the base case, average wait time for an infected kidney is

Table 2. Results of the Base-Case Analysis

Strategy	Cost, $	Effectiveness, QALYs	Incremental Cost, $	Incremental Effectiveness, QALYs	Incremental Cost-Effectiveness, $/QALY
Discounted at 3% per year					
Transplant of HCV-infected kidney followed by HCV treatment	566 626	6.26	–	–	–
Transplant of HCV-uninfected kidney preceded by HCV treatment	608 217	5.76	41 591	−0.50	Dominated*
Results of base-case analysis not discounted					
Transplant of HCV-infected kidney followed by HCV treatment	698 824	8.42	–	–	–
Transplant of HCV-uninfected kidney preceded by HCV treatment	734 002	7.79	35 179	−0.63	Dominated*

HCV = hepatitis C virus; QALY = quality-adjusted life-year.
* Indicates that the less expensive strategy (in this case transplant with an HCV-infected kidney followed by HCV treatment) is also more effective.

0.63 year (231 days) and the additional time required to receive an uninfected kidney is 1.48 years (540 days). Transplant of an HCV-uninfected kidney preceded by HCV treatment is not preferred unless the additional wait time for an uninfected kidney decreases to less than 0.44 years (161 days). Figure 1 also shows that the incremental cost-effectiveness ratio of transplanting an uninfected kidney preceded by HCV treatment compared with transplanting an infected kidney followed by treatment is roughly $50 000 per QALY when the additional wait time is 0 and exceeds $100 000 per QALY beyond an additional wait time of 0.2 year (73 days).

We also explored the additional risk for death associated with transplanting HCV-infected kidneys. As shown in Figure 1 (*bottom*), transplant of infected kidneys followed by antiviral therapy is best unless 30-day mortality after transplant exceeds 10% (base case, 1.5%) for patients receiving infected kidneys versus 0.85% for those receiving HCV-uninfected kidneys.

Figure 2 depicts a 2-way sensitivity analysis of annual excess mortality after transplant of a kidney from a deceased donor (horizontal axis) and annual excess mortality among patients receiving hemodialysis (vertical axis). The diagonal threshold line shows that transplant of an uninfected kidney preceded by HCV treatment could be the preferred strategy if annual excess mortality for patients receiving hemodialysis were substantially lower and if excess mortality after transplant were higher. The base-case values fall well within the region in which transplanting HCV-infected kidneys is preferred.

Figure 3 shows a 2-way sensitivity analysis of patients' quality of life while receiving hemodialysis (horizontal axis) and after kidney transplant (vertical axis). Transplant of an uninfected kidney preceded by HCV treatment would be preferred only if, compared with base-case values, the patient's quality of life while receiving dialysis were substantially higher and quality of life after transplant were substantially lower.

We analyzed an alternative scenario in which all patients received glecaprevir–pibrentasvir. Recipients of HCV-uninfected kidneys, regardless of genotype, were treated for 8 or 12 weeks depending on the absence or presence, respectively, of compensated cirrhosis. As in the base case, all patients receiving treatment after transplant of an HCV-infected kidney received 12 weeks of treatment regardless of genotype. Transplanting an infected kidney resulted in a similar gain (0.50 QALY) at a smaller lifetime cost savings ($19 762) compared with transplanting an uninfected kidney. We also explored the effect of additional wait time to receive an HCV-uninfected kidney in this scenario. Although transplanting an uninfected kidney was more effective and less expensive if there was no additional wait time, transplanting an infected kidney dominated (that is, was more effective and less costly) beyond a wait time of 0.45 year (164 days).

In another sensitivity analysis, we explored the effect of decreasing the cost of all direct-acting antiviral agents by up to 50%. Transplant of an HCV-infected kidney continued to dominate the analysis; however, at a cost reduction of 50%, savings decreased to $36 402. In an analysis examining the effect of patient age, deferred antiviral therapy continued to dominate. At younger ages, cost savings were lower but the gain in effectiveness was larger (for example, at age 30 years, cost savings was $37 735 and effectiveness 0.58). At older ages, cost savings increased but the gain in effectiveness decreased (for example, at age 70 years, cost savings was $44 701 and effectiveness 0.43). In sensitivity analyses exploring the effects of sex and race, results changed little. We also considered an alternative scenario in which the patient already had compensated cirrhosis. Transplanting HCV-infected kidneys continued to dominate the analysis, but the gain in effectiveness was smaller (0.25 QALY). In this scenario, transplanting an infected kidney increased the lifetime probability of dying of end-stage liver disease to 19% (vs. 14% in patients receiving an HCV-uninfected kidney) but decreased that of dying of chronic kidney disease to 26% (vs. 32%).

Probabilistic Sensitivity Analysis

Over 10 000 iterations, transplanting HCV-infected kidneys followed by HCV treatment was preferred over transplanting HCV-uninfected kidneys preceded by

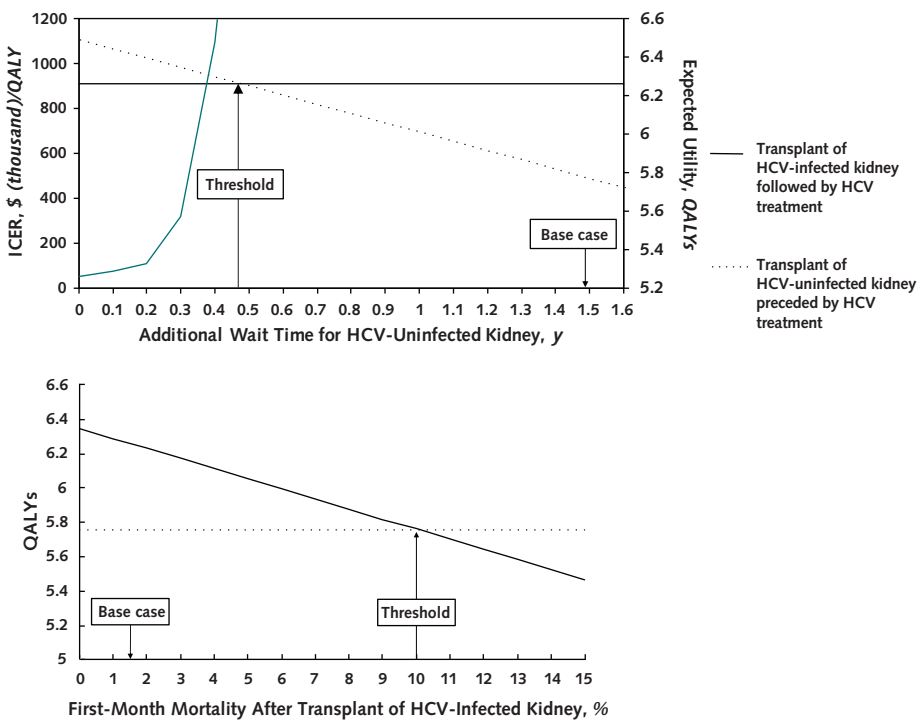
HCV treatment 100% of the time, yielding an average gain of 0.52 QALY (SD, 0.16) (**Supplement Figure 5**, available at Annals.org) at an average cost savings of $38 691 (SD, $9141). Transplanting infected kidneys was less costly and more effective—that is, it dominated transplanting uninfected kidneys 99.99% of the time and was cost-saving or had an incremental cost-effectiveness ratio less than $50 000 per QALY 100% of the time.

DISCUSSION

The recent availability of direct-acting antivirals that can be used in ESRD has created new opportunities and questions regarding the optimal timing of treatment of chronic HCV infection in patients awaiting kidney transplant. Despite our newfound ability to treat such patients before transplant, our analysis shows that the benefit of earlier transplant afforded by using HCV-infected kidneys outweighs the risk for progressive liver disease due to untreated HCV infection while awaiting transplant. Additional wait times for HCV-uninfected kidneys would have to decrease below 161 days before treating with uninfected kidneys would be preferred. We believe that our analysis supports transplanting HCV-infected kidneys into patients with ESRD who already are infected with HCV, and we hope that these results will be used to guide decision making by individual patients and treatment centers. Nevertheless, given the wide range of wait times at different centers, we recognize that some patients will prefer transplant of HCV-uninfected kidneys preceded by treatment of HCV infection.

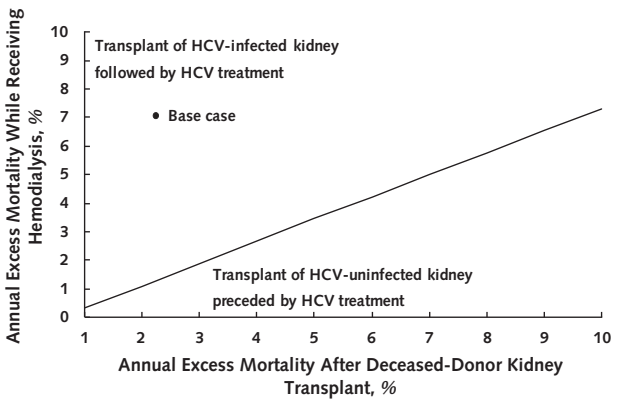
In the past, treatment of HCV infection in transplant recipients has been limited by interferon-mediated graft rejection and poor efficacy. Recent studies of direct-acting antivirals in kidney transplant recipients have shown high rates of sustained virologic response with minimal adverse events or graft rejection (45). However, experience is still limited, and some physicians have raised concerns about the safety and efficacy of HCV therapy for transplant recipients (46). A recent meta-analysis of 6 studies involving 360 renal transplant recipients found that 98.3% of patients achieved sustained virologic response within 12 weeks. Roughly 1% of patients had significant adverse events (47). In our analysis, the superiority of transplanting

Figure 1. One-way sensitivity analysis.



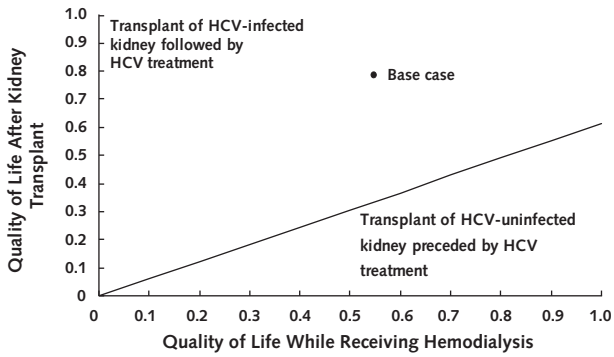
HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year. **Top.** The effect of changes in the additional wait time required for HCV-uninfected vs. HCV-infected kidneys. The primary vertical axis (*left*) shows the ICER for transplant of an HCV-uninfected deceased-donor kidney preceded by HCV treatment compared with transplant of an HCV-infected kidney followed by HCV treatment. The ICER is roughly $50 000 per QALY when wait time is 0 and >$100 000 per QALY when wait time is >0.2 y (73 d). Beyond a threshold of 0.44 y (161 d), transplant of an infected kidney followed by HCV treatment dominates (is more effective and less costly). The secondary vertical axis (*right*) shows expected utility in QALYs. The 2 lines represent the 2 treatment strategies, transplant of an HCV-uninfected kidney preceded by HCV treatment and transplant of an HCV-infected kidney followed by HCV treatment. Along the horizontal axis, the base case for wait time is 1.48 y (540 d). Transplanting an infected kidney is the preferred strategy unless the wait time for an uninfected kidney is <0.44 y (161 d). **Bottom.** The effect of mortality in the first month after kidney transplant for patients receiving an HCV-infected kidney. The base-case value is 1.5%. Transplant of an HCV-infected kidney remains preferred unless first-month mortality is >10%.

Figure 2. Two-way sensitivity analysis examining annual excess mortality rates after deceased-donor kidney transplant (*horizontal axis*) and while receiving hemodialysis (*vertical axis*).



The diagonal threshold line divides the decision space into 2 regions. At the top left, where annual excess mortality for patients receiving dialysis is high and annual excess mortality after kidney transplant is low, transplanting HCV-infected kidneys is preferred. The base-case values for these 2 variables fall in this region, far from the threshold. At the bottom right, where annual excess mortality after transplant is higher and annual excess mortality for patients receiving hemodialysis is lower, transplanting HCV-uninfected kidneys is preferred. HCV = hepatitis C virus.

Figure 3. Two-way sensitivity analysis examining quality of life while receiving hemodialysis (*horizontal axis*) and after deceased-donor kidney transplant (*vertical axis*).



At the top left, where quality of life after transplant is higher and quality of life while receiving hemodialysis is lower, transplanting HCV-infected kidneys is preferred. At the bottom right, where quality of life while receiving hemodialysis is higher and quality of life after transplant is lower, transplanting HCV-uninfected kidneys is preferred. The base-case values for these 2 variables fall in the upper-left region in which transplanting HCV-infected kidneys is preferred. HCV = hepatitis C virus.

HCV-infected kidneys depends on the high efficacy of new interferon-free regimens. This net benefit persists despite the slightly higher risk for death in the 30 days after transplant of infected kidneys. In sensitivity analyses, we found that 30-day mortality for these patients would have to increase considerably from base-case values before transplant of HCV-uninfected kidneys would be preferred.

Our analysis has several limitations. Our base case considered an "average" patient with chronic HCV infection awaiting a kidney transplant. We did not consider more specific patient characteristics or comorbid conditions. For instance, patients with diabetes mellitus have higher mortality rates while receiving hemodialysis and after kidney transplant (5). Thus, a more individualized approach may be warranted for some patients. We did not address the issue of co-infection with hepatitis B virus or HIV. Treatment of kidney transplant recipients who are co-infected with HIV and HCV requires continued awareness and attention to the complex drug interactions that can occur among direct-acting antivirals, antiretroviral medications, and immunosuppressive medications. Reactivation of hepatitis B viral infection has been reported in patients starting direct-acting antiviral therapy for HCV who are not receiving medications for hepatitis B virus infection. We also assumed that the small fraction of patients in whom initial HCV treatment failed would not receive salvage therapy. Studies in posttransplant patients are limited for this rapidly evolving area. We did sensitivity analyses in which we provided high-efficacy therapy for treatment-experienced patients, and results were not substantially different from those of our base case. Finally, we did not consider the benefits of decreased prevalence of HCV infection in dialysis units and decreased HCV transmission that would result from treating HCV-infected patients who are receiving dialysis.

In summary, the availability of interferon-free direct-acting antivirals to treat chronic HCV infection in kidney transplant recipients creates a new opportunity to provide access to HCV-infected kidneys for HCV-infected patients with ESRD. Doing so can greatly reduce the wait time for a donated kidney and improve survival by decreasing time spent receiving hemodialysis. In an era of increasing success for kidney transplants and demand that far outstrips supply, deferring antiviral therapy until after transplant of HCV-infected kidneys, when available, should be both cost-saving and effective.

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