Long-Term Viral Negativity After Interferon for Chronic Hepatitis C Virus Infection in Hemodialysis

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Summary

Background and objectives Interferon (IFN) and pegylated-IFN treatment of hepatitis C virus (HCV) infection in hemodialysis patients result in sustained virological response (SVR) rates of 45% and 37%, respectively. Although most nonhemodialysis patients who achieve SVR remain persistently viral negative, the durability of SVR in hemodialysis patients is unknown. We analyzed the rate of long-term virological negativity in hemodialysis patients who achieved SVR after IFN or pegylated-IFN through analysis of patient-level data.

Design, setting, participants, & measurements After performing a systematic literature review for IFN-based treatment of hemodialysis patients with chronic HCV infection, we extracted patient-level data on patients who achieved SVR. We performed life table analysis to estimate long-term virological negativity rates after SVR in patients who continued on hemodialysis or subsequently underwent kidney transplantation.

Results Long-term HCV RNA outcomes following SVR were available for 121 hemodialysis patients (20 studies) and 45 patients who subsequently underwent transplantation (11 studies). The probability of remaining HCV RNA negative was 86% (95% confidence interval, 77% to 96%) for patients followed on hemodialysis 48 months after SVR and 95% (95% confidence interval, 89% to 100%) for kidney recipients followed 48 months after transplant.

Conclusions Viral negativity from IFN-based HCV treatment in hemodialysis patient appears durable during extended follow-up, including after kidney transplantation. The certainty of the viral negativity estimate is limited by the small number with follow-up beyond 48 months or longer. Transplantation does not confer an increased risk of relapse. Future research should investigate whether IFN-based treatment improves clinical outcomes for hemodialysis patients.

Clin J Am Soc Nephrol 6: 2226–2234, 2011. doi: 10.2215/CJN.00410111

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Introduction

Hepatitis C virus (HCV) infects an estimated 170 million people worldwide (1), with prevalence rates of 13% in hemodialysis (HD) patients from European countries, the United States, and Japan (2). Compared with noninfected patients, HCV infection is associated with higher mortality in HD patients (3,4) and higher mortality and graft loss in kidney transplant recipients (5). The rate of spontaneous viral clearance is 0.5% per year for chronic HCV infection, (6) highlighting the importance of effective treatment.

The standard measure of successful HCV treatment is sustained virological response (SVR). In non-HD patients, SVR is achieved in 50% to 60% of patients treated with pegylated-IFN and ribavirin combination therapy (7,8), and over 90% of patients who achieve SVR remain persistently HCV RNA negative after 3 to 5 years of follow-up (9–13). IFN-based treatment or SVR in non-HD patients are associated with improved liver histology scores (11,14), lower incidences of hepatocellular carcinoma (15,16), and lower mortality (16,17).

Because of reduced renal clearance, higher adverse event rates with IFN and ribavirin therapy make HCV treatment of patients with chronic kidney disease (CKD) challenging (18). In kidney transplant recipients, IFN-based treatment is contraindicated because of a 6% to 20% rate of allograft loss from acute rejection (19,20), and ribavirin monotherapy is ineffective in kidney recipients (21). Treatments for HD patients have primarily focused on IFN or pegylated-IFN monotherapy because ribavirin is contraindicated in HD due to high rates of hemolytic anemia except in research settings with careful monitoring of ribavirin plasma levels. Our recent meta-analysis in chronic HCV-infected HD patients found that 45% of IFN-treated and 37% of pegylated-IFN-treated patients achieved SVR (18,22).

It is unknown whether achieving SVR in HD patients results in similar long-term persistence of viral negativity to that observed in non-HD patients. Compromised immunity associated with end-stage renal disease might theoretically increase the risk of viro-

logical relapse. Whether relapse occurs in kidney transplant recipients who previously achieved SVR while on HD is particularly important for HD patients who are transplant candidates. In IFN and ribavirin-treated liver transplant recipients, SVR was persistent in 93% (23). We summarized individual patient data from IFN or pegylated-IFN treated HD patients with SVR to determine the long-term rates of viral negativity while on HD or after subsequent transplantation.

Materials and Methods

Patient Selection for Long-Term HCV RNA Analysis

The literature search strategy and process of study selection for our systematic review have been described previously (18) and followed the protocol for meta-analysis of observational studies in epidemiology (MOOSE) (24). Briefly, we included prospective studies of HD patients with chronic HCV infection (documented by HCV RNA testing) who achieved SVR with IFN or pegylated-IFN treatment. Treatment studies of patients with CKD stages 1 to 5 not on HD and kidney transplant recipients (CKD stage 5-T) were excluded. Studies that did not assess for SVR were excluded, as were those with sample sizes less than 5. We performed a MEDLINE literature search on January 3, 2011 (Figure 1).

Retrieved studies often reported patient-level data on long-term virological outcomes in patients who achieved SVR. Of 21 IFN treatment studies, 16 reported patient-level data on long-term virological outcomes following SVR (25–40), and of 21 pegylated-IFN studies, six studies provided such data (41–46). For unpublished data on long-term HCV RNA outcomes, we directly contacted authors. Patient-level data on long-term clinical outcomes, including mortality and graft loss, were unavailable.

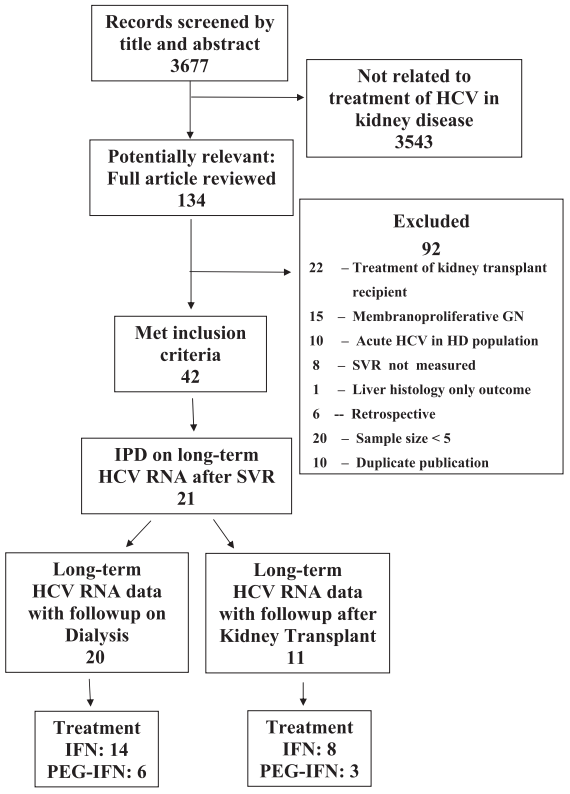


Figure 1. | Systematic review of the literature. GN, glomerulonephritis; HCV, hepatitis C virus; HD, hemodialysis; IFN, interferon; IPD, individual patient data; PEG-IFN, pegylated-IFN; SVR, sustained virological response.

Statistical Analysis

To explore the long-term persistence of HCV RNA negativity in patients who achieved SVR after IFN-based treatment while on HD, we performed life table analysis of patient-level data after accounting for censoring. Because of immunosuppressive agents used for kidney transplantation recipients, we analyzed HD patients and transplant recipients separately. The HD group comprised HD patients who had long-term HCV RNA data after SVR, with censoring at the time of kidney transplantation. The kidney transplantation group included patients achieving SVR while on HD who remained HCV RNA negative until kidney transplantation and had long-term HCV RNA values thereafter (Figure 2). In our analysis, follow-up began from the time SVR was achieved for the HD group, and from the time of transplantation for the kidney transplantation group. For inclusion, patients must have had both documented long-term HCV RNA results and specified duration of follow-up, but we did not require a minimum follow-up duration beyond SVR or transplantation for inclusion into either group.

Based on our review of previous publications on long-term response in non-HD patients (9–13) and the follow-up duration observed in our data, we investigated the probability of remaining HCV RNA negative after 48 months of follow-up in the HD and transplant groups, with separate analyses for IFN, pegylated-IFN, and either treatment. We also examined the probability of HCV RNA negativity at last follow-up.

Results

Characteristics of Studies

We identified 16 studies of IFN and 6 of pegylated-IFN that met inclusion criteria and had long-term HCV RNA data following SVR. Twenty studies of 121 patients (25–37,40–46) and 11 studies of 45 patients (25,26,28,31,32,38–40,42,43,45) contributed patient-level data on long-term HCV RNA outcomes in patients who achieved SVR and were followed on HD or after kidney transplantation, respectively (Tables 1 and 2). Although, in most cases, long-term data were presented on all patients who achieved SVR, some studies only reported on a subset of those who achieved SVR. Long-term data were available for 32 patients from 9 studies, with both pre- and post-transplant status reported separately (25,26,28,31,32,40,42,43,45). These patients contributed data to both analyses, with the HD and transplant states examined separately. The majority of patients were treated with IFN, but pegylated-IFN was used in 25 patients followed on HD and seven patients who underwent kidney transplantation.

The HD group had a mean age of 43 years and 51% were male. Before treatment, the mean duration of HD was 74 months and the mean duration of HCV infection was 56 months. Mean pretreatment HCV RNA was 172,300 IU/

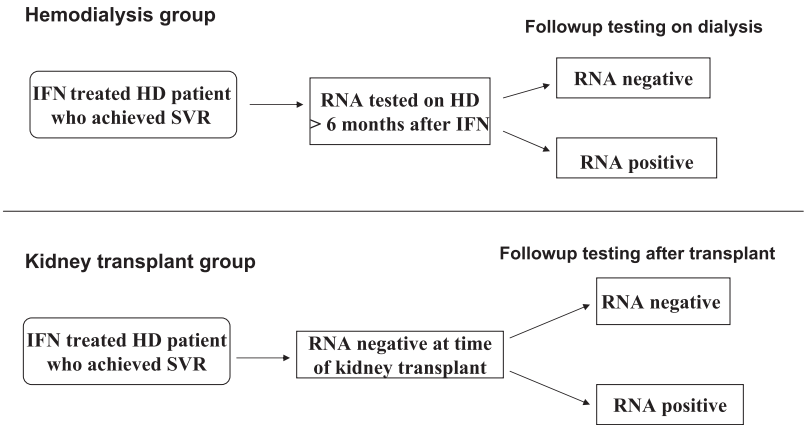


Figure 2. | **Persistence of HCV RNA negativity after SVR.** HCV, hepatitis C virus; HD, hemodialysis; IFN, interferon; SVR, sustained virological response.

ml. The prevalence of HCV genotype 1 was 66%. IFN dose was 3 million units, three times weekly, in 91% of patients, with higher doses in 3% and lower doses in 6%. For studies of pegylated-IFN, 74% of patients received the alfa-2a formulation, with alfa-2b used in the remainder. Half of the patients were prescribed treatment duration of 6 months, with 12 months intended for the remainder.

In the kidney transplant group, mean age was 40 years and 58% were male. The mean pretreatment duration of HD and HCV were 45 and 65 months, respectively. Mean pretreatment HCV RNA was 342,400 IU/ml. The proportion with HCV genotype 1 was 65%. Treatment dose was 3 million units of standard IFN, three times weekly, or 135 μg of pegylated-IFN alfa-2a once weekly. The intended treatment duration was 6 months in 29%, with the remainder intended for 12 months.

Long-Term Persistence of HCV RNA Negativity

Hemodialysis Patients. Long-term HCV RNA results were available for 121 HD patients from 20 studies (25–37,40–46) with median follow-up of 18 months (range 1 to 78 months) after achieving SVR (Table 1). Relapse to HCV RNA positivity during follow-up occurred in 10 of 121 (8%) including 6 of 97 (6%) receiving IFN and 4 of 24 (17%) receiving pegylated-IFN. By life table analysis, the probability of remaining HCV RNA negative 48 months after achieving SVR on HD in the overall group was 86% (95% confidence interval [CI], 77% to 96%; Figure 2), was 89% (95% CI, 78% to 98%) for IFN-treated patients, and was 79% (95% CI, 61% to 98%) for patients treated with pegylated-IFN. Those who were HCV RNA negative 48 months after SVR (n = 10) remained negative through last follow-up (62 to 78 months after SVR). An additional 22 patients from two studies (38,39) achieved SVR after IFN and remained HCV RNA negative on HD before undergoing kidney transplantation but were not analyzed because follow-up time on HD was not specified.

Kidney Transplantation Recipients. From 11 studies, 45 HD patients achieved SVR and remained HCV RNA negative until transplantation (Table 2) (25,26,28,31,32,38–40,42,43,45). Median follow-up after transplantation was 20 months (range 2 to 88 months). No patient underwent combined liver and kidney transplant. Out of 38 IFN-treated patients who were negative at the time of transplantation, three (8%) relapsed following transplantation but none of seven pegylated-IFN treated patients experienced a relapse with a 6-month median follow-up (range, 3 to 24 months). Transplantation patients had a 95% (95% CI, 89% to 100%) probability of remaining HCV RNA negative 48 months after transplantation but the probability decreased to 74% (95% CI, 47% to 100%) at 60 months (Figure 3). However, only 10 post transplant patients had HCV RNA data beyond 48 months, and two of these patients relapsed at 50 and 55 months after transplant, respectively.

Discussion

The decision to treat HCV infection in HD patients is complex and requires weighing the potential benefits and risks of treatment. We previously demonstrated that IFN treatment in HD patients results in SVR rates of 45% (22), higher than the 10% to 20% SVR reported for IFN monotherapy in non-HD patients (47–49). However, IFN-treated HD patients have higher rates of treatment discontinuation due to adverse events compared with non-HD patients (18,47–49). Other factors considered in the decision of which HD patients to treat include an individual's comorbidities, life expectancy, transplantation candidacy, as well as the persistence of viral negativity in patients who achieve SVR.

This patient-level meta-analysis extends our understanding of the persistence of HCV RNA negativity in HD patients who achieve SVR. Among HD patients who achieved SVR, 86% remained HCV RNA negative after 48 months of follow-up on HD. Of those who achieved SVR and were HCV negative at the time of kidney transplantation, 95% remained HCV RNA negative 48 months after transplantation. These findings are similar to reports in non-HD patients, where over 90% of patients who achieve SVR remain persistently HCV RNA negative after approximately 4 years of follow-up (Table 3) (10,12,13). However, most studies of non-HD patients did not perform life table analysis and instead analyzed the raw proportion of patients who remained viral negative in long-term follow-up after achieving SVR. We used the more conservative life

Table 1. Characteristics of studies of interferon or pegylated-interferon treatment of chronic HCV-infected hemodialysis patients with long-term HCV RNA outcomes on hemodialysis

Study, Country, Year	Overall Sample Size (n)	Number with SVR (n)	Number with Long-Term HCV RNA Outcomes (n)	Treatment Dose[a]	Treatment Duration (mo)[b]	Long-Term Follow-Up, Median (mo)
Studies with long-term HCV RNA outcomes with interferon						
Pol, France, 1995	19	6	6	3	6	17
Raptopoulou-Gigi, Greece, 1995	19	13	13	3	6	8
Okuda, Japan, 1995	15	8	1	6	6	18
Izopet, France, 1997	23	13	12	3	6 ($n = 5$) 12 ($n = 7$)	28
Fernandez, Argentina, 1997[c]	14	3	3	1.5	6	12
Chan, Hong Kong, 1997	11	3	3	3	6	18
Campistol, Spain, 1999[c]	19	11	11	3	6	20
Huraib, Saudi Arabia, 1999	17	12	2	3	12	10
Espinosa, Spain, 2001	13	6	6	3	12	27
Hanrotel, France, 2001	12	4	2	3	12	24
Kamar, France, 2003	55	21	16	3	6 ($n = 3$) 12 ($n = 13$)	37
Ozdemir, Turkey, 2004	20	8	8	6 ($n = 5$) 3 ($n = 3$)	6 ($n = 5$) 12 ($n = 3$)	64
Mousa, Saudi Arabia, 2004	20	11	10	3 RBV (200 TIW)	6 ($n = 6$) 12 ($n = 4$)	6
Buargub, Libya, 2006	35	9	4	3	12	12
Studies with long-term HCV RNA outcomes with pegylated-interferon						
Bruchfeld, Sweden, 2006	6	3	3	135 (α-2a), $n = 2$ 50 (α-2b), $n = 1$ 200–300 daily (RBV)	6 ($n = 1$) 12 ($n = 2$)	23
Amarapurkar, India, 2007	6	3	3	1.0/kg (α-2b)	6	12
Ucmaky, Turkey, 2008	12	9	9	135 (α-2a)	12	30
Zoppoli, Italy, 2008	10	2	2	135 (α-2a)	12	22
Kose, Turkey, 2009	26	9	2	135 (α-2a)	12	9
Dzekova, Macedonia, 2009	14	5	5	135 (α-2a)	12	18
All hemodialysis	366	159	121	Variable	6 ($n = 60$) 12 ($n = 61$)	18

α-2a, pegylated-interferon alpha-2a; α-2b, pegylated-interferon alpha-2b; RBV, ribavirin; TIW, three times weekly.

[a]Doses presented for interferon are in million units, three times weekly, and for pegylated interferon alpha-2a or 2b are in micrograms, once weekly. When studies used more than one treatment dose, the numbers reported are based on the group with long-term data.

[b]Intended treatment duration in months. When studies used different durations, the numbers reported in parentheses are from the group with long-term data. More recent studies selected treatment duration based on HCV genotype with 12 months of treatment for genotypes 1 or 4 and 6 months for genotypes 2 or 3.

[c]Randomized controlled trial comparing treated patients versus untreated controls. Sample size reported is the treatment group only.

Table 2. Characteristics of studies of interferon or pegylated-interferon treatment of chronic HCV-infected hemodialysis patients with long-term HCV RNA outcomes after transplantation

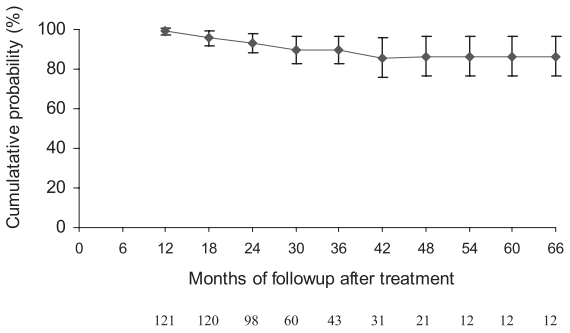
Study, Country, Year	Overall Sample Size (n)	Number with SVR (n)	Number with Long-Term HCV RNA Outcomes (n)	Treatment Dose[a]	Treatment Duration (mo)[b]	Long-Term Follow-Up, Median (mo)
Studies with long-term HCV RNA outcomes after interferon						
Izopet, France, 1997	23	13	2	3	ND	21
Campistol, Spain, 1999[c]	19	11	3	3	6	20
Huraib, Saudi Arabia, 1999	17	12	2	3	12	23
Casanovas-Taltavull, Spain, 2001	29	18	9	3	12	50
Huraib, Saudi Arabia, 2001[c]	11	4	4	3	12	12
Espinosa, Spain, 2001	13	6	1	3	12	27
Kamar, France, 2003	55	21	16	3	6 ($n = 3$) 12 ($n = 13$)	24
Buargub, Libya, 2006	35	9	1	3	12	12
Studies with long-term HCV RNA outcomes after pegylated-interferon						
Bruchfeld, Sweden, 2006	6	3	2	135 (α-2a), $n = 1$ 50 (α-2b), $n = 1$ 200–300 daily (RBV)	6 ($n = 1$) 12 ($n = 1$)	5
Amarapurkar, India, 2007	6	3	3	1.0/kg (α-2b)	6	6
Kose, Turkey, 2009	26	9	2	135 (α-2a)	12	24
All transplant	240	109	45	Variable	6 ($n = 10$) 12 ($n = 33$)	20

α-2a, pegylated-interferon alpha-2a; α-2b, pegylated-interferon alpha-2b; ND, not documented; RBV, ribavirin; TIW, three times weekly.

[a]Doses presented for interferon are in million units, three times weekly, and for pegylated interferon alpha-2a or 2b are in micrograms, once weekly. When studies used more than one treatment dose, the numbers reported are based on the group with long-term data.

[b]Intended treatment duration in months. When studies used different durations, the numbers reported in parentheses are from the group with long-term data. More recent studies selected treatment duration based on HCV genotype with 12 months treatment for genotypes 1 or 4 and 6 months for genotypes 2 or 3.

[c]Randomized controlled trial comparing treated patients versus untreated controls. Sample size reported is the treatment group only.



Numbers at bottom of figure represent number of patients at risk at each time interval.

Figure 3. | Probability of long-term viral negativity in patients followed on hemodialysis.

table analysis, which is the preferable manner to perform time-to-event analysis.

To compare our results to studies of non-HD patients, we determined the raw probability of long-term virological negativity for two groups, which was 92% and 93% for HD patients and kidney transplant recipients with median 18 and 20 months of follow-up, respectively. Adding the virological outcomes of the 22 excluded patients with long-term virological negativity before transplantation, but without specified follow-up time on HD (38,39), increased the probability of HCV RNA negativity in the HD group to 93%. These results in HD patients are comparable to those observed in non-HD patients (Table 3). After kidney transplantation, our results are similar to one study of IFN and ribavirin-treated liver transplant recipients receiving immunosuppressive agents, where the probability of long-term viral negativity was 93% at 30 months of follow-up (23).

Thus, the long-term virological response appears to be high both for patients who remain on HD and for those who undergo kidney transplantation. The late decrease in the probability of remaining HCV RNA negative observed beyond 60 months following transplantation may be attributable to having two relapses in the only 10 patients with this duration of follow-up, as supported by the wide confidence limits around the 60-month estimate. We would expect relapses after transplantation to be more common

Table 3. Comparison of previous studies of long-term viral response following interferon-based treatment

Author, Year	Study Design	Treatment	Number with SVR	Follow-Up (mo)[a]	Long-Term Response Methodology	Long-Term Response (%)
Studies in nonhemodialysis population						
Shindo, 1995	Single center	IFN	21	6	Probability	95
Marcellin, 1997	Single center	IFN	75	42 (6–85)	Probability	96
Larghi, 1998	Single center	IFN	25	33 (15–74)	Probability	92
Lau, 1998	Single center	IFN	5	NR (72–156)	Probability	100
Reichard, 1999	3 RCT	IFN	26	59 (36–100)	Probability	92
Scvarcz, 1999	Single center	IFN + RBV	12	18	Probability	92
Bruno, 2001	2 RCT	IFN	36	78	Probability	100
McHutchison, 2001[b]	3 RCT	IFN + RBV (24)	112	42	Kaplan–Meier	97
		IFN + RBV (48)	151	42	Kaplan–Meier	99
		IFN	73	42	Probability	96
Veldt, 2004	Meta-analysis[c]	IFN	286	59 (12–120)	Kaplan–Meier	95
Tsuda, 2004	Single center	IFN	38	82 (53–144)	Probability	100
Dalgard, 2005	1 RCT	IFN +/− RBV	27	59 (7–77)	Probability	98
Formann, 2006	Single center	PEG-IFN	187	29 (12–172)	Probability	100
Camma, 1999	Meta-analysis	IFN	453	NR (18–93)	Pooled probability	91
Studies in transplant recipients						
Bizollon, 2002	Single center study of liver transplant recipients	IFN + RBV	14	30	Probability	93
Current study						
Gordon	Hemodialysis	IFN or PEG-IFN	121	18 (1–78)	Probability	92
					Life table analysis	86 (77–96)
Gordon	Hemodialysis with subsequent kidney transplant	IFN or PEG-IFN	45[d]	20 (2–88)	Probability	93
					Life table analysis	95 (89–100)

IFN, interferon, NR, not reported; PEG-IFN, pegylated-interferon; RBV, ribavirin; RCT, randomized controlled trial.
[a]Follow-up time reported is median, with range in parentheses, unless otherwise specified. Follow-up times reported are after sustained virologic response for consistency with our analysis. Original studies largely reported follow-up time from end of treatment.
[b]Published as abstract in 2001 American Association for the Study of Liver Diseases meeting.
[c]Meta-analysis of individual patient data from eight randomized controlled trials or prospective studies of interferon.
[d]Thirty two patients had long-term HCV RNA data for both the HD and kidney transplant states. We analyzed these patients in both groups.

early after transplantation when immunosuppression is typically greatest.

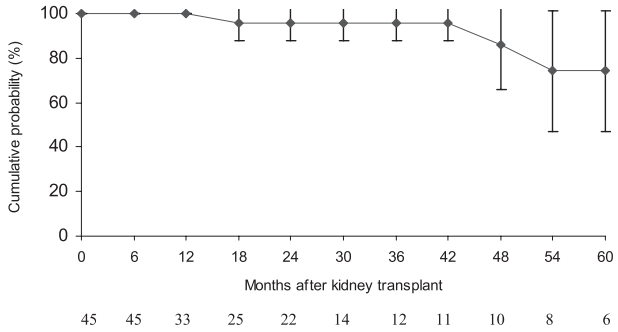
One possible explanation for the observed late "relapses" involves primary reinfection with HCV, which has been described in HD patients due to breaches in infection control practices but can occur in any setting if patients use injection drugs or perform other risky behaviors. Molecular epidemiology techniques have confirmed reinfection with different HCV genotypes in successfully treated HD patients who appear to have a late virologic relapse (50). Future studies of long-term virological outcomes should determine HCV genotype and use molecular epidemiology techniques to ensure that "relapses" are not actually newly acquired infections.

This study has several limitations. Publication bias is always a concern with systematic reviews. We addressed this by searching for unpublished abstracts from recent nephrology and hepatology meetings, but we did not identify additional studies. Even among the retrieved studies, reporting bias may have occurred such that only studies with favorable results reported long-term outcomes, leading to a systematic overestimate of long-term virological outcomes following SVR. Additionally, selection bias may have occurred, particularly in the kidney transplantation group, such that only patients who remained viral negative were selected to undergo transplantation. Each of these limitations may have led us to overestimate the true long-term of viral negativity.

Missing data are a frequent problem for meta-analysis of patient-level data and may have affected our results; for example, we excluded 22 patients who had long-term HCV RNA negativity but did not have a specified follow-up time. In addition, few patients had follow-up durations beyond 48 months, thereby limiting the accuracy and precision of estimates at longer-term follow-up. However, this study's follow-up duration is similar to that reported in non-HD patients (10–12), and our choice of duration for analysis balanced the problem of overestimating the persistence of long-term viral negativity from using a shorter follow-up with the imprecision from using a smaller sample with longer follow-up. Ideally, we would have performed survival analysis with transplantation as a time-dependent covariate but were unable to because of missing data and the imprecision of the available data.

In the reviewed studies, clinical outcomes, such as mortality, were inconsistently reported, so we were unable to link the surrogate outcome, SVR, to clinical outcomes. In non-HD patients, IFN treatment and achieving SVR are associated with lower incidences of hepatocellular carcinoma (15,16) and mortality (16,17). However, the multiple competing risks for mortality among HD patients would diminish any mortality benefit of eradicating HCV infection. Future studies should investigate the clinical benefits of HCV treatment in HD patients.

Despite these limitations, this is the first systematic review to provide data on the long-term persistence of viral negativity in IFN and pegylated-IFN-treated HD patients who achieved SVR. More than 80% of HD patients who achieve SVR remain HCV RNA negative after 48 months of follow-up on dialysis. Long-term viral negativity was also observed in 95% of treated HD patients 48 months after kidney transplantation, an important finding for clinicians considering whether to treat HCV infection before transplantation. Future research should assess the clinical benefits of achieving SVR in HD patients and HCV RNA outcomes beyond 48 months after SVR to allow more precise long-term estimates of viral negativity. IFN-based treatment should be considered for HD patients who are good treatment candidates, particularly kidney transplant candidates, because SVR rates can be achieved in one third to one half of patients and, in most, viral negativity persists long term.



Numbers at bottom of figure represent number of patients at risk at each time interval.

Figure 4. | Probability of long-term viral negativity for treated hemodialysis patients followed after kidney transplantation.

Acknowledgments

We are indebted to the following individuals who provided individual patient data for this analysis that were not available in the original publication: Ali Akcay, M.D., Baskent University Faculty of Medicine, Ankara, Turkey; Mahdia Buargub, M.D., Tripoli Central Hospital, Tripoli, Libya; T M Chan, M.D., University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong; Jacques Chanard, M.D., Centre-Hospitalier et Universitaire, Reims, France; Jacques Izopet, M.D., and Florence Nicot, M.D., Hopital Purpan, Toulouse, France; Dujanaj Mousa, M.D. and Abdullah Al Waili, M.D., Riyadh Armed Forces Hospital, Riyadh Kingdom of Saudi Arabia; Maria Raptopolou-Gigi, M.D., University of Thessaloniki, Thessaloniki, Greece.

We are particularly grateful for the contributions of Dr. Joseph Lau to early portions of the analysis and writing of the manuscript.

Disclosures

None.

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Received: January 14, 2011. **Accepted:** May 2, 2011

Published online ahead of print. Publication date available at www.cjasn.org.