MAJOR ARTICLE

Pegylated Interferon Alfa-2a Monotherapy for Hemodialysis Patients with Acute Hepatitis C

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Background. Hemodialysis patients are at risk of hepatitis C virus (HCV) infection. However, little is known about the efficacy and safety of pegylated interferon (IFN) therapy for hemodialysis patients with acute hepatitis C.

Methods. From 2005 through 2008, 35 hemodialysis patients with acute hepatitis C who did not have spontaneous clearance of HCV by 16 weeks were treated with pegylated IFN alfa-2a at a dosage of 135 μg weekly for 24 weeks. In contrast, 7 patients with clearance of HCV by 16 weeks were under observation only. Thirty-six hemodialysis patients from 2002–2005 who had acute hepatitis C but did not receive treatment served as historical controls. The primary efficacy and safety end points were sustained virologic response (undetectable HCV RNA levels at 24 weeks after therapy) by intention-to-treat analysis and treatment-related withdrawal.

Results. The rate of sustained virologic response in the treatment group was significantly higher than the rate of spontaneous HCV clearance in the control group (88.6% vs 16.7%; $P < .001$). Two patients (5.7%) prematurely terminated treatment at 8 and 10 weeks because of constitutional symptoms, and both did not have sustained virologic response. All but one patient had rapid virologic response (undetectable HCV RNA levels at 4 weeks of therapy), and all patients who received >12 weeks of therapy had early and end-of-treatment virologic responses. All patients who had clearance of HCV by 16 weeks had undetectable HCV RNA levels until the end of follow-up.

Conclusions. Pegylated IFN alfa-2a monotherapy is safe and efficacious for hemodialysis patients with acute hepatitis C. It is suggested that patients without spontaneous clearance of HCV by week 16 should receive therapy.

Despite the introduction of universal precautions and blood product screening, hepatitis C virus (HCV) infection remains a major health problem in patients with end-stage renal disease who undergo hemodialysis. It is estimated that the prevalence and incidence rates of HCV infection are 3%–80% and 0.33%–2.59%, respectively [1–3]. Furthermore, in ~90% of hemodialysis patients with acute hepatitis C, their condition evolves into chronic disease if no treatment is given [4, 5]. Although hemodialysis patients with chronic hepatitis C are usually asymptomatic, with mildly elevated serum alanine aminotransferase (ALT) levels, they are at risk for liver-related morbidity and mortality [6, 7]. Therefore, early treatment with interferon (IFN) monotherapy for hemodialysis patients with acute hepatitis C is helpful to prevent chronic infection and to avoid ribavirin-induced severe anemia in the hemodialysis patients with chronic hepatitis C who receive conventional or pegylated IFN plus ribavirin therapy [8–10].

IFN-based monotherapy has been used successfully to treat acute hepatitis C. Treatment with conventional IFN at a dosage of 3–6 million units 3 times per week for 4–24 weeks had sustained virologic response (SVR) rates of 32%–98% [11–15]. The recent introduction of pegylated IFN alfa-2b at a dosage of 1.0–1.66 μg/kg/week for 12–24 weeks further increased the SVR rates to 82%–95% [16–20]. In addition, 12–16 weeks of ob-

Received 21 February 2010; accepted 1 June 2010; electronically published 20 July 2010.

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Clinical Infectious Diseases 2010; 51(5):541–549

1058-4838/2010/5105-0010$15.00
DOI: 10.1086/655682

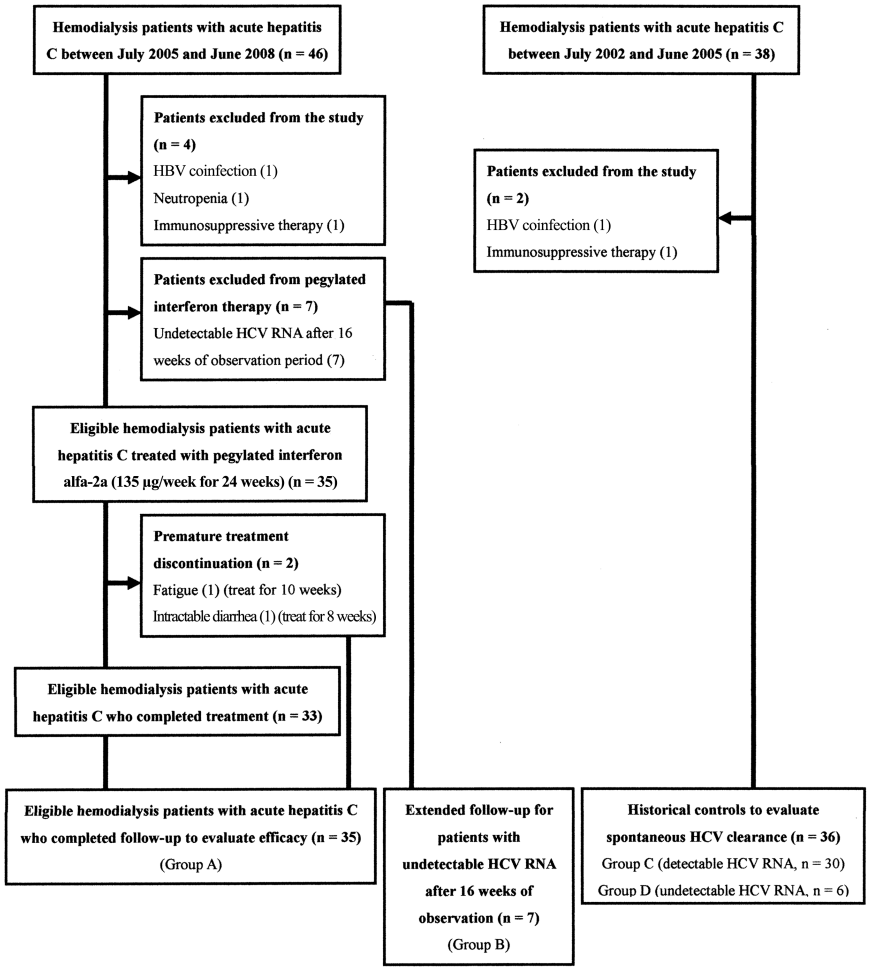

Figure 1. Flow diagram of the study. HBV, hepatitis B virus; HCV, hepatitis C virus.

servation is suggested, to avoid unnecessary treatment for self-limited acute hepatitis C [21–23].

Treatment of acute hepatitis C in hemodialysis patients with conventional IFN at a dosage of 3–10 million units 3 times/week for 12–48 weeks achieved SVR rates of 26%–72%, with divergent safety profiles across different treatment dosages and durations [24–27]. A recent study showed that the SVR rate was 40% with pegylated IFN alfa-2b at a dosage of 1.0 μg/kg/week for 24 weeks [28]. However, the study was small and enrolled hemodialysis patients with possible evidence of chronic disease, making the actual SVR rate lower than expected. Thus, a larger study of patients with well-defined acute hepatitis C is warranted.

Pegylated IFN alfa-2a has been shown to have pharmacokinetics and safety profiles more favorable than those of pegylated IFN alfa-2b or conventional IFN for hemodialysis patients with chronic hepatitis C [29, 30]. In this study, we evaluated the safety and efficacy of pegylated IFN alfa-2a monotherapy for hemodialysis patients with acute hepatitis C and compared the treatment-induced and spontaneous HCV clearance rates.

MATERIALS AND METHODS

Patients. From July 2005 through June 2008, 46 consecutive hemodialysis patients aged 18–65 years with acute hepatitis C were enrolled at 4 centers in Taiwan. Because hemodialysis patients are at high risk of HCV infection, all patients routinely receive monthly ALT and quarterly anti-HCV surveillance for early detection of acute hepatitis C. Hemodialysis patients were defined as patients with creatinine clearance <10 mL/min per 1.73 m^2 of body surface area who received maintenance renal replacement therapy through vascular routes. Acute hepatitis C was defined as documentation of seroconversion to anti-HCV (Abbott HCV EIA 3.0; Abbott Diagnostic) and elevated serum ALT levels >15 times the upper limit of normal (ULN; 17 IU/mL for dialysis patients) [16, 17, 31]. Patients were excluded if they had anemia (hemoglobin level, <10 g/dL), neutropenia (neu-

Table 1. Baseline Characteristics of Hemodialysis Patients with Acute Hepatitis C

Characteristic	July 2005–June 2008			July 2002–June 2005		
	All patients (n = 42)	Group A: patients r eceiving pegylated IFN (n = 35)	Group B: patients under observation (n = 7)	All patients (n = 36)	Group C[a]: patients with detectable HCV RNA (n = 30)	Group D: patients with undetectable HCV RNA (n = 6)
Age, years	45.8 ± 9.2	46.1 ± 8.7	44.4 ± 12.3	48.4 ± 8.9	49.4 ± 8.4	43.2 ± 10.0
Male sex, no. (%) of patients	28 (66.7)	23 (65.7)	5 (71.4)	26 (66.7)	19 (63.3)	4 (66.7)
Duration of hemodialysis, years	5.2 ± 2.1	5.4 ± 2.1	4.3 ± 1.7	5.2 ± 2.6	5.3 ± 2.7	4.7 ± 2.2
BMI	22.9 ± 3.8	22.9 ± 3.8	22.8 ± 3.9	23.7 ± 3.6	24.1 ± 3.7	21.7 ± 2.0
Hemoglobin, g/L	11.7 ± 1.4	11.6 ± 1.4	12.1 ± 1.4	11.9 ± 1.9	12.0 ± 2.0	11.6 ± 1.0
White blood cell count, 10^9 cells/L	6.5 ± 2.3	6.5 ± 2.3	6.5 ± 2.8	6.5 ± 1.7	6.6 ± 1.5	6.4 ± 2.8
Platelet count, 10^9 platelets/L	200 ± 57	200 ± 56	202 ± 68	195 ± 50	192 ± 46	211 ± 69
Albumin level, g/dL	4.2 ± 0.4	4.2 ± 0.4	4.3 ± 0.4	4.1 ± 0.3	4.0 ± 0.2	4.4 ± 0.4
Total bilirubin level, mg/dL	0.5 ± 0.2	0.5 ± 0.3	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.2	0.4 ± 0.1
ALT level (divided by ULN)	18.4 ± 3.1	18.1 ± 3.0	19.5 ± 3.8	18.2 ± 3.0	18.2 ± 3.2	18.0 ± 2.4
Blood urea nitrogen level, mg/dL	57.9 ± 20.8	58.4 ± 21.6	55.6 ± 17.0	60.0 ± 21.6	61.1 ± 22.8	54.9 ± 14.5
Creatinine level, mg/dL	10.2 ± 2.9	10.3 ± 3.1	10.1 ± 1.9	10.5 ± 3.2	10.5 ± 3.4	10.5 ± 1.5
HCV RNA level,[a] $\log_{10}$ IU/mL	…	5.7 ± 0.9	…	…	6.0 ± 0.6	…
HCV genotype,[b] no. (%) of patients						
1a; 1b; 1a+1b	…	3; 20; 1 (68.6)	1; 3; 0 (57.1)	…	2; 21; 0 (76.7)	…
2a; 2b; 2a+2b	…	7; 2; 1 (28.6)	1; 1; 0 (28.6)	…	6; 1; 0 (23.3)	…
6	…	1 (2.8)	0 (0)	…	0 (0)	…
NA	…	0 (0)	1 (14.3)	…	…	…

NOTE. Data are mean ± standard deviation, unless otherwise indicated. ALT, alanine aminotransferase; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HCV, hepatitis C virus; IFN, interferon; IU, international units; NA, not available; ULN, upper limit of normal.

[a] For group C patients, HCV RNA levels were tested in June 2009, rather than at the onset of acute hepatitis C.

[b] HCV genotyping testing was performed during the observation period for group B patients and in June 2009 for group C patients.

Table 2. Hepatitis C Virus (HCV) RNA Monitoring during the Observation Period for Hemodialysis Patients with Acute Hepatitis C

Patients with serum available for HCV RNA analysis	No. (%) of patients in groups A+B		No. of group A patients		No. of group B patients	
	Undetectable HCV RNA	Detectable HCV RNA	Undetectable HCV RNA	Detectable HCV RNA	Undetectable HCV RNA	Detectable HCV RNA
At onset of acute hepatitis C (n = 28)	3 (10.7)	25 (89.3)	3	20	0	5
At 4 weeks of observation (n = 37)	12 (32.4)	25 (67.6)	10	21	2	4
At 8 weeks of observation (n = 40)	13 (32.5)	27 (67.5)	9	24	4	3
At 12 weeks of observation (n = 42)	15 (35.7)	27 (64.3)	9	26	6	1
At 16 weeks of observation (n = 42)	7 (16.7)	35 (83.3)	0	35	7	0

trophil count, <1500 cells/mm^3), thrombocytopenia (platelet count, <90,000 cells/mm^3), coinfection with hepatitis B virus or human immunodeficiency virus, chronic alcohol abuse (daily alcohol consumption, >20 g/day), decompensated cirrhosis, autoimmune liver diseases, neoplastic diseases, organ transplantation or immunosuppressive therapy, drug abuse, pregnancy, poorly controlled autoimmune diseases, cardiopulmonary diseases, neuropsychiatric disorders, or diabetes mellitus with retinopathy or were unwilling to have contraception during the study. All patients received each blood test before hemodialysis to avoid dialysis-induced transient reduction of HCV RNA [32]. The study conformed to the Helsinki Declaration, was approved by the institutional review board, and was registered with ClinicalTrials.gov (NCT00917358). Written informed consent was obtained from all patients before enrollment.

Study design. To avoid unnecessary treatment for patients who might have spontaneous clearance of HCV infection, all eligible patients were enrolled and observed for 16 weeks after the onset of disease. Monthly serum ALT level measurement and quantitative HCV RNA testing (Cobas TaqMan HCV Test, version 2.0; Roche Diagnostics; detection limit, 15 IU/mL) were performed during the observation period. Patients who had detectable HCV RNA at the end of the observation were given treatment with pegylated IFN alfa-2a (Pegasys; Hoffman-LaRoche) at a dosage of 135 μg/week for 24 weeks, which was considered safe for patients with end-stage renal disease [33]. Participants received the study drug at outpatient clinics for 24 weeks and were followed up for 24 weeks after the end of therapy. In addition, they received outpatient visits to assess the efficacy and safety at weeks 1, 2, 4, 6, and 8 during therapy and then monthly until the end of follow-up. On the other hand, patients who had undetectable HCV RNA at the end of observation received extended follow-up at weeks 24, 36, and 48 with measurement of serum ALT and quantitative HCV RNA testing to monitor the spontaneous clearance rate.

For patients receiving pegylated IFN, complete blood count and serum ALT level were assessed at each outpatient visit; serum albumin, bilirubin, and creatinine levels; prothrombin time; and thyroid function were assessed at enrollment and every 12 weeks until the end of follow-up. Serum HCV RNA levels were evaluated at baseline, week 4, week 12, the end of therapy, and 24 weeks after the end of therapy. HCV genotyping was performed using a commercial assay (Inno-LiPA HCV II; Innogenetics). Rapid virologic response (RVR) was defined as an undetectable HCV RNA level (<15 IU/mL) at week 4 of therapy. Early virologic response was defined as at least 2-log decrease in HCV RNA level from baseline to week 12 of therapy. The end-of-treatment virologic response and SVR were defined as undetectable HCV RNA at the end of treatment and the end of follow-up, respectively.

Because prior studies showed that patients with acute hepatitis C who had HCV viremia after 12–20 weeks of observation have high risks of chronic infection, we did not set the active-comparative group without IFN-based treatment for patients who had detectable HCV RNA levels at 16 weeks after the onset of disease [4, 5, 16, 21]. To compare the treatment-induced and spontaneous HCV clearance rates, we enrolled hemodialysis patients with acute hepatitis C who met the same inclusion and exclusion criteria but who did not receive treatment from July 2002 through June 2005 to serve as the historical control subjects. All received HCV RNA and HCV genotyping assays in June 2009 to evaluate the spontaneous clearance rate.

Assessment of efficacy and safety. The primary efficacy end point was SVR rate by intention-to-treat analysis. Patients without data at the end of follow-up were considered not to have SVR. Participants who received at least 1 dose of treatment were evaluated for adverse events, and laboratory tests were done to assess the safety. Patients were considered to have withdrawn from the study if they missed 4 consecutive doses of

Table 3. Pattern of Hepatitis C Virus (HCV) RNA Changes in Hemodialysis Patients with Acute Hepatitis C

Pattern of HCV RNA changes	No. (%) of patients		
	Groups A+B (n = 42)	Group A (n = 35)	Group B (n = 7)
Persistent HCV viremia	15 (35.7)	15 (42.9)	0 (0)
Persistent no HCV viremia	1 (2.4)	0 (0)	1 (14.3)
Intermittent HCV viremia	26 (61.9)	20 (57.1)	6 (85.7)

Table 4. Adverse Events in 35 Patients Who Received Pegylated Interferon Therapy

Adverse event	No. (%) of patients
Fever	4 (11.4)
Rigor	4 (11.4)
Fatigue	17 (48.6)
Headache	5 (14.3)
Myalgia	6 (17.1)
Insomnia	10 (28.6)
Irritability	2 (5.7)
Depression	2 (5.7)
Anorexia	12 (34)
Vomiting	4 (11.4)
Diarrhea	3 (8.6)
Constipation	2 (5.7)
Cough	3 (8.6)
Dermatitis	9 (25.7)
Injection reaction	4 (11.4)
Hair loss/alopecia	5 (14.3)
Anemia[a]	5 (14.3)
Leukopenia[a]	3 (8.6)
Thrombocytopenia[a]	1 (2.9)
Serious adverse events[b]	0 (0)
Dose reduction due to adverse events	7 (20.0)
Premature withdrawal due to adverse events[c]	2 (5.7)

[a] Anemia was defined by a hemoglobin level <8.5 g/dL, leukopenia was defined by a neutrophil count <750 cells/mm^3, and thrombocytopenia was defined by a platelet count <50,000 cells/mm^3.

[b] There were no deaths and no treatment-related serious adverse events.

[c] Two patients stopped treatment prematurely at weeks 8 and 10 because of fatigue and intractable diarrhea. The symptoms were relieved 4 weeks after the cessation of therapy.

pegylated IFN or if the investigator was concerned for their safety and had them withdraw from the study. Patients who withdrew from the study were encouraged to receive follow-up without treatment until the end of the follow-up period. Dose reduction to 90 or 45 μg/week or cessation of treatment was determined according to the severity of adverse events and the laboratory abnormalities (dose was reduced for neutrophil count <750 cells/mm^3 or platelet count <50,000 cells/mm^3; treatment was stopped for neutrophil count <500 cells/mm^3 or platelet count <30,000 cells/mm^3). If the laboratory abnormalities or adverse events improved after dose reduction or treatment cessation, a return to the initial dose was permitted. The primary safety end point was treatment-related withdrawal rate.

Statistics. The estimated sample size was 30 for each group, under the assumption of 40% improvement in SVR rate of patients receiving pegylated IFN treatment, compared with that of historical control subjects, with a power of 0.90 and a 2-sided significance level of 0.05. Patient characteristics were expressed as mean ± standard deviation and percentages, as appropriate. Characteristics were compared by χ^2 test, Fisher's exact test, or Student's *t* tests when appropriate. Intention-to-treat analyses for the primary efficacy and safety end points were performed for patients receiving treatment. The predictive factors for treatment-induced or spontaneous HCV clearance were analyzed by univariate or multivariate analysis when appropriate. All statistical tests were 2-tailed, and the results were considered statistically significant when the *P* value was <.05.

RESULTS

Patient characteristics. Figure 1 shows the study flow diagram. Of 46 hemodialysis patients with acute hepatitis C, 11 were excluded from receiving treatment because of undetectable HCV RNA after 16 weeks of observation (7 patients), hepatitis B virus coinfection (1 patient), neutropenia (1 patient), immunosuppressive therapy (1 patient), or declining to receive treatment (1 patient). Of the remaining 35 patients (group A) who were eligible for therapy, 2 (5.7%) did not complete treatment because of fatigue and intractable diarrhea. All group A and group B patients completed follow-up. In addition, 38 hemodialysis patients had documented acute hepatitis C before the interventional study, and 2 were excluded because of hepatitis B virus coinfection (1 patient) or the concurrent use of immunosuppressive therapy (1 patient). Among the remaining 36 hemodialysis patients, 30 had detectable HCV RNA (group C) and 6 had undetectable HCV RNA (group D). The annual incidence of hemodialysis patients with acute hepatitis C in our study was 1.36%. Patient characteristics are summarized in Table 1. Baseline characteristics were not statistically different between different patient groups. The HCV genotypes were similar between group A and group B patients ($P = 1.00$) and between group A and group C patients ($P = .77$).

Monitoring HCV RNA levels during the observation period. Tables 2 and 3 show the serial HCV RNA levels of 42 patients during the observation period. At the onset of disease, 89.3% of the patients had detectable HCV RNA. The rates of detectable HCV RNA decreased to 64.3%–67.6% after 4–12 weeks of observation. However, it then increased to 83.3% after 16 weeks of observation. Among group A patients, 42.9% had persistent HCV viremia, and the remaining 57.1% had intermittent HCV viremia; among group B patients, 14.3% had persistent *no* HCV viremia, and the remaining 85.7% had intermittent HCV viremia ($P = .01$). The mean HCV RNA level was 485,227 IU/mL (range, 4220–2,300,000 IU/mL), and the mean nadir HCV RNA level was 26,170 IU/mL (range, 4220–85,100 IU/mL) during the observation period in group B patients. At onset and weeks 4, 8, and 12 of observation, the positive predictive rates of HCV RNA were 80%, 84%, 88.9%, and 96.3% for HCV viremia at week 16, respectively; negative predictive rates were 0%, 20%, 30.8%, and 40% for no HCV viremia at week 16, respectively.

Safety of pegylated IFN alfa-2a monotherapy. The adverse

Table 5. Virologic Responses in Patients Receiving Pegylated Interferon (IFN) Therapy, Patients under Extended Observation without Therapy, and Historical Control Patients without Therapy

Virologic response	Group A (receiving pegylated IFN therapy) ($n = 35$)	Group B (under extended observation without therapy) ($n = 7$)	Groups C+D (historical controls without therapy) ($n = 36$)	*P*	
				Group A vs Groups C+D	Groups A+B vs Groups C+D
Rapid virologic response	34 (97.1)	…	…		
Early virologic response	33 (94.3)	…	…		
End-of-treatment virologic response	35 (100.0)	…	…		
SVR or spontaneous HCV clearance[a]	31 (88.6)[b]	7 (100.0)	6 (16.7)	<.001	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. HCV, hepatitis C virus; SVR, sustained virologic response.

[a] SVR was defined as undetectable HCV RNA levels at 24 weeks after the end of therapy for group A patients. Spontaneous HCV clearance was measured at 48 weeks after the onset of acute hepatitis C for group B patients and at 5–7 years after the onset of acute hepatitis C for patients in groups C and D.

[b] Four patients did not achieve SVR: 2 patients who received 8 and 10 weeks of treatment (baseline HCV RNA levels, 3.36×10^6 and 1.98×10^6 IU/mL, respectively; HCV genotype 1b for both patients), 1 who did not achieve rapid virologic response but achieved early virologic response and end-of-treatment virologic response (baseline HCV RNA level, 6.86×10^6 IU/mL; HCV genotype 1a+1b), and 1 who achieved rapid virologic response, early virologic response, and end-of-treatment virologic response (baseline HCV RNA level, 9.51×10^6 IU/mL; HCV genotype 1b).

event rates are shown in Table 4. Of 35 patients receiving therapy, 2 (5.7%) withdrew from the study at weeks 8 and 10 because of fatigue and intractable diarrhea. The symptoms were relieved in both patients after therapy was stopped. Dose reduction was required for 7 patients (20.0%), because of constitutional symptoms in 3 and laboratory abnormalities in 4. All of their conditions improved after dose reduction. Twenty-nine patients (82.9%) received ⩾80% of the scheduled treatment dosage and duration. None had serious adverse events during the study.

Efficacy of pegylated IFN alfa-2a monotherapy. The virologic response rate in group A patients and the spontaneous HCV clearance rates in group B, C, and D patients are shown in Table 5. Thirty-four of the group A patients (97.1%) had RVR, and all but 2 who prematurely stopped therapy had early virologic response (94.3%). All patients (100%) had end-of-treatment virologic response, and 31 patients (88.6%) achieved SVR. Furthermore, all group B patients who had spontaneous clearance of the virus after extended follow-up. The treatment-induced HCV clearance rate in group A patients was significantly higher than the spontaneous HCV clearance rate in group C and D patients (88.6% vs 16.7%; $P < .001$).

Factors predictive of SVR and spontaneous HCV clearance. Table 6 shows the univariate analyses of factors at baseline or during treatment that predict SVR in group A patients and spontaneous HCV clearance in group B, C, and D patients. Among patients receiving treatment, those who received ⩾80% of the scheduled dosage and duration had a higher SVR rate than that of patients who did not ($P = .01$). Low baseline HCV RNA lvel ($P = .08$) and RVR during treatment ($P = .09$) tended to predict SVR, although both did not reach statistical significance. In contrast, baseline ALT levels and HCV genotypes were not associated with SVR. No baseline demographic, hematological, or biochemical factors were associated with spontaneous HCV clearance.

DISCUSSION

Although accumulating evidence indicates that early initiation of pegylated IFN monotherapy can successfully treat patients with acute hepatitis C, little is known about the timing of initiation, safety, and efficacy of pegylated IFN for treatment of hemodialysis patients with acute hepatitis C. Our data showed that hemodialysis patients with acute hepatitis C who continued to have viremia after 16 weeks of observation could achieve a satisfactory SVR rate with reasonable safety with receipt of 24 weeks of pegylated IFN alfa-2a therapy. In addition, patients with acute hepatitis C who had spontaneous clearance of HCV after 16 weeks of observation could sustain viral clearance without treatment. Although low-dose ribavirin therapy can be administered to hemodialysis patients with chronic hepatitis C, these patients need to receive high-dose erythropoietin therapy and close monitoring of ribavirin plasma concentrations to prevent life-threatening anemia [8–10]. Therefore, early treatment with IFN-based monotherapy for hemodialysis patients with acute hepatitis C could achieve a high SVR rate and prevent chronic infection for those who do not have spontaneous clearance of HCV after 16 weeks. In contrast to the policy of 12 weeks of observation for patients with acute hepatitis C, our data indicated that 16 weeks of watchful surveillance could prevent hemodialysis patients with acute self-limiting hepatitis C from receiving unnecessary treatment [18, 21]. The discrepancy in the duration of observation may be explained by the monthly ALT and quarterly anti-HCV surveillance for hemo-

Table 6. Factors Predictive of Sustained Virologic Response (SVR) in Patients Receiving Pegylated Interferon Therapy and Those with Spontaneous Hepatitis C Virus (HCV) Clearance

	Group A (n = 35)			Groups B+C+D (n = 43)		
Variable	SVR (n = 31)	No SVR (n = 4)	P	Spontaneous HCV clearance (n = 13)	Persistent HCV viremia (n = 30)	P
Age, years	45.2 ± 8.4	53.5 ± 8.8	.80	43.9 ± 10.9	49.4 ± 0.4	.18
Male sex	19 (61.3)	2 (50.0)	.65	9 (69.2)	19 (63.3)	1.00
Duration of hemodialysis, years	5.4 ± 2.1	5.8 ± 2.4	.98	4.5 ±1.9	5.3 ±2.7	.18
Adherent to treatment[a]	28 (90)	1 (25)	.01	…	…	
BMI	23.3 ± 3.8	20.1 ± 2.9	.79	22.3 ± 3.1	24.1 ± 3.7	.39
White blood cell count, 10^9 cells/L	6.5 ± 2.4	6.1 ± 1.7	.71	6.5 ± 2.7	6.6 ± 2.1	.25
Platelet count, 10^9 platelets/L	201 ± 58	189 ± 43	.92	206 ± 66	198 ± 46	.31
Albumin level, g/dL	4.2 ± 0.4	4.4 ± 0.6	.13	4.3 ± 0.4	4.1 ± 0.2	.27
Total bilirubin level, mg/dL	0.5 ± 0.3	0.5 ± 0.3	.94	0.4 ± 0.1	0.3 ± 0.2	.17
ALT level (divided by ULN)	18.3 ± 3.1	17.3 ± 1.5	.22	18.8 ± 3.2	18.2 ± 3.2	.95
HCV RNA level, $\log_{10}$ IU/mL	5.6 ± 0.8	6.7 ± 0.3	.08	…	…	
HCV genotype (1 and 6 vs 2)	21 (67.7)	4 (100.0)	.30	…	…	
Rapid virologic response (yes vs no)	31 (100)	3 (75)	.09	…	…	
Early virologic response (yes vs no)	31 (100)	2 (100)[b]	NC[c]	…	…	
End-of-treatment virologic response (yes vs no)	31 (100)	4 (100)	NC[c]	…	…	

NOTE. Data are no. (%) of patients or mean ± standard deviation. ALT, alanine aminotransferase; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); NC, not calculated; ULN, upper limit of normal.

[a] Received treatment with ⩾80% of scheduled pegylated interferon alfa-2a dosage and treatment duration.

[b] Two patients who prematurely discontinued pegylated interferon therapy at weeks 8 and 10 did not have data on early virologic response, and both did not achieve SVR.

[c] These P values were not calculated because all patients with or without SVR had 100% rates of early virologic response and end-of-treatment virologic response.

dialysis patients, which makes the diagnosis of acute hepatitis C in these patients more definite and earlier than that in other patients.

In line with prior reports that ~90% of hemodialysis patients had acute hepatitis C that evolved into chronic infection, only 16.7% of the historical control subjects in this study had spontaneous clearance of HCV [4, 5]. Of particular note is that the rate of persistent HCV infection in patients who did not have clearance of HCV at 16 weeks after the onset of disease was comparable to that in historical control subjects (83.3% and 86.7%), which suggests that patients who continue to have viremia after 16 weeks of observation are prone to chronic infection. Although detectable HCV RNA levels after 12 weeks of observation had high predictive rates for HCV viremia at week 16 in hemodialysis patients with acute hepatitis C, transient undetectable HCV RNA before 12 weeks of observation had low predictive rates for subsequent viral clearance [34]. Our data also showed that hemodialysis patients with acute hepatitis C who had spontaneous clearance of HCV had low-level viremia and viral load fluctuation during the observation period [35]. This may be reasoned by the complex virus-host interaction at the early stage of infection, resulting in fluctuating HCV RNA levels in most patients [36–38]. Adopting the 16-week observation strategy to determine the necessity of intervention may be more appropriate to prevent 88.6% patients from having chronic infection and to avoid unnecessary treatment for those with self-limiting acute hepatitis C.

Early prediction of virologic responses can help physicians choose the optimal therapeutic strategies for hemodialysis patients with acute hepatitis C. Prior studies indicated that RVR and low baseline HCV RNA levels are strong predictors for SVR in hemodialysis patients with acute hepatitis C or chronic hepatitis C receiving IFN-based therapy [10, 29, 39]. Our study showed the RVR rate in patients with acute hepatitis C who received pegylated IFN was higher than that in patients with chronic hepatitis C who received either pegylated or conventional IFN (97.1% vs 60% and 44%) [29]. However, RVR and baseline HCV RNA level showed only borderline significance in predicting SVR, probably because of the small number of cases [39]. Adherence to ⩾80% of the scheduled treatment dosage and duration strongly affected SVR, highlighting the importance of improving viral kinetics during treatment and reducing relapse after treatment [16]. Furthermore, our data also showed that HCV genotype and pretreatment ALT level were not significant factors to predict SVR [15, 18, 39]. In terms of safety, we demonstrated that pegylated IFN alfa-2a

was well tolerated by hemodialysis patients with acute hepatitis C. Although several studies showed that the premature discontinuation rate in patients receiving conventional IFN was comparable to that in our patients (10.5% vs 5.7%), the choice of pegylated IFN therapy may improve patient compliance while the SVR rates are not compromised [25–27]. In addition, the safety of our patients is comparable to that of hemodialysis patients receiving pegylated IFN alfa-2a and is superior to that of hemodialysis patients receiving pegylated IFN alfa-2a plus ribavirin to treat chronic hepatitis C [8–10, 29].

For 43 patients who did not receive treatment, we further examined whether baseline factors could predict spontaneous HCV clearance. Our data consistently showed that baseline host factors could not predict spontaneous clearance, as was observed in patients with acute hepatitis C [15, 21, 40]. Therefore, close monitoring of HCV RNA dynamics during the first 16 weeks of disease might be more appropriate to predict outcomes of acute hepatitis C.

In this study, several limitations existed. First, the sample size was relatively small; thus, it is difficult to draw definite conclusions. Nevertheless, this is the first prospective study aimed at identifying the optimal timing for intervention and at evaluating the safety and efficacy of pegylated IFN alfa-2a monotherapy in this special clinical situation. Second, the study did not contain a simple observation group for patients who continued to have viremia for >16 weeks. Therefore, the possibility of spontaneous HCV clearance after 16 weeks cannot be excluded. However, since a high rate of chronic disease was observed in patients with acute hepatitis C who continued to have viremia after 12–20 weeks of observation, it is plausible that treating hemodialysis patients with acute hepatitis C who do not have spontaneous clearance of HCV in a given period may improve outcomes [14, 17, 22]. Third, we failed to assay serial HCV RNA levels after the onset of acute hepatitis C in historical control subjects because of the lack of stored serum samples. Therefore, we cannot validate the 16-week observation guideline to manage hemodialysis patients with acute hepatitis C. Further prospective studies are necessary to confirm the optimal timing for intervention.

Considering the high incidence rates of acute hepatitis C in hemodialysis patients, universal precautions should be strictly followed to decrease the number of new HCV infections [1, 2]. Furthermore, routine surveillance of anti-HCV and ALT levels may identify early the hemodialysis patients with acute hepatitis C who may benefit from IFN therapy. In conclusion, our data suggest that early initiation of pegylated IFN therapy for hemodialysis patients who have failure to clear HCV at 16 weeks after the onset of acute hepatitis C can achieve a high SVR rate with satisfactory safety. In contrast, simple observation is warranted for those who have spontaneous clearance of HCV at 16 weeks after the onset of acute hepatitis C, to avoid unnecessary treatment.

Acknowledgments

Financial support. National Taiwan University Hospital; National Science Council; and Department of Health, Executive Yuan, Taiwan.

Potential conflicts of interest. P.-J.C. is a consultant for Novartis and Roche. D.-S.C. is a consultant for Novartis and GlaxoSmithKline. J.-H.K. is a consultant for Bristol-Myers Squibb, GlaxoSmithKline, Novartis, Omrix, Roche, and Schering-Plough and is on the speakers' bureau for Roche, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, and Schering-Plough. All other authors: no conflicts.

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