

Lack of Efficacy of Pegylated Interferon Monotherapy for Hepatitis C in Patients With End-Stage Renal Disease on Dialysis

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Keywords

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Abstract:

Objectives To evaluate the efficacy, safety and tolerability of pegylated interferon monotherapy for chronic hepatitis C virus (HCV) in patients who are on dialysis.

Methods From the University of Chicago Clinical Hepatology Database dated May 2001 to July 2005, 13 patients on dialysis with hepatitis C who have been treated with pegylated interferon were identified. Demographic and laboratory data were obtained from medical records. Patients received pegylated interferon alfa-2a at 135 μ g subcutaneous (SQ) weekly (n=8) or pegylated interferon alfa-2b at 1 μ g/kg SQ weekly (n=5). Side effects from the medication were noted.

Results There were 7 men and 6 women, with a mean age of 54 ± 11 years; 11 patients (85%) were African American and 11 patients (85%) were infected with HCV genotype 1. The median serum HCV RNA level was 3,273,000 copies/mL (range, 207,000 to >40,000,000), and the median serum alanine aminotransferase level was 29 IU/mL (range, 19–77). Four patients (30%) had bridging fibrosis or cirrhosis on liver biopsy. None of the 13 patients achieved sustained virologic response; 2 patients (15%) had an undetectable viral load at the end of therapy but relapsed within 6 months of follow-up. The most common side effects were fatigue (100%), anemia defined as 2 g/dL or greater drop in hemoglobin level (60%), and psychiatric symptoms (30%).

Conclusions Pegylated interferon is ineffective for HCV infection in patients on dialysis. Furthermore, worsening anemia, which is usually prevalent at baseline in dialysis patients, is a common adverse event even in the absence of ribavirin use.

In the United States, approximately 2% of the general population have chronic infection with the hepatitis C virus (HCV).¹ However, prevalence is higher in the dialysis-dependent population, affecting 8–36% of all patients with end-stage renal disease (ESRD).^{2,3} The increased risk for HCV infection in this population is attributed to nosocomial exposures through blood transfusions, contamination within the dialysis unit, and frequent procedures performed on these patients for dialysis access.⁴⁻⁷ The risk is higher for patients who have been on dialysis for at least 2 years⁶ and for those receiving hemodialysis at a dialysis center compared to those who are on peritoneal dialysis or home hemodialysis.⁸⁻¹⁰

HCV-infected patients with ESRD experience higher mortality and morbidity rates than do their nondialysis counterparts.¹¹⁻¹³ In addition, HCV-infected dialysis patients have lower survival rates than uninfected dialysis patients, with chronic liver disease implicated as a major contributor to less favorable outcomes.¹⁴ Among patients awaiting renal transplantation, HCV is the main cause of chronic liver disease, with many patients being asymptomatic but having significant histologic disease.¹⁵⁻¹⁸ Furthermore, HCV infection has been implicated in reduced patient and graft survival following renal transplantation.¹⁹⁻²¹ Treatment of HCV infection following renal transplantation has also been hindered by reports of variable efficacy and frequent high risk of graft injury.²² However, most of these studies were comprised of small numbers of patients. Therefore, treatment to eradicate HCV in ESRD patients before renal transplantation has been advocated.²³

The main objective of this retrospective study was to determine the efficacy, safety, and tolerability of pegylated interferon treatment for patients with HCV infection who are on dialysis. Randomized controlled trials using pegylated interferon alfa-2a (Pegasys, Roche) or pegylated interferon alfa-2b (Peg-Intron, Schering-Plough) monotherapy proved to be more efficacious than standard nonpegylated interferon in patients with normal renal function.²⁴⁻²⁶ The use of pegylated interferon therapy in patients on dialysis has been adopted in clinical practice; however, data on its efficacy, safety, and tolerability in the this population have yet to be determined.

Methods

From the University of Chicago Clinical Hepatology Database dated May 2001 to July 2005, thirteen dialysis patient with HCV infection who received therapy with pegylated interferon were identified. HCV infection was confirmed by HCV RNA assay or by HCV genotype determination. Demographic (including age, race, gender, weight), clinical (type and duration of dialysis, history

of failed renal transplant), laboratory (HCV genotype, HCV RNA levels, and other routine laboratory tests), and histologic data were obtained from medical records. Medication regimen, dosing schedules, and duration of therapy were also obtained. All patients had liver biopsies performed prior to treatment. All liver biopsy slides were graded according to the Modified Ishak Histologic Activity Index.²⁷

Treatment was administered as pegylated interferon alfa-2a at 135 µg subcutaneous (SQ) weekly (n=8) or as pegylated interferon alfa-2b at 1 µg/kg SQ weekly (n=5), with a goal of 48 weeks of therapy for patients with HCV genotypes 1 and 4 and 24 weeks of therapy for those with genotypes 2 and 3. Nonresponse was defined either by an absence of a 2-log decline in serum HCV viral load at 12 weeks of therapy or a positive serum HCV RNA at anytime between 24 and 48 weeks of therapy. Treatment was discontinued after 12 weeks of therapy in patients deemed to be nonresponders. Sustained virologic response (SVR) was defined as a persistently negative serum HCV RNA at 6 months follow-up after the end of treatment.

Laboratory tests, including a complete blood count (CBC), comprehensive metabolic panel, prothrombin time, and thyroid stimulating hormone test, were performed at weeks 0 (pretherapy) and 4, 12, 24, 36, and 48 while the patient was on therapy and at weeks 12 and 24 of follow-up after completion of treatment. In addition, a CBC was performed every 4 weeks or more frequently if indicated. The serum HCV RNA level was measured quantitatively (Bayer bDNA version 3.0; <3,200 copies/mL) at baseline and week 12 and qualitatively by polymerase chain reaction assay (Mayo Medical Laboratories; <10 IU/mL) at weeks 24, 36, and 48 and at follow-up weeks 12 and 24. Side effects from the medication and early termination of therapy due to severe adverse events were noted. All patients were on erythropoietin prior to initiation of therapy as part of the standard of care for hemodialysis patients with anemia.

This study protocol was approved by the University of Chicago Institutional Review Board.

Results

Demographic and Clinical Data

There were 7 men and 6 women in the study. Eleven of these patients (85%) were African American, and 11 (85%) were infected with HCV genotype 1. Nine of these genotype 1–infected patients were African American. The median serum HCV RNA level was 3,273,000 copies/mL (range, 207,000 to >40,000,000), and the median serum alanine aminotransferase level was 29 IU/mL (range, 19–77). Four patients (30%) had bridging fibrosis or cirrhosis (Table 1).

Efficacy, Safety, and Tolerability of Therapy

None of the 13 patients achieved SVR; 2 patients (15%) had an undetectable serum HCV RNA at the end of therapy but relapsed within 6 months of follow-up. Ten patients were nonresponders, and 1 patient terminated treatment after 2 weeks due to significant side effects. The most common side effects were fatigue (100%), anemia defined as a drop of 2 g/dL or more in hemoglobin level (60%), and psychiatric symptoms (30%) (Table 2). Serious adverse events included intractable emesis leading to dehydration that required hospitalization and early termination of therapy at week 2 in 1 patient and a myocardial infarction at the end of therapy in another.

Discussion

Eradication of HCV infection in the dialysis population would be an ideal strategy to improve patient survival while on dialysis and to optimize patient and graft survival following renal transplantation for those who receive a graft. However, treatment of this population has been hindered by variable results in studies of small numbers of patients and concern about the ability of this population to tolerate interferon. Furthermore, the use of ribavirin, which clearly enhances the efficacy of interferon in the nondialysis population, increasing SVR to standard interferon from approximately 20% to 40% with combination therapy,^{1,28,29} has been limited by its renal clearance profile, which leads to accumulation of ribavirin that is not removed by dialysis. This scenario enhances its hemolytic anemia effect in a population that usually has concomitant anemia from renal disease. Published data on the use of low-dose ribavirin in this population is very limited. Average doses of ribavirin at 170–300 mg daily were given starting at week 5 of standard interferon therapy by Bruchfeld and associates³⁰ in 6 dialysis patients, with close monitoring of plasma concentrations and administration of high-dose erythropoietin to increase erythropoiesis; however, only 1 patient achieved SVR. Another small group of patients (N=5) was treated with standard interferon and ribavirin 200 mg daily to 200 mg three times weekly by Tan and colleagues,³¹ and again trough ribavirin levels were closely monitored; 2 patients had to discontinue therapy due to adverse events and although a decline in HCV RNA was noted, no SVR data were reported.

Standard interferon alfa-2a or -2b monotherapy has been shown to achieve SVR in approximately 20% of treated HCV patients who have normal renal function.^{1,28,29} In dialysis patients, however, uncontrolled studies of small populations have reported SVRs of 19–64% using standard interferon monotherapy at 3M IU, thrice weekly for 6–12 months.⁹ Two meta-analyses^{32,33} found mean overall SVRs with standard interferon monotherapy in the dialysis population of 33% and 37%, with geno-

Table 1. Demographic and Clinical Characteristics of Study Population

Mean age, years	54 ± 11
Men, n (%)	7 (54)
Weight, kg	75 ± 12
African American, n (%)	11 (85)
Hemodialysis, n (%)	11 (85)
Prior failed kidney transplant, n (%)	2 (15)
Median duration of HD, years	2.5
HCV genotype 1, n (%)	11 (85)
HCV genotype 2, n (%)	1 (7.7)
HCV genotype 4, n (%)	1 (7.7)
Median serum ALT, IU/mL	29
Median serum HCV RNA, # copies/mL	3,273,000
Bridging fibrosis or cirrhosis on liver biopsy, n (%)	4 (30)

Table 2. Side Effects With Pegylated Interferon Monotherapy

Side Effects	Number of Patients (%)
Fatigue	13 (100)
Myalgias	3 (23)
Hematologic (anemia)	8 (62)
Gastrointestinal	5 (38)
• Dry mouth	1
• Nausea	4
• Vomiting	1
• Abdominal pain	2
Cardiovascular	1 (8)
• Palpitations	1
Respiratory	0 (0)
Neurologic	2 (15)
• Tinnitus	1
• Headache	1
Psychiatric	5 (39)
• Depression	4
• Psychosis	2

type 1–infected patients having SVRs of 26% and 30%. Standard interferon is known to have a short half-life of approximately 8 hours,³⁴ and several studies have suggested that renal filtration plays a role in its clearance, which is significantly reduced in patients with ESRD.^{35–37} Those ESRD patients who received interferon alfa-2b

have been shown to have a significantly higher mean maximum serum interferon concentration and a longer interferon half-life than their nonuremic counterparts.³⁸ Therefore, ESRD patients with HCV infection have been postulated to experience a higher SVR due to prolonged serum interferon concentrations, which may translate to greater antiviral activity.³²

The advent of pegylated interferon therapy with its lower clearance and longer half-life has significantly increased SVRs in nondialysis patients from 12% to 25% as compared to standard interferon. Other studies have reported even higher SVRs with pegylated interferon monotherapy in the range of 30% to 39% in nondialysis patients^{24,26}; however, few data on the efficacy and safety of this drug in the dialysis population exist. A case series of 6 ESRD patients with HCV genotype 1 reported SVR in 2/6 (33%) of patients after 24 weeks of treatment with pegylated interferon alfa-2b monotherapy; therapy was discontinued in 2 patients due to anemia.³⁹ Sporea and coworkers⁴⁰ treated 10 dialysis patients with pegylated interferon alfa-2a monotherapy for 48 weeks and reported on-treatment response in 7/10 (70%) of patients, but no SVR data have been reported. Teta and associates⁴¹ reported SVR in 1 of 2 ESRD patients with chronic HCV treated with pegylated interferon alfa-2a 180 µg weekly with few side effects; a third patient who received treatment and also achieved SVR had acute HCV. However, Pawa and colleagues⁴² reported a lack of SVR in any of their 6 ESRD patients who were treated with pegylated interferon and Luxon and associates⁴³ also reported a similar experience in ten ESRD patients who received pegylated interferon alfa-2b at 1 µg/kg weekly with or without ribavirin. Of note, the majority of the patients in both studies were African American and were infected with HCV genotype 1, a known predictor of lower rates of SVR in the nondialysis population.⁴⁴⁻⁴⁶

To our knowledge, the present study has the largest number of ESRD patients treated with pegylated interferon monotherapy. Similar to the studies led by Pawa and Luxon, there was no SVR achieved in any of our population which also consisted mostly of HCV genotype 1-infected African Americans with high viral loads, a recognized difficult-to-treat population.^{45,46} Perhaps these three factors are the main determinants of the lack of SVR in our population regardless of renal function. However, in reality, a large proportion of patients afflicted with ESRD are of African American descent and pose a major challenge to successful HCV eradication with the current standard regimen unless newer treatment modalities and/or strategies are developed. Future studies should compare SVR in African American genotype 1 patients with impaired renal function and those with normal renal function to evaluate the effect of dialysis on the success of interferon treatment in this specific group.

Of note, there is a case report of an ESRD patient infected with HCV genotype 1b who did not respond to pegylated interferon alfa-2b at 120 µg weekly and ribavirin 400 mg thrice weekly but achieved SVR after being switched to standard interferon alfa-2b at 3M IU thrice weekly.⁴⁷ Pegylated interferons were developed on the premise that longer half-life may lead to better drug efficacy. Covalent attachment of a polyethylene glycol moiety to standard interferon molecules results in more sustained absorption, decreased clearance, and a smaller volume of distribution.⁴⁸ Although pegylated interferon alfa-2a is mostly cleared by the liver, a 30% relative reduction in clearance of pegylated interferon alfa-2a in patients on maintenance hemodialysis compared to healthy individuals has been reported.⁴⁹ In contrast, renal clearance accounts for a third of the total clearance of pegylated interferon alfa-2b, although a regression analysis indicated that renal clearance accounted for a smaller proportion of the total clearance of pegylated interferon alfa-2b than for nonpegylated interferon.³⁶ Therefore, alternative routes of clearance for pegylated interferons in ESRD patients may potentially have a larger impact on the efficacy of these drugs in this population. Although a decline in renal function appears to bestow higher efficacy for standard interferons, such a benefit may not be present with the use of pegylated forms. Studies comparing the efficacy of standard interferon and pegylated interferon in the ESRD population are also warranted.

Hemodialysis patients with HCV who have been treated with standard interferon have been shown to have higher dropout rates (17%) when compared historically to patients with normal renal function (5-9%).^{28,33} In our study, only 1 patient terminated treatment prematurely due to intractable emesis that required hospitalization. Fatigue, psychiatric symptoms, and anemia were the most common side effects, but none of these alone led to treatment discontinuation. In this anemia-prone patient population, anemia was exacerbated even in the absence of ribavirin use, consistent with the suppressive effect of interferon on bone marrow erythropoiesis. It appears that pegylated interferon may be better tolerated than standard interferon, but whether this improved tolerability is truly accompanied by a compromised efficacy remains to be established.

Our study suggests that pegylated interferon monotherapy in ESRD patients does not lead to achievement of SVR. Furthermore, worsening of anemia, which is usually prevalent at baseline in dialysis patients, is a common adverse event even in the absence of ribavirin use. Our patients were mostly African American and were infected with genotype 1, two known deterrents to response to interferon therapy. Yet, these characteristics are commonly found in the ESRD population in the United States, particularly in those who are managed by institutions located

in inner cities, such as ours. The small sample size and retrospective nature of this study pose limitations that are acknowledged by the authors. Larger studies are needed to evaluate the efficacy (or lack thereof) of pegylated interferon as compared to standard interferon, and future studies are needed to explore better therapeutic options in this patient population.

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