INTERNAL MEDICINE

□ CASE REPORT □

Treatment of a Serotype-1 Hepatitis C Virus Infection Using Interferon-Beta in a Patient with a High RNA Titer Who Had Been Receiving Long-Term Hemodialysis Therapy

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Abstract

A serotype-1 hepatitis C virus (HCV) infection in a 67-year-old hemodialysis patient was treated using interferon (IFN)-beta. Although the patient had a high RNA titer (5.1 log IU/mL) and had been receiving long-term hemodialysis therapy (30 years), the initial 4-week IFN-beta administration enabled a rapid virological response without any major adverse effects. However, the final outcome after 24 weeks of IFN beta treatment was classified as unchanged based on the criteria of the Conference on Intractable Hepatitis. Here, we describe our experience treating HCV infection using IFN-beta and discuss the indications for such therapy.

Key words: depression, hemodialysis, hepatitis C virus, interferon beta

(Intern Med 50: 733-737, 2011)
(DOI: 10.2169/internalmedicine.50.4453)

Introduction

Hepatitis C virus (HCV) infection may affect kidney function by causing hepatorenal syndrome, hepatic glomerulosclerosis, HCV-associated glomerulonephritis or diabetic nephropathy. On the other hand, patients with end-stage kidney disease are thought to be susceptible to HCV infection because of a decline in immune competence. Thus, HCV infection can be both a cause and a complication of chronic kidney disease, and the prevalence rate of HCV infection is relatively high among patients who have just begun to receive hemodialysis (1). Moreover, a high prevalence of chronic hepatitis C in extremely long-term (more than 30 years) hemodialysis patients (25.0%) has been reported (2). HCV infection affects the survival of patients with chronic kidney disease stage 5D (3, 4), but the clinical course of hepatitis C in hemodialysis patients is usually silent and asymptomatic, with normal or only slightly elevated serum aminotransferase levels (3, 5). The ALT values are lower in hemodialysis patients than in healthy individuals (6). Thus, the normal reference levels for liver enzymes in hemodialysis patients may need to be lowered to enable a better correlation with hepatic disease (6, 7). Consequently, many hemodialysis patients have not had the opportunity to receive anti-HCV therapy, even though HCV infection increases mortality among hemodialysis patients, with reported relative risks of 1.25 to 1.57 (8, 9).

Recently, safe and effective treatment of hemodialysis patients with hepatitis C using interferon (IFN)-beta has been reported (10, 11). However, IFN-beta therapy for hemodialysis patients with a high RNA titer of serotype 1 HCV has not been previously reported. Based on these reports, an extremely long-term hemodialysis patient with a high titer of serotype 1 HCV was treated using IFN-beta.

Case Report

A 67-year-old man with chronic glomerulonephritis had begun receiving hemodialysis therapy at the age of 37 years. He had undergone a hyperparathyroidectomy at the age of 47 years because of secondary hyperparathyroidism and a

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Received for publication August 30, 2010; Accepted for publication December 17, 2010

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Table 1. Clinical Data.

Demographics	
Age	67 years
Duration of hemodialysis	30 years
Estimated infection period	30 years
Blood chemistry	
Total protein	6.9 mg/dL
Albumin	3.9 mg/dL
Total bilirubin	1.43 mg/dL
Asparate aminotransferase	13 U/L
Alanine aminofransferase	16 U/L
Alkaline phosphatase	216 U/L
Thymol turbidity test	1.0 U
Zinc sulfate turbidity test	6.5 U
Lactate dehydrogenase	151 U/L
Cholinesterase	187 U/L
Urea nitrogen	71.3 mg/dL
Creatinine	13.19 mg/dL
Sodium	137 mEq/L
Potassium	4.2 mEq/L
Chlorine	95 mEq/L
Calcium	9.8 mg/dL
Phosphorus	5.3 mg/dL
C-reactive protein	0.18 mg/dL

Complete blood count		
White blood cell count	5200	/μL
Red blood cell count	3.92×10^6	/μL
Hemoglobin	11.9	g/dL
Hematocrit	36.5	%
Platelet count	11.6×10^4	/μL

Coagulation system	
PT INR	1.02
APTT INR	1.13

Others	
HCV serotype	1
HCV-RNA	5.1 Log IU/mL
Alpha-fetoprotein	2.0> ng/mL
PIVKA-Ⅱ	15 mAU/mL

PT: prothrombin time, APTT: activated partial thromboplastin time, INR: international normalized ratio, PIVKA: protein induced by vitamin K absence or antagonist, HCV: hepatitis C virus, RNA: ribonucleic acid

kidney resection because of renal cell carcinoma at the age of 50 years. An operation for carpal tunnel syndrome was performed at the age of 54 years, and a bipolar hemiarthroplasty was performed for amyloid-filled bone cysts in the femoral neck area at the age of 62 years. He had a drug allergy for loxoprofen sodium hydrate. He had received a blood transfusion because of renal anemia at the age of 37 years. After a national movement for the treatment of hepatitis C was initiated in Japan, the patient requested IFN therapy. Informed consent was obtained from the patient, and the treatment was approved by a board-certified hepatologist of the Japan Society of Hepatology and a board-certified senior member of the Japanese Society for Dialysis Therapy.

His clinical data are shown in Table 1. The serotype of the virus was 1, and the HCV-ribonucleic acid (RNA) level was 5.1 Log IU/mL. His platelet level was 11.6×10^4/mL, and his serum alanine aminotransferase (ALT) level was 16 U/L. Splenomegaly was observed during an abdominal computed tomography (CT) examination, but no clear evidence of liver cirrhosis was present. He had no signs of esophageal varices or ascites.

His clinical course is shown in Fig. 1. IFN-beta (Feron; TORAY Industries, Tokyo, Japan) was infused at 3 million units for 30 minutes three times a week during hemodialysis therapy (Tuesday, Thursday and Saturday) for 2 weeks. The patient developed flu-like symptoms after administration, but these symptoms were controllable with acetaminophen. No other severe adverse effects were observed, and the dose of IFN-beta was increased to 6 million units. The patient tested negative for HCV-RNA 4 weeks after the initiation of the IFN-beta treatment. Thus, the patient was able to achieve a rapid virological response (RVR). The patient's serum ALT level immediately decreased from 16 U/L to 6 U/L. IFN-beta was administered for a total of 24 weeks. Regarding adverse events, flu-like symptoms that were controllable with acetaminophen occurred, but no other severe adverse effects were observed throughout the IFN-beta therapy. The patient tested negative for HCV-RNA at 2 months after the end of treatment but tested positive once again at 3 months after the end of IFN-beta therapy. The patient's serum ALT level remained at below 10 U/L.

Discussion

An HCV-infected patient with several disadvantageous factors including old age, a long duration of hemodialysis therapy, a long infection period, serotype 1, and a high HCV RNA titer was treated with INF-beta. An RVR without any major adverse effects was obtained, but the patient subsequently relapsed.

A high prevalence of chronic hepatitis C in extremely long-term (more than 30 years) hemodialysis patients (25.0%) has been reported (2). HCV screening has been performed for blood transfusions since 1989, and the use of recombinant human erythropoietin has been covered by the national health insurance program in Japan since 1990. These factors may be one reason for the high rate of HCV infection among patients receiving extremely long-term hemodialysis therapy. The present patient had also received a blood transfusion prior to the start of HCV screening.

Regarding the hepatitis activity in this patient, liver cirrhosis was not observed during an abdominal echo and CT examination. The serum AST level was within the normal range, but as the ALT values are lower in hemodialysis pa-

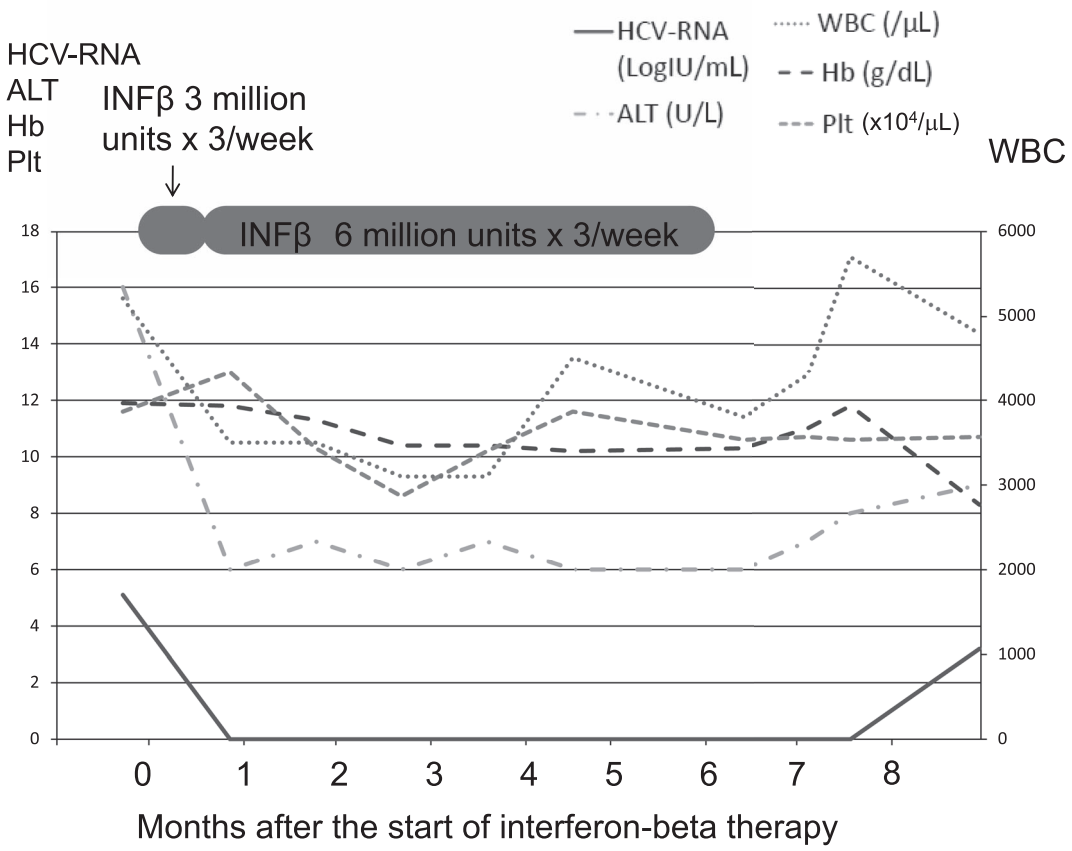

Figure 1. **Clinical course. HCV-RNA: hepatitis C virus - ribonucleic acid, ALT: alanine aminotransferase, WBC: white blood cell, Hb: hemoglobin, Plt: platelet**

tients than in healthy individuals, caution must be exercised when evaluating ALT levels in hemodialysis patients. As the patient's platelet level was rather low, we could not deny the presence of active hepatitis. A liver biopsy is the gold standard for estimating the activity of hepatitis, but this patient did not agree to undergo a biopsy. As this patient had serotype 1 and a relatively high virus titer, the infection might have been present for a long period; consequently, we did not recommend aggressive IFN therapy and instead followed the patient's liver function. However, after a national movement for the treatment of hepatitis C was initiated in Japan, the patient requested IFN therapy. A consensus conference of the Japanese Society for Dialysis Therapy (2010) recommended INF therapy for the treatment of HCV infection, if possible (12). INF therapy not only improves patient outcome but also eliminates the source of nosocomial infection (12). Predictors of the successful treatment of IFN include a low titer of HCV RNA, a genotype of 2a and 2b, a low grade of liver fibrosis, an age of 45 years or younger, and an infection period of 5 years or less (12). However, the present patient had virtually none of these factors. INF therapy is an expensive therapy, and this patient had several factors that were disadvantageous for treatment. Consequently, we once again did not recommend IFN treatment. Nevertheless, the patient continued to request the therapy. Thus, we decided to treat the patient with IFN. As ribavirin is generally not suitable for use in hemodialysis patients, we only used IFN, even though the patient had serotype 1 virus.

IFN-beta-related adverse effects, especially mental disorders, are mild and uncommon, compared with those for IFN-alpha (13-17). IFN-beta can be given to elderly patients because of its mild adverse effects (18). On the other hand, a high prevalence of depressive symptoms has been reported among hemodialysis patients (19, 20). Hemodialysis patients also have a high risk of adverse effects from IFN therapy for hepatitis C. Consequently, relatively safe IFN-beta therapy may be attempted in hemodialysis patients with hepatitis C. The mechanism responsible for the better tolerability of IFN-beta is unclear. However, the following mechanism might be possible: 1) IFN-beta is not a recombinant IFN, but is produced from human white blood cells. Thus, IFN-beta may have a tendency not to produce some immune complexes leading to IFN-related side effects. 2) The intracellular mechanisms of IFN-beta might differ from those of IFN-alpha, although the receptors for IFN-alpha and IFN-beta are the same (21). Recently, some case reports examining the serum level of IFN have confirmed the safety of using IFN-beta in hemodialysis patients without causing severe adverse effects (10, 11). The successful treatment of a hemodialysis patient with a high titer of type 2b hepatitis C using IFN-beta monotherapy has been reported (10). Araoka et al recommended infusion of 600 million units of IFN-beta for 30 minutes at the start of hemodialysis therapy (11). Based on the results of these reports, we treated the present

patient, who had a high titer of serotype 1 hepatitis C and had been receiving hemodialysis for an extremely long period, using IFN-beta. IFN-beta therapy can be performed by intravascular injection, which is more advantageous for hemodialysis patients than subcutaneous or intramuscular injections. As almost all regular hemodialysis patients undergo hemodialysis therapy 3 times a week, the advantage of peg-IFN, which is administered once a week, is not as important for hemodialysis patients as it is for other patients. Hemodialysis patients can also receive IFN-beta therapy without requiring hospitalization, as in the present case.

Festi et al reported that IFN-beta has sufficient tolerability (22). However, some researchers have reported that IFN monotherapy does not result in a satisfactory outcome in patients with genotype 1b and a high virus load in the general population (23, 24). Even though most rapid virological response (RVR) cases achieve a sustained virological response (SVR), relapse was observed in the present case. Based on the findings of the Conference on Intractable Hepatitis (Ministry of Welfare, Japan), which estimated the effect of therapy according to the glutamic pyruvic transaminase level, this case was classified as belonging to the unchanged group (25). At that time, Japanese health insurance allowed the use of interferon therapy for only 24 weeks. If we had continued the therapy for 48 weeks, a sustained virological response might have been achieved.

IFN therapy significantly lowered the incidence of hepatocellular carcinoma among patients with chronic hepatitis C who exhibited transient effects of IFN therapy. The 3-year cumulative incidences of HCC among transient responders and non-responders were calculated to be 2.4% and 5.6%, respectively; the 5-year incidences were 3.7% and 10.0%, respectively; and the 7-year incidences were 3.7%, and 22.4%, respectively (26). We hoped that some preventative effect against HCC might have been achieved in the present case. Virus removal and eradication by DFPP (VRAD) has been allowed by Japanese health insurance since 2008 and has been reported to be effective among patients with normal kidney function (27). Since ribavirin is not generally suitable for use in hemodialysis patients, VARD therapy might be one of the next therapeutic options for this patient.

Conclusion

In the present case, the patient had been receiving hemodialysis therapy for a markedly prolonged period (30 years), was of somewhat advanced age, and had a long infection period, serotype 1, hepatitis C and a high HCV RNA titer. IFN-beta therapy can be performed using an intravascular injection, which is advantageous for hemodialysis patients, and adverse effects are uncommon. Treatment with IFN-beta enabled an RVR without any severe adverse effects and without requiring hospital admission, but the patient subsequently relapsed.

The authors state that they have no Conflict of Interest (COI).

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