Efficacy and tolerability of low-dose interferon-α in hemodialysis patients with chronic hepatitis C virus infection

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Abstract

AIM: To evaluate the efficacy and tolerability of low-dose standard or pegylated interferon (PEG-IFN) in hepatitis C virus (HCV)-positive hemodialysis patients.

METHODS: In total, 19 patients were enrolled in this study, of which 12 received PEG-IFNα-2a 67.5 μg 1 time/wk (Group 1) and 7 received standard interferon α-2b subcutaneously 1.5 × 10^6 U 3 times/wk (Group 2). The treatment durations were 48 wk for patients infected with HCV genotype 1 and 24 wk for patients infected with HCV genotype 2/3. All patients were prospectively followed after the completion of therapy. The efficacy and tolerability of the treatment were evaluated based on the sustained virological response (SVR) and treatment-related drop-out rate.

RESULTS: In Group 1, 11 of the 12 patients completed the treatment. Early virological response (EVR) and sustained virological response (SVR) rates were 83.3% and 91.7%, respectively. One patient withdrew from treatment due to an adverse event (leukopenia). The drop-out rate was 8.3% in this group. In Group 2, 5 of the 7 patients completed the treatment with an EVR and SVR of 85.7% and 71.4%, respectively. Two patients withdrew due to treatment-related adverse events (nausea and depression). In this group, the drop-out rate was 28.6%. In total, 16 of the patients attained EVR, and 15 of them completed the treatment. The SVR rate for the patients who attained EVR was 93.7%. Anemia was the most frequent side effect and was observed in 10/19 patients (55.5%), but could be effectively managed with erythropoietin.

CONCLUSION: Low-dose interferon monotherapy, either with PEG-IFNα-2a or standard interferon α-2b, is an effective treatment option for hemodialysis patients with chronic hepatitis C.

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Key words: Chronic hepatitis C; End-stage renal disease; Hemodialysis; Hepatitis C virus; Peginterferon

Core tip: The most appropriate treatment for hepatitis C virus (HCV)-positive hemodialysis patients is unknown, and the available treatments have only been assessed in a limited manner. Therefore, this study evaluated the efficacy and tolerability of treatment with low-dose standard or pegylated interferon (PEG-IFN) in HCV-positive hemodialysis patients. The results of the study indicated that low-dose interferon monotherapy, either PEG-IFNα-2a or standard interferon α-2b, is an effective treatment option for HCV-positive hemodialysis patients. Anemia was the most frequently encountered adverse event, but this could be managed with erythropoietin. These results provide important information for clinicians faced with these treatment decisions.
INTRODUCTION

End-stage renal disease (ESRD) is a significant problem worldwide. In China, more than 65000 ESRD patients have received maintenance hemodialysis (HD)[1]. These patients have a higher rate of chronic hepatitis C virus (HCV) infection compared with the overall population[2], with an estimated prevalence and incidence of 3%-80% and 0.33%-2.59%, respectively[3-5]. Moreover, chronic HCV infection might ultimately lead to severe liver lesions, cirrhosis, and hepatocellular cancer, further increasing the morbidity and mortality of ESRD patients[6,7].

Interferon combined with oral ribavirin is the standard treatment for chronic HCV[8]. However, the use of ribavirin is currently contraindicated in dialysis patients[9,10], as the drug is not removed during conventional dialysis and its accumulation causes dose-dependent hemolytic anemia[11,12]. Interferon monotherapy is therefore recommended for the treatment of dialysis patients with chronic hepatitis C[13]. However, experience with monotherapy in ESRD patients is still limited.

The available data suggest that the rate of adverse events and drop-outs in this patient population is high[14-16]. We hypothesized that a lower dose of interferon monotherapy may decrease the incidence of adverse events and drop-outs, thus improving the likelihood of completing treatment. Therefore, the objective of this study was to evaluate the relative efficacy and tolerability of treatments consisting of either 1.5 × 10^6 U 3 times/wk of standard interferon or 67.5 µg/wk of pegylated interferon (PEG-IFN) α-2a (40 kDa). The treatments lasted for 48 wk in ESRD patients infected with HCV genotype 1 and for 24 wk in ESRD patients infected with HCV genotype 2/3.

MATERIALS AND METHODS

Patients

A total of 19 patients (11 male and 8 female) with a mean age of 37.7 years (range: 27-58 years) were enrolled in this study. The subjects had been undergoing dialysis for an average of 7.3 ± 4.5 (range: 2-16) years. All patients were on a maintenance HD program for ESRD, with 4-h dialysis sessions, 3 times/wk, using high-flux synthetic membranes, and bicarbonate dialysate. All patients were positive for HCV antibodies and had demonstrated detectable HCV RNA by polymerase chain reaction for at least 3 mo. The patients’ HCV genotypes were confirmed before treatment. All the treated patients met the criteria for treatment with PEG-IFNα-2a or standard interferon α-2b.

Treatment and follow-up

All patients were recommended to receive intramuscular injections of 67.5 µg PEG-IFNα-2a once/wk after their HD session. For economic reasons, only 12 patients (8 male and 4 female; mean age: 39.4 ± 9.4 years) received this treatment (Group 1). The other 7 patients (3 male and 4 female; mean age: 34.7 ± 6.5 years) received subcutaneous injections of standard interferon α-2b, 1.5 × 10^6 U 3 times/wk, which was also administered after each HD session (Group 2). The treatment durations were 48 wk for patients infected with HCV genotype 1 and 24 wks for patients infected with HCV genotypes 2/3/6.

All treated patients were prospectively followed until week 96, which corresponded to 48 wk after the completion of the treatment, to assess the long-term efficacy and tolerability of the lower-dose interferon monotherapy. Blood samples were collected weekly to determine blood cell counts, and monthly to determine liver function. The presence of HCV RNA was assessed prior to treatment and then every 3 mo after treatment. Early virological response (EVR), defined as a ≥ 2 log-fold decrease in HCV RNA from baseline, was evaluated after 12 wk of treatment. The efficacy of the treatment was determined by the achieved end treatment virological response (ETR), defined as the absence of detectable serum levels of HCV RNA at week 48, and sustained virological response (SVR), defined as the absence of detectable serum levels of HCV RNA at week 72. Tolerability was evaluated by assessing the drop-out rates and serious adverse events.

Statistical analysis

The data were analyzed using SPSS software (Windows version 15.0; SPSS, Chicago, IL, United States) and are presented as the means ± SD for parameter variables.

RESULTS

The baseline values of the patients are shown in Table 1, and the outcomes are presented in Table 2.

Efficacy

In Group 1, 11 of the 12 patients completed the treatment, with 1 patient withdrawing from treatment due to an adverse event. In this group, EVR was observed in 10 patients at week 12, and ETR was achieved in 11 patients. The 11 patients who attained ETR also achieved a SVR.

In Group 2, ETR was observed in 6 patients. In total, 5 patients completed the treatment, and ETR and SVR were recorded in all of these patients. In Group 2, 2 patients withdrew from treatment.

The HCV genotype was type 1 in 16 patients, with 13 patients achieving a SVR, yielding a genotype 1 SVR of 81.3%. The 3 patients with HCV genotype 2 all attained a SVR. In total, 16 of the patients attained ETR, and 15 of them completed the treatment. The SVR rate for the patients who attained EVR was 93.7%.
All patients were followed post-treatment, and those who achieved a SVR had undetectable HCV RNA levels at week 96. Notably, 2 patients continued to have undetectable levels of HCV RNA at 144 wk, which was the last follow-up prior to the writing of this manuscript.

Tolerability
In Group 1, 1 patient withdrew from treatment due to significant leukopenia (8.2% drop-out rate). Two patients discontinued the standard interferon α-2b treatment (Group 2) due to treatment-related adverse events; one patient developed nausea (which required treatment cessation after 4 wk of therapy) and the other patient withdrew from treatment at week 20 because of depression (28.6% drop-out rate).

Anemia was one of the treatment-related adverse events observed in both groups. This adverse event was observed in 3 of the 7 (42.8%) patients in the standard interferon group and in 7 of the 12 (58.3%) patients treated with PEG-IFN. In these patients, the erythropoietin dose had to be increased to improve hemoglobin levels. However, the treatment protocol did not have to be discontinued in any patients due to anemia.

Other adverse events included influenza-like symptoms, nausea, poor appetite, leukopenia, and thrombocytopenia, as has been reported in other studies.

Table 1  Patient baseline characteristics

| Case | Sex | Age (yr) | Weight (kg) | HD duration (yr) | Cirrhosis | Genotype | HCV RNA (IU/mL) |
|------|-----|----------|-------------|------------------|-----------|----------|----------------|
| 1    | M   | 52       | 62          | 5                | N         | 1b       | 4805000        |
| 2    | F   | 28       | 40          | 10               | N         | 1b       | 3150000        |
| 3    | M   | 28       | 69          | 14               | N         | 1b       | 15840          |
| 4    | M   | 38       | 52          | 6                | N         | 1b       | 3600000        |
| 5    | F   | 38       | 54          | 16               | N         | 1b       | 3786000        |
| 6    | F   | 36       | 47          | 2                | N         | 1b       | 167000         |
| 7    | F   | 47       | 48          | 14               | N         | 1b       | 663000         |
| 8    | M   | 40       | 59          | 9                | N         | 1b       | 356000         |
| 9    | M   | 39       | 63          | 13               | N         | 1b       | 156000         |
| 10   | M   | 41       | 67          | 2                | N         | 2a       | 15580          |
| 11   | F   | 58       | 50          | 6                | N         | 2a       | 9590           |
| 12   | M   | 28       | 55          | 2                | N         | 1b       | 209200         |
| 13   | M   | 41       | 63          | 3                | N         | 1b       | 39460          |
| 14   | M   | 33       | 59          | 6                | N         | 1b       | 143000         |
| 15   | F   | 32       | 52          | 7                | N         | 2a       | 446400         |
| 16   | M   | 36       | 67          | 6                | N         | 1b       | 456000         |
| 17   | F   | 27       | 51          | 4                | N         | 1b       | 14500          |
| 18   | F   | 29       | 49          | 4                | N         | 1b       | 12200          |
| 19   | M   | 45       | 62          | 11               | Y         | 1b       | 266000         |

HCV: Hepatitis C virus; HD: Hemodialysis; F: Female; M: Male.

Table 2  Patient treatment results

| Case | IFN-α type | HCV RNA (IU/mL) |
|------|------------|-----------------|
|      | 12 wk      | 48 wk           | 72 wk | 96 wk | 144 wk |
| 1    | PegIFNα-2a | 405100          | Positive | Positive | Positive | Positive |
| 2    | PegIFNα-2a | Negative        | Negative | Negative | Negative | Negative |
| 3    | PegIFNα-2a | Negative        | Negative | Negative | Negative | Negative |
| 4    | PegIFNα-2a | Negative        | Negative | Negative | Negative | Negative |
| 5    | PegIFNα-2a | Negative        | Negative | Negative | Negative | Negative |
| 6    | PegIFNα-2a | Negative        | Negative | Negative | Negative | Negative |
| 7    | PegIFNα-2a | 2380            | Negative | Negative | Negative | Negative |
| 8    | PegIFNα-2a | Negative        | Negative | Negative | Negative | Negative |
| 9    | PegIFNα-2a | Negative        | Negative | Negative | Negative | Negative |
| 10   | PegIFNα-2a | Negative        | Negative | Negative | Negative | Negative |
| 11   | PegIFNα-2a | Negative        | Negative | Negative | Negative | Negative |
| 12   | PegIFNα-2a | Negative        | Negative | Negative | Negative | Negative |
| 13   | IFNα-2b    | Negative        | Negative | Negative | Negative | Negative |
| 14   | IFNα-2b    | Negative        | Negative | Negative | Negative | Negative |
| 15   | IFNα-2b    | Negative        | Negative | Negative | Negative | Negative |
| 16   | IFNα-2b    | 268000          | Positive | Positive | Positive | Positive |
| 17   | IFNα-2b    | Negative        | Negative | Negative | Negative | Negative |
| 18   | IFNα-2b    | Negative        | Negative | Negative | Negative | Negative |
| 19   | IFNα-2b    | Negative        | Positive | Positive | Positive | Positive |

IFN: Interferon; PEG-IFN: Pegylated interferon; HCV: Hepatitis C virus.
**DISCUSSION**

Interferon monotherapy trials involving small numbers of dialysis patients infected with chronic hepatitis C have previously been reported. In addition, 3 meta-analysis studies have shown that the SVR of ESRD patients infected with chronic hepatitis C and treated with standard IFN monotherapy was approximately 31%-41%[17-19]. However, the corresponding treatment-related withdrawal rate ranged from 20% to 30%[16,17,23]. Similarly, studies have also shown that the SVR and treatment-related withdrawal rates in patients receiving PEG-IFN were 31%-37% and 23%-28%, respectively[j7-20]. Based on these studies, treatment of patients with either standard interferon or PEG-IFN had similar efficacy and tolerability.

In our study, 7 hemodialysis patients were treated with standard interferon α-2b for 48 wk. Six patients (85.7%) achieved EVR by week 12. In total, 2 patients discontinued treatment because of adverse events (1 due to nausea at week 4 and 1 due to depression at week 20), with both having a high viral load at baseline. At the end of week 72, the SVR rate was 71.4% (5/7 patients), with a drop-out rate of 28.6%. The drop-out rate was similar to that previously described in the meta-analyses. The 11 patients treated with PEG-IFNα-2a completed the treatment, and the EVR and SVR were 83.3% and 91.7%, respectively. For the patients who achieved a SVR, this subsequently remained stable.

Contrary to the concept that HCV genotype 1 is associated with a poor SVR rate in response to interferon monotherapy in HCV patients with normal renal function[22,23], our results showed a good SVR rate in HD patients. Although the 3 patients who dropped out all had genotype 1, the SVR rate for the remaining 16 patients with genotype 1 HCV was 61.3%, higher than that reported for HCV patients with normal renal function. Notably, all of the patients who dropped out had a very high HCV RNA load, which is considered as a negative predictor of a SVR[24,25].

In our study, 16 patients achieved an EVR, and 15 of them achieved a SVR. Therefore, patients with an EVR might be encouraged to continue therapy, as EVR appears to be a good predictor of a SVR. In this respect, our study is in agreement with the current literature.

The overall SVR for the 19 patients in this study was 84.2%, higher than that for interferon therapy in HD patients with normal renal function. This study showed that low-dose interferon monotherapy, either with pegylated interferon α-2a or standard interferon α-2b, is an effective treatment for hemodialysis patients with chronic hepatitis C.

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