**Name of journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO: 12828**

**Columns: CASE REPORT**

**Retreatment with peginterferon and ribavirin in chronic hepatitis C**

Jo YM *et al.* Retreatment with peginterferon and ribavirin

Yong Min Jo, Sung Wook Lee, Sang Young Han, Yang Hyun Baek, Soo Young Kim, Woo Jae Kim, Ji Hye Ahn, Ji Young Lee

**Yong Min Jo, Sung Wook Lee, Sang Young Han, Yang Hyun Baek, Soo Young Kim, Woo Jae Kim, Ji Hye Ahn, Ji Young Lee,** Department of Internal Medicine, Dong-A University School of Medicine, Busan 602-715, South Korea

**Author contributions:** Jo YM and Lee SW performed the majority of clinical practice and experiments; Han SY and Baek YH provided the collection of all the patient medical records; Kim SY and Kim WJ involved in editing the manuscript; Jo YM, Ahn JH and Lee JY designed the study and wrote the manuscript.

**Correspondence to**: **Sung Wook Lee, MD, PhD,** Department of Internal Medicine, Dong-A University School of Medicine, 3 Ga 1, Dongdaesin-dong, Seo-gu, Busan 602-715, South Korea. sunglee@dau.ac.kr

**Telephone:** +82-51-2405627 **Fax**: +82-51-2402087

**Received:** July 27, 2014  **Revised:** October 27, 2014

**Accepted:** November 7, 2014

**Published online:**

**Abstract**

The development of boceprevir and telaprevir was a major step forward in the treatment of chronic hepatitis C. In addition, the treatment of these infections has been recently revolutionized by the approval of sofosbuvir and simeprevir. However, there are several challenges associated with the application of novel drugs, such as new and more frequent adverse events, new drug interactions and excessively high treatment costs. An additional concern is viral resistance. These considerations highlight the fact that direct-acting antiviral agents are not a panacea and may not be the best option for all patients who are in need of therapy. This retrospective study revealed that the sustained virologic response was not significantly reduced following peginterferon and ribavirin retreatment compared with the new therapy. We suggest that patients who experience relapse shortly after completing treatment with peginterferon and ribavirin have a reasonable chance of achieving a sustained virologic response when retreated with these drugs alone.

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**Key words:** Chronic hepatitis C; Direct-acting antiviral agents; Peginterferon; Ribavirin; Retreatment

**Core tip:** Chronic hepatitis C-infected patients who experience relapse shortly after completing treatment with peginterferon and ribavirin have a reasonable chance of achieving a sustained virologic response when retreated with these drugs alone. Thus, it would be very reasonable to proceed with peginterferon and ribavirin retreatment alone, particularly in patients with factors associated with high rates of sustained virologic response, such as a low viral load at relapse (< 400000 IU/mL) and an early virologic response at week 12 of retreatment.

Jo YM, Lee SW, Han SY, Baek YH, Kim SY, Kim WJ, Ahn JH, Lee JY. Retreatment with peginterferon and ribavirin in chronic hepatitis c. *World J Gastroenterol* 2014; In press

**INTRODUCTION**

Hepatitis C is an infection caused by a virus attacks the liver and leads to inflammation and chronic liver disease. The long-term consequences of hepatitis C virus (HCV) infection are minimal changes, chronic hepatitis, and cirrhosis, and hepatocellular carcinoma[1-3]. From 1995-2000, the overall prevalence of HCV infection among Koreans over 40 years of age was estimated to be 1.29%[4]. Approximately 25% of chronically infected patients ultimately progress cirrhosis and other complications[5-8].

The aim of HCV treatment is to achieve sustained eradication of virus and prevent progression to cirrhosis and related complications[9]. Sustained virologic response (SVR) is the term that means successfully treatment of HCV, which is the aviremia 24 wk after completion of antiviral therapy[10,11].

The initial treatment for chronic hepatitis C is carried out using a combination of conventional interferon-alpha and ribavirin over a period of 24-48 wk according to the patient’s genotype. Interferon-alpha has progressively been replaced by peginterferon, which has emerged as the most effective regimen[12].

The recommended treatment for chronic hepatitis C infection consisted of combination therapy with peginterferon and ribavirin until May 2011, which is when the US Food and Drug Administration (FDA) licensed the first direct-acting antiviral agents that directly impede viral replication. In clinical trials of chronic hepatitis C patients receiving peginterferon and ribavirin combined with boceprevir or telaprevir, SVR has been accomplished in 63%-75% of treatment-naïve patients, in 69%-88% of peginterferon and ribavirin relapsers and in up to 33% of peginterferon and ribavirin nonresponders[13-16]. Recently, the FDA has approved sofosbuvir and simeprevir for the treatment of chronic hepatitis C as components of a combination treatment regimen.

Triple therapy is connected with increased adverse events, and it requires closer patient observation compared with previous treatment. Additionally, boceprevir and telaprevir may induce HCV-resistant mutations, and it is likely that cross-resistance to direct-acting antiviral agents will emerge in some patients who without SVR[17,18]. The clinical impacts of resistance to sofosbuvir and simeprevir have not been well established.

The aim of this retrospective study was to assess the efficacy of peginterferon and ribavirin therapy in patients with chronic hepatitis who have relapsed following an initial course of peginterferon-based therapy to facilitate the development of a novel treatment for HCV infection.

**CASE REPORT**

***CASE 1***

This was a 37-year-old man with a history of intravenous drug abuse. HCV infection was diagnosed in September 2008 on the basis of amplification of HCV RNA genotype 1b. The serum HCV RNA level was 585,026 IU/mL at baseline. It was suggested that his HCV infection was caused by intravenous drug abuse. Physical examination was unremarkable. The serum aspartate aminotransferase (AST) level was 56 IU/L. The serum alanine aminotransferase (ALT), the gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) were normal. The bilirubin, serum creatinine and prothrombin time (PT) were normal. Liver function was reported as Child-Turcotte-Pugh (CTP) class A. Liver ultrasonography indicated chronic liver disease with mild splenomegaly.

In January 2009, combination therapy with peginterferon alpha-2a and ribavirin was initiated with the informed consent of the patient. Peginterferon alpha-2a was administered subcutaneously at a weekly dose of 180 μg together with a 1200 mg/d ribavirin for 48 wk. Serum HCV RNA levels were determined at baseline and at week 12 by quantitative PCR. The patient accomplished a complete early virologic response (EVR). Additionally, he accomplished an end-of-treatment response (ETR) at week 48.

However, in March 2010, at 15 wk after the completion of treatment, the reappearance of serum HCV RNA was documented. The serum HCV RNA level was 13367 IU/mL. Immediately after virologic relapse was documented, combination therapy with peginterferon alpha-2b and ribavirin was initiated as retreatment. A weekly dose of 120 μg peginterferon alpha-2b was administered subcutaneously together with 1200 mg/d ribavirin for 12 wk. The patient did not achieve a rapid virologic response (RVR) at week 4 of retreatment, but he achieved a complete EVR at week 12. Additionally, undetectable serum HCV RNA was determined at week 24 by qualitative PCR. The patient attained an SVR at 24 wk following the discontinuation of retreatment.

***CASE 2***

This patient was a 58-year-old man with a chronic hepatitis C-infected spouse. HCV infection was diagnosed in February 2007 on the basis of amplification of HCV RNA genotype 1b. The serum HCV RNA level was 3420000 IU/mL at baseline, as determined by quantitative PCR. It was suggested that his hepatitis C virus infection had been transmitted by sexual intercourse. Physical examination was unremarkable. The serum ALT level was 54 IU/L, and the serum AST level was normal. The GGT level was 103 IU/L. The ALP level was normal. The serum creatinine, total bilirubin were normal. Liver function was reported as CTP class A. Liver ultrasonography indicated chronic liver disease with mild splenomegaly.

In February 2007, combination therapy with peginterferon alpha-2b and ribavirin was initiated with the informed consent of the patient. A weekly dose of 100 μg of peginterferon alpha-2b was administered subcutaneously together with 1200 mg/d of ribavirin for 29 wk. This patient tolerated the ribavirin well. Because of leukopenia, peginterferon alpha-2b was administered at a weekly dose of 80 μg for the remaining treatment period. Serum HCV RNA levels were determined at baseline and at weeks 4 and 12 by quantitative PCR. Because of his partial EVR, undetectable serum HCV RNA was confirmed at week 24. This patient achieved ETR at week 48 of therapy.

However, in May 2008, at 11 wk after the end of antiviral therapy, the reappearance of serum HCV RNA was documented. The serum HCV RNA level was 536 IU/mL, as determined by quantitative PCR assay. Immediate virologic relapse was documented, and combination therapy with peginterferon alpha-2b and ribavirin was initiated as retreatment. Peginterferon alpha-2b was administered at a weekly dose of 80 μg together with a 1200 mg/d ribavirin for 12 wk. The patient did not accomplish an RVR at week 4 of retreatment but did achieve a complete EVR at week 12. Additionally, undetectable serum HCV RNA was determined at week 24. This patient achieved an SVR at 24 wk following the discontinuation of retreatment.

***CASE 3***

The third patient was 60-year-old with a chronic hepatitis C-infected spouse. HCV infection was diagnosed in April 2007 on the basis of amplification of HCV RNA genotype 1b. The serum HCV RNA level was 7710000 IU/mL at baseline, as determined by quantitative PCR. It was suggested that his HCV infection was transmitted by sexual intercourse. Physical examination was unremarkable. The serum AST level was 78 IU/L. The ALT, GGT and ALP were normal. The PT, bilirubin and serum creatinine were normal. Liver function was reported as CTP class A. Liver ultrasonography indicated chronic liver disease with mild splenomegaly.

In April 2007, combination therapy with peginterferon alpha-2b and ribavirin was initiated with the informed consent of the patient. Peginterferon alpha-2b was administered at a weekly dose of 80 μg together with a daily dose of 1000 mg of ribavirin for 48 wk. Serum HCV RNA levels were determined at baseline and at weeks 4 and 12 by quantitative PCR. This patient did not achieve an RVR but did achieve a partial EVR. Because he did not attain a complete EVR, undetectable serum HCV RNA was determined at week 24 by qualitative PCR. This patient attained an ETR at week 48 of therapy.

However, in May 2008, at 12 wk after the completion of antiviral therapy, the reappearance of HCV RNA in his serum was determined by qualitative PCR and a serum ALT level of 45 IU/L. Virologic relapse was immediately documented, and peginterferon alpha-2b and ribavirin combination therapy was initiated as retreatment. Peginterferon alpha-2b was administered subcutaneously at a weekly dose of 80 μg together with 1000 mg/d ribavirin for 12 wk. The serum ALT levels were 16, 23, and 20 IU/L at weeks 4, 12, and 24 of retreatment. This patient did not accomplish an RVR at week 4 of retreatment but did accomplish a complete EVR at week 12. Additionally, undetectable serum HCV RNA was determined at week 24 by qualitative PCR. This patient attained an SVR at 24 wk following the discontinuation of retreatment.

***CASE 4***

The fourth patient was 40-year-old with a chronic hepatitis C-infected spouse. HCV infection was diagnosed in July 2006 on the basis of amplification of HCV genotype 2a/2c. The serum HCV RNA level was 113000 IU/mL at baseline. It was suggested that his HCV infection was transmitted by sexual intercourse. Physical examination was unremarkable. The serum AST was 56 IU/L. The ALT, GGT and ALP were normal. The PT, bilirubin and serum creatinine were normal. Liver function was reported as CTP class A. Liver ultrasonography indicated chronic liver disease with mild splenomegaly.

In October 2006, combination therapy with peginterferon alpha-2b and ribavirin was initiated with the informed consent of the patient. Peginterferon alpha-2b was administered at a weekly dose of 120 μg together with a 800 mg/d of ribavirin for 24 wk. Serum HCV RNA levels were determined at baseline, at weeks 4 and 12 by quantitative PCR. This patient did not achieve an RVR but did achieve a complete EVR. However, he lacked an ETR at week 24 of therapy. The serum HCV RNA level was 155 IU/mL, as determined by quantitative PCR.

Combination therapy with peginterferon alpha-2a and ribavirin was immediately initiated as retreatment. Peginterferon alpha-2a was subcutaneously administered at a weekly dose of 180 μg together with a 800 mg/d of ribavirin for 12 wk. The patient did not accomplish an RVR at week 4 of retreatment but did accomplish a complete EVR at week 12. Additionally, undetectable serum HCV RNA was determined at week 24 by qualitative PCR. He accomplished an SVR at 24 wk following interruption of retreatment.

The baseline characteristics and antiviral therapy regimens of these patients are presented in Table 1.

**DISCUSSION**

The first-line treatment for chronic hepatitis C was peginterferon-ribavirin treatment until May 2011, which is when the first direct-acting antiviral agents were licensed by the FDA for use with peginterferon and ribavirin in treatment-naïve and treatment-experienced HCV-infected patients with compensated liver cirrhosis. HCV-infected patients following the addition of the first direct-acting antiviral agents to combined peginterferon and ribavirin treatment are accomplished higher SVR rates compared with the use of peginterferon-ribavirin treatment. Recently, the FDA approved sofosbuvir and simeprevir for the treatment of chronic hepatitis C. The addition of direct-acting antiviral agents to combined peginterferon and ribavirin treatment represents a significant advancement in the HCV treatment[13-16].

Nonresponders to peginterferon-based therapy or those who relapse following this therapy are increasing in number, and these individuals have decompensated liver cirrhosis. Before the availability of direct-acting antiviral agents, limited retreatment options were available for these patients. Recently, retreatment with peginterferon and ribavirin plus a direct-acting antiviral agent has been shown to lead to a higher SVR rate compared with peginterferon-ribavirin treatment[15-18].

The development of direct-acting antiviral agents marks a major step towards the eventual aim of more potent and shorter courses of treatment, and other compounds are also being developed with different viral targets. This is the rapidly changing time in HCV treatment, in which major developments are being achieved, including new compounds that can cooperate with clinicians manage this hard-to-cure virus.

A new time of treatment for HCV is dawning with the development of direct-acting antiviral agents, but these new agents are not a magic bullet. Unfortunately, clinical trials have recognized that the use of this new agents in isolation leads to the prompt emergence of viral resistance and mutations[19,20].

The onset of the acquired immune deficiency syndrome pandemic led to that the antiviral drugs with diverse mechanisms were developed. However, human immunodeficiency virus (HIV) have not been conquered because of viral resistance. Many properties of HCV are similar to that of HIV. Thus, resistance can be the primary scourge of anti-HCV treatment.

Almost patients will experience treatment related adverse events, that cause poor tolerability which can result in early treatment interruption. The addition of direct-acting antiviral agents to peginterferon based treatment is connected by adverse events, requiring interruption of the direct-acting antiviral agents in 10%-12% of patients[21]. Adverse events that occur with increased frequency in subjects receiving direct-acting antiviral agents include anemia, leukopenia, taste disorder, gastrointestinal discomfort, fatigue, skin eruption, and perianal discomfort[13-16].

These considerations highlight the fact that direct-acting antiviral agents are not a cure-all and cannot be the best choice for all patients who need the treatment.

This retrospective study revealed that retreatment with peginterferon-ribavirin treatment may be of value in some patients in whom previous peginterferon and ribavirin combination therapy has failed.

 After the finish of initial antiviral treatment, patients are monitored to assess their treatment response and the occurrence of adverse events. Laboratory monitoring includes measurements of white blood cell count, aminotransferase, serum creatinine and HCV RNA at 4, 8, 12 and 24 wk after finish of treatment. Patients with virologic relapse are immediately retreated with peginterferon and ribavirin. This retrospective study indicated that the SVR was not significantly decreased in the patients retreated with peginterferon and ribavirin compared with the new therapy.

 Pre-retreatment predictors of response may be helpful for counselling patients of their probability of an SVR. SVR rates were higher in the treatment-naïve patients with a viral load of less than 400000 IU/mL[11]. Likewise, the results of this study clearly demonstrate that viral load at relapse is very important in predicting the outcome of retreatment. The changes in the HCV RNA levels in these patients are presented in Table 2.

The absence of an EVR is the most powerful means of identifying nonresponders in treatment-naïve patients[22,23]. All patients achieving a complete EVR also achieved an SVR in this study. The outcomes of this study clearly show that a complete EVR is very important in predicting the outcome of retreatment (Table 2).

Now, there is no common consents regarding the retreatment period for chronic hepatitis C-infected patients who have previously relapsed. Almost all patients treated with peginterferon-ribavirin treatment have experienced adverse events. Adverse events represent a major cause that patients give up treatment. Therefore, the optimal duration of retreatment should be based on virologic clearance to promote the adherence of patients to the regimen. In this study, after peginterferon plus ribavirin was administered for 12 wk, patients achieved a complete EVR at week 12 of retreatment and an SVR at 24 wk following discontinuation of retreatment.

The evolution of compounds that inhibit virus replication by inhibiting either HCV protease or polymerase will refine the treatment of hepatitis C. Many drugs are currently under development. New drugs promise to increase the SVR rates for chronic hepatitis C-infected patients and to possibly shorten the treatment duration. However, this enhanced response comes with an increased incidence of adverse events and high cost. An additional concern with regard to newer therapies is that of viral resistance. The emergence of resistant variants has not been observed with the current peginterferon and ribavirin therapy. In addition, adherence to the new therapeutic regimens cannot be omnipotent.

Retreatment with peginterferon and ribavirin plus a direct-acting antiviral agent in chronic hepatitis C-infected patients has led to higher SVR rates compared with those achieved with previous treatment in clinical trials. SVR was achieved in 69%-88% of relapsers and in 29%-33% of null responders[13-16]. This retrospective study determined that SVR was not significantly reduced by the peginterferon and ribavirin combination therapy compared with the new therapy.

Collectively, we suggest that patients who relapse shortly after completing treatment with peginterferon plus ribavirin have a reasonable chance of achieving an SVR when retreated with peginterferon and ribavirin alone. It would be very reasonable to proceed with this retreatment, particularly in those patients possessing factors connected by high rates of SVR, such as a low viral load at relapse (< 400000 IU/mL) and a complete EVR at week 12 of retreatment

New direct-acting antiviral agents cannot be the best retreatment option for motivated patients who have previously relapsed. When making the decision to treat using a new therapy, the clinician have to consider the benefits of the simpler, less-toxic regimen connected by lower SVR rate with the new therapy and its associated higher toxicity, complexity, increased risk of resistance development and potentially higher SVR rate.

A limitation of our study is that there were insufficient numbers of patients to strongly substantiate our findings. Second, information regarding liver histology and interleukin 28B gene polymorphism was not reported.

**COMMENTS**

***Case characteristics***

Case 1: He was a 37-year-old with a history of chronic hepatitis C virus infection caused by intravenous drug abuse.

Case 2: He was a 58-year-old with a chronic hepatitis C-infected spouse, and it was suggested that his hepatitis C virus infection had been transmitted by sexual intercourse.

***Clinical diagnosis***

Hepatitis C virus was diagnosed on the basis of amplification of HCV RNA.

***Differential diagnosis***

Viral hepatitis, drug-induced hepatitis, autoimmune hepatitis, steatohepatitis.

***Laboratory diagnosis***

Case 1:HCV RNA level of 585026 IU/mL.

Case 2: HCV RNA level of 3420000 IU/mL.

***Imaging diagnosis***

Case 1: Liver ultrasonography showed early liver cirrhosis with splenomegaly.

Case 2: Liver ultrasonography showed chronic liver disease with mild splenomegaly.

***Treatment***

Two patients were treated with peginterferon and ribavirin.

***Related reports***

There was no consensus on a retreatment method for patients with HCV who have previously relapsed.

***Term explanation***

Sustained virologic response is the absence of HCV RNA in the blood at 24 wk after the treatment completion.

***Experiences and lessons***

This findings suggest that patients who relapse shortly after completing treatment with peginterferon plus ribavirin have a reasonable chance of a SVR when retreated with previous treatment.

***Peer review***

This article discusses chronic hepatitis C retreatment methods in patients who have previously relapsed.

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**P-Reviewers:** Oshiumi H **S-Editor:** Yu J

**L-Editor: E-Editor:**

**Table1 Baseline characteristics of patients**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Characteristics | Case 1 | Case 2 | Case 3 | Case 4 |
| Gender | Male | Male | Male | Male |
| Age (yr) | 37 | 58 | 60 | 40 |
| Body weight (kg) | 80 | 69 | 63 | 84 |
| Height (m) | 1.75 | 1.69 | 1.65 | 1.84 |
| Body mass index (kg/㎡) | 26.1 | 24.2 | 23.1 | 24.8 |
| HCV genotype | 1b | 1b | 1b | 2a/2c |
| HCV infection route | Intravenous drug abuse | Sexual intercourse | Sexual intercourse | Sexual intercourse |
| Serum HCV RNA level at baseline (IU/mL) | 585026 | 3420000 | 7710000 | 113000 |
| Antiviral therapy regimen | Peginterferon α-2a and ribavirin for 48 wk↓Peginterferon α-2b and ribavirin for 12 wk | Peginterferon α-2b and ribavirin for 48 wk↓Peginterferon α-2b and ribavirin for 12 wk | Peginterferon α-2b and ribavirin for 48 wk↓Peginterferon α-2b and ribavirin for 12 wk | Peginterferon α-2b and ribavirin for 48 wk↓Peginterferon α-2a and ribavirin for 12 wk |

HCV: Hepatitis C virus.

**Table2 Changes in hepatitis C virus RNA level (IU/mL)**

|  |  |  |
| --- | --- | --- |
|  | Previous treatment | Retreatment |
| Weeks of Treatment | 0 | 12 | 24 | 48 | 0 | 12 | 36 |
| Case 1 | 585026 | < 50 | negative | negative | 13367 | < 50 (complete EVR) | Negative (SVR) |
| Case 2 | 3420000 | 63 | negative | negative | 536 | < 50 (complete EVR) | Negative (SVR) |
| Case 3 | 7710000 | 226 | negative | negative | Positive1 | < 50 (complete EVR) | Negative (SVR) |
| Case 4 | 113000 | < 50 | positive | ∙ | 155 | < 50 (complete EVR) | Negative (SVR) |

1Positive of hepatitis C virus RNA was determined by qualitative PCR. EVR: Early virologic response; SVR: Sustained virologic response.