Retreatment with peginterferon and ribavirin in chronic hepatitis C

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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.

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

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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.

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INTRODUCTION

Hepatitis C is an infection caused by a viral attack on 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, cirrhosis, and hepatocellular carcinoma. From 1995-2000, the overall prevalence of HCV infection among Koreans over 40 years of age was estimated to be 1.29%. Approximately 25% of chronically infected patients ultimately progress to cirrhosis and other complications.

The aim of HCV treatment is to achieve sustained eradication of the virus and prevent progression to cirrhosis and related complications. Sustained virologic response (SVR) is the term used for successful treatment of HCV, and refers to the viremia 24 wk after completion of antiviral therapy.

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.

The recommended treatment for chronic hepatitis C infection consisted of combination therapy with peginterferon and ribavirin until May 2011, when the US Food and Drug Administration (FDA) licensed the first direct-acting antiviral agents that directly impeded 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-naive patients, in 69%-88% of peginterferon and ribavirin relapers, and in up to 33% of peginterferon and ribavirin non-responders. 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 thus requires closer patient observation compared with the 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 are without SVR. 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

The patient in this case was a 37-year-old male with a history of intravenous drug abuse. HCV infection was diagnosed in September 2008 on the basis of amplification of HCV RNA genotype 1b. Serum HCV RNA level was 585026 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. Serum alanine aminotransferase (ALT), 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 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 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 did achieve complete EVR at week 12. Additionally, undetectable serum HCV RNA was determined at week 24 by qualitative PCR. The patient attained SVR at 24 wk following the discontinuation of retreatment.

Case 2

The patient in this case was a 58-year-old male 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 HCV 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 and 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. The 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 RVR at week 4 of retreatment, but did achieve complete EVR at week 12. Additionally, undetectable serum HCV RNA was determined at week 24. The patient achieved SVR at 24 wk following the discontinuation of retreatment.

**Case 3**

The third patient was a 60-year-old male 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. The patient did not achieve RVR, but did achieve a partial EVR. Because he did not attain complete EVR, undetectable serum HCV RNA was determined at week 24 by qualitative PCR. The patient attained SVR at 24 wk following interruption of retreatment.

**DISCUSSION**

The first-line treatment for chronic hepatitis C was peginterferon-ribavirin treatment until May 2011, 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 accomplished
higher SVR rates compared with 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 HCV treatment\(^{[13-16]}\).

Non-responders to peginterferon-based therapy or those who relapse following this therapy are increasing in number, with such individuals displaying 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 a rapidly-changing era in HCV treatment, with such major developments being achieved as new compounds that can cooperate with clinicians to manage this hard-to-cure virus.

A new era 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 these 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 antiviral drugs with diverse mechanisms being developed. However, human immunodeficiency virus (HIV) remains un conquered due to its viral resistance. Many properties of HCV are similar to that of HIV. Thus, resistance can be the primary scourge of anti-HCV treatment.

Almost all patients will experience treatment-related adverse events that lead to poor tolerability, which can in turn result in early treatment interruption. The addition of direct-acting antiviral agents to peginterferon-based treatment is connected by adverse events, and thus requires the interruption of 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 may not be the best choice for all patients who need 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 completion 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 end 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 patients retreated with peginterferon and ribavirin compared with the new therapy.

Pre-retreatment predictors of response may be helpful for informing patients of their probability of SVR. SVR rates were higher in treatment-naïve patients with a viral load of less than 400000 IU/mL\(^{[21]}\). 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 EVR is the most powerful means
of identifying non-responders in treatment-naïve patients. All patients achieving complete EVR also achieved SVR in this study. The outcomes of this study clearly show that complete EVR is very important in predicting the outcome of retreatment (Table 2).

There is no common consent 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 for patients giving up on the 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 complete EVR at week 12 of retreatment and 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 such drugs are currently under development. New drugs promise to increase the SVR rates for chronic hepatitis C-infected patients and possibly shorten treatment duration. However, this enhanced response comes with an increased incidence of adverse events and a higher 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 relapers and in 29%-33% of null responders. 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 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 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 must 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. Secondly, information regarding liver histology and interleukin 28B gene polymorphism was not reported.

### Table 2  Changes in hepatitis C virus RNA level (IU/mL)

| Weeks of treatment | Previous treatment | Retreatment |
|--------------------|--------------------|-------------|
| 0                  |                    |             |
| 12                 |                    |             |
| 24                 |                    |             |
| 48                 |                    |             |
| 0                  |                    |             |
| 12                 |                    |             |
| 36                 |                    |             |

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

**Case characteristics**

Case 1: A 37-year-old male with a history of chronic hepatitis C virus (HCV) infection caused by intravenous drug abuse. Case 2: A 58-year-old male with a chronic hepatitis C-infected spouse; it was suggested that his HCV infection had been transmitted by sexual intercourse.

**Clinical diagnosis**

HCV was diagnosed on the basis of amplification of HCV RNA.

**Differential diagnosis**

Viral hepatitis, drug-induced hepatitis, autoimmune hepatitis, and 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**

The two patients were treated with peginterferon and ribavirin.

**Related reports**

There is 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 treatment completion.

**Experiences and lessons**

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

1. Lavanchy D. Global burden of hepatitis C. Liver Int 2009; 29 Suppl: 1-74 [PMID: 19207969 DOI: 10.1111/j.1478-3231.2008.0 1934.x]

2. Williams R. Global challenges in liver disease. Hepatology 2006; 44: 521-526 [PMID: 16941687 DOI: 10.1002/hep.21347]

3. European Association for Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2014; 60: 392-420 [PMID: 24331294 DOI: 10.1016/j.jhep.2013.11.003]

4. Shin HR. Epidemiology of hepatitis C virus in Korea. Interirovirology 2006; 49: 18-22 [PMID: 16166784 DOI: 10.1159/000087258]

5. Seeff LB. Natural history of chronic hepatitis C. Hepatology 2002; 36: S35-S46 [PMID: 12407575 DOI: 10.1002/hep.160360706]

6. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol 2013; 10: 553-562 [PMID: 23817321 DOI: 10.1038/nrgastro.2013.107]

7. Holmes J, Thompson A, Bell S. Hepatitis C -- an update. Aust Fam Physician 2013; 42: 452-456 [PMID: 23826595]

8. Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. Best Pract Res Clin Gastroenterol 2012; 26: 401-412 [PMID: 23199500 DOI: 10.1016/j.bpg.2012.09.009]

9. Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut 2006; 55: 1350-1359 [PMID: 16905701 DOI: 10.1136/gut.2005.076646]

10. Linday KL. Introduction to therapy of hepatitis C. Hepatology 2002; 36: SI14-SI20 [PMID: 12407584 DOI: 10.1002/hep.160360715]

11. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009; 49: 1335-1374 [PMID: 19330875 DOI: 10.1002/hep.22759]

12. Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C virus infection. 2004; 39: 1147-1171 [PMID: 15057920 DOI: 10.1002/hep.20119]

13. Poordad F, McConne J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson JM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1195-1206 [PMID: 21449783 DOI: 10.1056/nejmoa1010494]

14. Jacobson IM, McHutchinson JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Murti AJ, Ferenci P, Filiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kaufman RS, Zeuzem S. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011; 364: 2405-2416 [PMID: 21696307 DOI: 10.1056/nejmoa1012912]

15. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M. Telaprevir for retreatment of HCV infection. N Engl J Med 2011; 364: 2417-2428 [PMID: 21696308 DOI: 10.1056/NEJMoa1013086]

16. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1207-1217 [PMID: 21449784 DOI: 10.1056/ NEJMoa1009482]

17. Victrrelis (boceprevir; package insert). Whitehouse Station, NJ: Schering Corporation, 2011

18. Sulkowski MS, Jacobson IM, Goodman ZD, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1207-1217 [PMID: 21449784 DOI: 10.1056/NEJMoa1009482]

19. Victrrelis (boceprevir; package insert). Whitehouse Station, NJ: Schering Corporation, 2011

20. Sarrazin C, Kieffer TL, Bartels D, Hanzelka B, Müh U, Welker M, Wincheringer D, Zhou Y, Chu HM, Lin C, Weegink C, Reesink H, Zeuzem S, Kwong AD. Dynamic hepatitis C virus genotype and phenotypic changes in patients treated with the protease inhibitor telaprevir. Gastroenterology 2010; 132: 1767-1777 [PMID: 17484874 DOI: 10.1053/j.gastro.2009.07.037]

21. Hézode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki JP, Bourlière M, Gharrakhani S, Bengtsson L, McNair L, George S, Kieffer T, Kwong A, Kauffman RS, Alam J, Pawlotsky JM, Zeuzem S, Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med 2009; 360: 1839-1850 [PMID: 19403903 DOI: 10.1056/nejmoa0807650]

22. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçalves FL, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-982 [PMID: 12324553 DOI: 10.1056/nejmoa020047]

23. Davis GI, Wong JB, McHutchinson JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. Hepatology 2003; 38: 645-652 [PMID: 12939591 DOI: 10.1053/jhep.2003.50364]

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