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CASE REPORT

Extended therapy duration for therapy-refractory hepatitis C patients with genotype 2

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Abstract

We devised an extended 72-wk peginterferon-α-2a/ribavirin therapy regimen for the retreatment of highly intractable cases, *i.e.*, 48-wk peginterferon-α-2b/ribavirin therapy-intractable cases. Although 2 cases achieved a rapid virological response to 72-wk peginterferon-α-2a/ribavirin therapy, 1 case failed to achieve a sustained virological response. Although the reason for this difference in the effectiveness of 72-wk peginterferon-α-2a/ribavirin therapy between the cases was unclear, the rebound phenomenon of serum transaminase after 48-wk peginterferon-α-2b/ribavirin therapy and the resultant lower viral load compared to that before 48-wk peginterferon-α-2b/ribavirin therapy might have influenced the treatment outcome. Thus, it may be beneficial to consider the rebound phenomenon of serum transaminase and the changes in viral load resulting from previous interferon-based therapy and then cautiously determine the indication and the timing of the administration of 72-wk peginterferon-α-2a/ribavirin in highly intractable cases. Further studies should be performed to confirm this strategy.

Key words: Hepatitis C; Genotype 2 and high viral loads; Interferon-based therapy; Highly intractable case; Extended therapy duration

Core tip: The optimal therapy for 48-wk peginterferon-α-2b/ribavirin therapy-intractable hepatitis C patients with genotype 2 and high viral loads remains unknown. Our cases are notable in that 72-wk peginterferon-α-2a/ribavirin therapy may have been effective for these highly intractable cases. Additionally, the rebound phenomenon of serum transaminase after the 48-wk peginterferon-α-2b/ribavirin therapy and the resultant lower viral load compared to that before the 48-wk peginterferon-α-2b/ribavirin therapy might have influenced the treatment outcome. Thus, our cases highlight the importance of the results of the previous 48-wk peginterferon-α-2b/ribavirin therapy in the indication and timing of the administration of 72-wk peginterferon-α-2a/ribavirin in highly intractable cases.

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INTRODUCTION

The American Association for the Study of Liver Diseases Practice Guidelines recommend treatment with

peginterferon/ribavirin for 24 wk using a ribavirin dose of 800 mg for interferon-based therapy-naïve patients with hepatitis C virus (HCV) genotype 2[1]. However, retreatment with peginterferon/ribavirin in patients who do not achieve a sustained virological response (SVR) after a full course of peginterferon/ribavirin is not recommended, even if a different type of peginterferon is administered[1]. However, some patients who have previously completed peginterferon-α-2b [PegIntron; Merck Sharp & Dohme (MSD), Tokyo, Japan]/ribavirin (Rebetol; MSD) therapy but failed to achieve an SVR can be treated with a 24- to 48-wk course of peginterferon/ribavirin[2-4]. Oze *et al*[2] suggested that the SVR rate was similar between 24-wk and 48-wk peginterferon/ribavirin therapy in patients with genotype 2 who achieved a rapid virological response (RVR) upon retreatment. We previously demonstrated the superiority of 48-wk therapy over 24-wk therapy for patients with genotype 2 and high viral loads $\geqslant 10^5$ international units (IU)/mL; 5 logIU/mL as determined using the quantitative reverse transcription polymerase chain reaction-based Cobas TaqMan HCV Test (Roche Diagnostics, Tokyo, Japan) who demonstrated serum HCV RNA levels [measured using the Cobas Amplicor Monitor HCV ver. 2.0 Assay (Roche Diagnostics)] $\geqslant$ 50 IU/mL at week 4 of therapy regardless of the history of interferon-based therapy[5]. The Japan Society of Hepatology also recommends a 24- to 48-wk course of peginterferon/ribavirin retreatment following peginterferon/ribavirin treatment in patients with HCV genotype 2 and high viral loads[6]. However, the effectiveness of retreatment in highly intractable cases, *i.e.*, 48-wk peginterferon-α-2b/ribavirin therapy-intractable cases, remains unknown. Therefore, we devised a 72-wk peginterferon/ribavirin therapy regimen for the retreatment of highly intractable cases, regardless of the time of disappearance of serum HCV RNA.

As for the type of peginterferon, the superiority of peginterferon-α-2a therapy over peginterferon-α-2b therapy for chronic hepatitis C has not been determined. However, given that peginterferon-α-2a therapy is significantly superior or has a tendency to increase the efficacy of treatment in patients with HCV genotype 2 compared to peginterferon-α-2b therapy according to randomized controlled trials[7,8] and a meta-analysis of randomized controlled trials[9], we selected peginterferon-α-2a (Pegasys; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan)/ribavirin (Copegus; Chugai Pharmaceutical Co., Ltd.) for the retreatment of 48-wk peginterferon α-2b/ribavirin therapy-intractable cases.

The submitted case reports comply with the Declaration of Helsinki. Informed consent was obtained from the patients.

CASE REPORT

Case 1

A 55-year-old male was referred to our hospital because of chronic HCV infection and abnormal transaminase levels. His medical history included an operation for the treatment of appendicitis at 8 years of age and acute hepatitis with jaundice at 23 years of age after he had acquired a tattoo and abused drugs at 25 years of age. He had neither a history of blood transfusion nor a family history of liver diseases. The transmission of hepatitis C in this case could have been mediated by either the tattoo or drug abuse. His complete blood counts appeared normal, although blood tests showed elevated levels of serum alanine aminotransferase (ALT) (44 IU/mL). The quantitative detection of HCV RNA [real-time polymerase chain reaction (PCR), COBAS TaqMan Test] revealed a level of 6.5 logIU/mL; the HCV genotype was 2b. The interleukin-28B (IL28B) locus single nucleotide polymorphisms (SNPs) previously reported to be associated with therapy outcome, including rs8099917, rs11881222 and rs8103142[10], were all major homozygous. The inosine triphosphatase (ITPA) locus SNP previously reported to be associated with ribavirin-induced hemolytic anemia[11] and interferon-induced thrombocytopenia[12] in Japanese chronic hepatitis C patients under peginterferon-α/ribavirin therapy (rs1127354) was major homozygous. A liver biopsy obtained prior to interferon-based therapy was graded F1/A2 according to the New Inuyama classification.

We initiated treatment with peginterferon-α-2b (100 μg once weekly, subcutaneously) and ribavirin (800 mg per day) based on the patient's body weight. Serum HCV RNA was not detectable at wk 8 of therapy. Thus, we extended the duration of therapy from the standard 24-wk regimen to a 48-wk regimen based on our prospective study[5]. The patient's adherence to peginterferon-α-2b/ribavirin was 100%, although his serum HCV RNA level became positive 4 wk after the completion of therapy. Notably, the rebound phenomenon of serum transaminase after completion of the 48-wk therapy occurred, and the viral load decreased below the pre-treatment level. He was retreated with peginterferon-α-2a (180 μg once weekly, subcutaneously) and ribavirin (800 mg per day) based on his body weight. Because the 48-wk therapy with peginterferon-α-2b and ribavirin resulted in viral relapse, we extended the duration of therapy from the recommended 24-48 wk to 72 wk, although the serum level of HCV RNA became undetectable after 4 wk of therapy. Although the patient's adherence to ribavirin was 74% due to anemia, he achieved an SVR. The laboratory findings, treatments and outcomes for case 1 are shown in Table 1.

Case 2

A 55-year-old male was referred to our hospital because of chronic HCV infection. His previous medical history included an operation due to appendicitis at 14 years of age and euthyroid sick syndrome, the onset of which was unclear. He had neither a history of blood transfusion nor a family history of liver disease. Thus, the transmission source of hepatitis C in this case could not be

Table 1 Laboratory findings at baseline, treatments and outcomes of highly intractable cases

Parameters	Case 1		Case 2	
Age (yr)	55		55	
Sex	Male		Male	
HCV genotype	2b		2b	
Transmission	Tattoo or drug abuse		Unknown	
IL28B SNPs (rs8099917:rs11881222:rs8103142)	T/T:A/A:T/T		T/T:A/A:T/T	
ITPA SNPs	C/C		C/C	
At the start of therapy	First therapy	Second therapy	First therapy	Second therapy
BMI (kg/m^2)	26	27.5	20.9	19.7
HCV RNA (logIU/mL)	6.5	3.7	7.2	7.5
Liver biopsy	F1/A2	Not performed	F1/A2	Not performed
ALT (IU/L)	36	26	32	40
AST (IU/L)	44	32	32	33
WBC (cells/μL)	4520	3880	3690	4020
Neutrophil (cells/μL)	2650	2420	1450	1950
Hemoglobin (g/dL)	15.7	14.6	11.9	12.9
Platelets (cells/μL)	16.4	15.7	14.5	15.3
Peak ALT after the first therapy (IU/L)	210		33	
Duration between the first therapy and the second therapy (wk)	17		10	
Treatment and outcome	First therapy	Second therapy	First therapy	Second therapy
Peginterferon α dosage (μg)	100	180	100	180
RBV dosage (mg)	800	800	800	800
Week at disappearance of serum HCV RNA	8	4	16	4
Adherence to peginterferon α	100%	100%	100%	100%
Adherence to RBV	100%	74%	96%	100%
Weeks of therapy	48	72	48	72
Response	Relapse	SVR	Relapse	Relapse

HCV: Hepatitis C virus; IL28B: Interleukin-28B; SNPs: Single nucleotide polymorphisms; ITPA: Inosine triphosphatase; first therapy: 48-wk peginterferon α-2b/ribavirin; second therapy: 72-wk peginterferon α-2a/ribavirin; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; WBC: White blood cell; RBV: Ribavirin; SVR: Sustained virological response.

identified. A complete blood count showed slight anemia, and blood tests showed a slightly high serum ALT level (32 IU/mL). The quantitative detection of HCV RNA (real-time PCR, COBAS TaqMan Test) revealed a level of 7.2 logIU/mL; the HCV genotype was 2b. The IL28B locus SNPs, including rs8099917, rs11881222 and rs8103142, were all major homozygous. The ITPA locus SNP rs1127354 was major homozygous. A liver biopsy obtained prior to interferon-based therapy was graded F1/A2 according to the New Inuyama classification.

We initiated treatment with peginterferon-α-2b (100 μg once weekly, subcutaneously) and ribavirin (800 mg per day) based on the patient's body weight. Serum HCV RNA disappeared at week 16 of therapy. Thus, we extended the therapy duration from the standard 24-wk regimen to a 48-wk regimen based on our prospective study[5]. Although the patient's adherence to peginterferon-α-2b/ribavirin was 100%, his serum HCV RNA level became positive 4 wk after the completion of therapy. In contrast to case 1, no obvious rebound phenomenon of serum transaminase was observed after completion of the 48-wk therapy, and the viral load returned to the pre-treatment level. He was retreated with peginterferon-α-2a (180 μg once weekly, subcutaneously) and ribavirin (800 mg per day) based on his body weight. Because the 48-wk therapy with peginterferon-α-2b and ribavirin resulted in viral relapse, we extended the duration of therapy from the recommended 24-48 wk to 72 wk, and his serum HCV RNA level became negative at wk 4 of therapy. Although the patient's adherence to both drugs was 100%, his serum HCV RNA level became positive again at 4 wk after the completion of therapy, and he therefore could not achieve an SVR. The laboratory findings, treatments and outcomes of case 2 are shown in Table 1.

DISCUSSION

The major findings from these case reports are twofold: 72-wk peginterferon-α-2a/ribavirin therapy may represent an effective therapy for 48-wk peginterferon-α-2b/ribavirin therapy-intractable cases, and by contrast, even 72-wk peginterferon-α-2a/ribavirin therapy-intractable HCV infection can occur in patients with genotype 2 and high viral loads. Although the difference in the effectiveness of 72-wk therapy between the 2 cases was not clear, the rebound phenomenon of serum transaminase after the 48-wk therapy and the resultant lower viral load compared to that before the 48-wk therapy might be possible contributing factors that could influence the treatment outcome, based on these case reports and our previous study[5]. Case 1 was consistent with a previous

report indicating that patients who showed biochemical relapse after initial interferon therapy had a significantly lower serum HCV RNA level at recovery after ALT relapse compared to before the initial interferon therapy[13]. Moreover, our cases showed that an RVR was not sufficient for predicting an SVR, even for 72-wk interferon-based therapy. Because both of our cases carried major homozygous IL28B SNPs, our findings support a limited role for *IL28B* genotypes regarding the virological responses achieved in chronic hepatitis C patients with genotype 2 and high viral loads[5]. However, because the number of our highly intractable cases was small, further studies are needed to test this hypothesis.

One possible solution for the treatment of highly intractable cases is telaprevir in combination with peginterferon-α-2b/ribavirin therapy. In fact, this therapy achieved an SVR in a 48-wk peginterferon-α-2b/ribavirin therapy-intractable female patient with genotype 2 and a high viral load in a phase Ⅲ clinical trial (unpublished data). In addition, direct-acting anti-viral (DAA) combination therapy may overcome this difficulty in highly intractable cases in the near future. However, for cases in which it is difficult to use DAA due to the risk of drug interactions between DAA and medicines administered to treat complications or for patients who are discouraged from waiting for antiviral therapy, such as those who developed hepatocellular carcinoma, 72-wk peginterferon-α-2a/ribavirin therapy may be one strategy for curing highly intractable patients with genotype 2 and high viral loads. For case 1 presented here, 24- to 48-wk peginterferon-α-2a/ribavirin therapy for retreatment may have been effective, although we selected 72-wk therapy to improve the likelihood of an SVR. However, 72-wk therapy is not always sufficient, as demonstrated in case 2 (although he did achieve an RVR). In case 1, the viral load after 48-wk peginterferon-α-2b/ribavirin therapy decreased significantly in comparison to the level prior to treatment, whereas the viral load returned to the pre-treatment level in case 2. We were able to initiate the 72-wk therapy under the condition that the viral load had become lower than that before the 48-wk therapy in case 1. This indicates that it may be a good strategy to consider the rebound phenomenon of serum transaminase and the changes in viral load as a result of previous interferon-based therapy and then cautiously determine the indication and timing of administration of the 72-wk peginterferon-α-2a/ribavirin in highly intractable cases. However, a therapy duration of less than 72 wk should also be considered as a second therapy if the pre-treatment viral load before the second therapy is low (less than 5 logIU/mL) because chronic hepatitis C patients with low viral loads are likely to achieve an SVR in short-term therapy. Further studies should be examined to confirm the strategy of extended therapy duration.

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