Interferon Therapy and New Antiviral Drugs for Chronic Hepatitis C

Norio HAYASHI,* Naoki HIRAMATSU,*2 Tsugiko OZE*3

Abstract

Antiviral therapy for hepatitis C, which started from the monotherapy of interferon (IFN), has progressed remarkably through the combination therapy using IFN and ribavirin (RBV) followed by the development of pegylated IFN (Peg-IFN). The combination therapy of Peg-IFN/RBV, which is currently the standard antiviral therapy for hepatitis C, shows dramatically improved therapeutic results. Consequently, the response rate for the cases of genotype 1 with high viral load, which are refractory, has risen from 5% when using IFN monotherapy to 40 to 50%, and the response rate for the cases of genotype 1 with low viral load or genotype 2 has risen from 50 to 60% when using IFN alone to 80 to 90%. Recent studies revealed a few findings; the amount of Peg-IFN administered is involved in the timing of viral disappearance, the amount of RBV dose-dependently affects the inhibition of post-treatment viral relapse, and, prolonging the treatment period suppresses the rate of post-treatment relapse in late virologic response cases. Therefore, in order to further improve the response rate for Peg-IFN/RBV combination therapy, the administration duration and dosage of Peg-IFN and RBV should be set in accordance with the response of individual patients to the treatment, not a uniform pattern method that only depends on genotypes and HCV-RNA levels at baseline. Furthermore, antiviral therapy for chronic hepatitis C is making new advances with HCV-selective antiviral agents such as protease inhibitors, which brings high expectations for clinical application in the future.

Key words  Hepatitis C, Interferon (IFN), Pegylated interferon (Peg-IFN), Ribavirin (RBV), Serine protease inhibitors

Introduction

Hepatitis C virus (HCV) was discovered in 1989 by Choo et al. in the United States.1 Over 90% of patients who had previously been diagnosed with non-A non-B (NANB) hepatitis and more than half of those who had been previously diagnosed with alcohol liver disease were found to suffer from liver disease caused by HCV. Today, there are estimated to be approximately 1.7 million HCV carriers in Japan and 170 million in worldwide. Even among healthy adults, once infected and develop acute hepatitis, only approximately 30% of patients are cured while the rest remain infected with HCV and progress to chronic liver disease.

This paper reviews the progress of interferon (IFN) therapy as a treatment for chronic hepatitis C and also discusses the combination therapy of pegylated IFN (Peg-IFN) and ribavirin (RBV) as the latest and most highly effective treatment for hepatitis C. Additionally, the latest knowledge and information about new antiviral agents, which development is being pursued internationally, are presented.

*1 Director, Kansai Rousai Hospital, Hyogo, Japan (hayashin@kanrou.net).
*2 Associate Professor, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan.
*3 Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan.
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IFN therapy for treating hepatitis C began in 1986 when Hoofnagle and others used human recombinant IFN-α against NANB hepatitis and confirmed transaminase normalization. Subsequently, the PCR (polymerase chain reaction) method for detecting viruses was developed, and it made evident that blood HCV-RNA became negative in the cases where the hepatitis subsided with IFN therapy.

Initially, with regard to the three levels of therapeutic efficacy, namely sustained virologic response (SVR), relapse, and non-response (NR), the IFN was said to be approximately one-third each. However, it later became clear that viral factors strongly influence the effectiveness, meaning that the HCV genotype 1 (1b) is more resistant to IFN therapy than genotype 2 (2a, 2b) and IFN therapy is less effective against the cases with high viral loads than low viral loads. Genotype 1 comprises approximately 70% of the hepatitis C cases in Japan. The highly viral cases with genotype 1 are extremely resistant, which lead to the SVR rate of only 5% with IFN monotherapy. Subsequently, various treatment methods have been taken to improve the effectiveness, especially against intractable hepatitis C. (Fig. 1).

Attempts to improve the effectiveness of IFN monotherapy included increasing the total amount of IFN. In high-dose IFN experiments, in which the dosage in each treatment was increased, the SVR rate failed to improve because side-effects became more pronounced in some cases and compliance was reduced. However, when IFN was administered to patients with genotype 1 for 12 months, the rate of post-treatment relapse decreased and the SVR rate increased when compared to the standard administration period of 6 months. Based on these results, national insurance coverage was expanded to cover prolonged IFN administration in 2002. With the introduction of self-injection of IFN in 2005, prolonged IFN administration became widely used in general clinical practice.

Peg-IFN, the basic pharmaceutical formulation used in IFN therapy today, is IFN with polyethylene glycol added. Because Peg-IFN is absorbed gradually and has a slower clearance than ordinary IFN, single administration per week is sufficient to maintain an effective blood concentration.
Peg-IFN(IFN)/RBV Combination Therapy

Discovered in 1972, ribavirin (RBV) is an oral nucleoside analogue that has a broad spectrum of antiviral activity in vitro against RNA and DNA viruses. Although RBV alone was not found to be effective against hepatitis C, the combination therapy of Peg-IFN and RBV was reported to have improved therapeutic efficacy in 1998.\(^5,6\)

Clinical trials in the United States and Europe

Large-scale clinical trials conducted in the Unites States and Europe have shown that, compared to IFN monotherapy, IFN/RBV combination therapy improved SVR rate regardless of the HCV genotype or viral load. Furthermore, large-scale clinical trials of Peg-IFN/RBV combination therapy for treatment-naïve patients with hepatitis C found the SVR rate of 42 to 52% (with 48-week treatment) for genotype 1 and 81 to 84% for genotypes 2 and 3 (with 24-week treatment), indicating a marked improvement.\(^7,9\)

When using Peg-IFN/RBV combination therapy to treat genotype 1, it is becoming clear that the decrease rate of HCV-RNA following the start of treatment is an important factor in predicting the SVR. Namely, the SVR rate was extremely low (0 to 3%) when the HCV-RNA level had not decreased to less than 1/100 of the pre-treatment level by week 12 in the course of treatment. Additionally, in most cases where it took 24 weeks or longer for the HCV-RNA to become negative, HCV-RNA relapsed after the treatment when the treatment duration was the standard 48 weeks. Therefore, in cases where response to this treatment is poor, there is virtually no possibility of obtaining SVR with the standard treatment of 48 weeks.

Clinical trials in Japan

In clinical trials of Peg-IFN/RBV combination therapy conducted in Japan,\(^10,11\) it was administered to 254 subjects of chronic hepatitis C with HCV genotype 1 and high viral load for 48 weeks and to 63 subjects of chronic hepatitis C with genotype 1 and low viral load or genotype 2 for 24 weeks. Dosage was 1.5µg/kg of Peg-IFNα-2b once a week, with daily administration of RBV of 600 mg (for body weight 40–60 kg), 800 mg (60–80 kg), or 1,000 mg (80–100 kg). The SVR rate for
subjects with genotype 1 and high viral load was 48%, while administration was discontinued in 18% of the cases. For subjects with genotype 1 and low viral load or genotype 2, the SVR rate was 87% with the discontinuation rate of 21%. In comparison with the conventional IFN monotherapy or IFN/RBV combination therapy, both achieved good results. Consequently, national insurance policy approved the 48-week treatment for patients with genotype 1 and high viral load in October 2002 and 24-week for patients with genotype 1 and low viral load or genotype 2 in December 2004.

Next, we present the results of the collaborative research led by Osaka University that involved multiple institutions participating in Osaka Liver Forum (OLF), which examined the effectiveness of Peg-IFN/RBV combination therapy in general clinical practice following the insurance coverage approval. Of the 2,788 cases of chronic hepatitis C that received Peg-IFN/RBV combination therapy, the target subjects were 1,173 cases of genotype 1 and high viral load that already assessed the SVR. Among the cases that completed the 48-week treatment and were HCV-RNA negative, 31% was found to be HCV-RNA relapse after the treatment, and the overall SVR rate for the cases of 48-week treatment was 48%.

With regard to SVR rate in terms of the timing to the first undetectable HCV-RNA level, it was 78% for the patient who became HCV-RNA negative within 12 weeks of a 48-week treatment (early virologic response, EVR) and 33% for those who became HCV-RNA negative between 13 and 24 weeks of the treatment (late virologic response, LVR). This indicates that the timing of HCV-RNA negativity during the Peg-IFN/RBV treatment strongly influences the likelihood of relapse after the treatment (Fig. 2).

Problems Concerning Peg-IFN/RBV Combination Therapy and the Countermeasures

Antiviral therapies for chronic hepatitis C have achieved marked progress in Peg-IFN/RBV combination therapy. However, the SVR rate for cases of genotype 1 and high viral load that are known to be difficult to treat is only about 50%, meaning elimination of HCV was not achieved in the other half, which suggests further improvement in effectiveness is desirable. The following is a summary of findings on adjustments to be made when treating hepatitis C with genotype 1.

Optimal treatment period

With regard to hepatitis C cases with HCV genotype 1, especially those in which HCV-RNA became negative late, the treatment period is being extended experimentally (to 72 weeks). Berg et al. conducted experiments on genotype 1 subjects by randomly assigning to either 48-week or 72-week of Peg-IFN/RBV administration. Their study found no significant difference between the two groups for the cases in which EVR was achieved, whereas the cases that failed to achieve EVR showed higher SVR rate in the 72-week group (17% in the 48-week group, 29% in the 72-week group). These results indicate that administration of Peg-IFN/RBV for 72 weeks is effective against genotype 1 cases when HCV-RNA became negative late, and that it is important to consider the timing to become HCV-RNA negative after the start of treatment when deciding the treatment duration (48 weeks or 72 weeks). In our research, the SVR rate in LVR cases were also significantly high for the 72-week treatment (64%) compared with the 48-week treatment (33%), suggesting the importance of extending the treatment period to 72 weeks for LVR cases.

Adherence and therapeutic efficacy

When treating hepatitis C genotype 1 cases using Peg-IFN/RBV combination therapy, drug adherence is evidently a significant factor for the SVR. McHutchison et al. have reported that it is important to maintain the amount of both Peg-IFN and RBV at the level of 80% or more for the planned treatment period of 80% or longer in order to achieve SVR. Furthermore, the results of the OLF found that the amount of Peg-IFN administered was important for EVR cases (HCV-RNA became negative within 12 weeks after the start of treatment) and that significantly high EVR was achieved at the 80% or more of the standard dosage (≥1.2 μg/kg/week). On the other hand, in cases where EVR was achieved, RBV amounts strongly influenced the likelihood of HCV-RNA relapse after the 48-week treatment, with relapse rate decreasing according to the RBV dosage. Considering dosage adjustment of pharmaceutical agents is the only mean of intervening for us physicians in therapeutic
efficacy, it is hoped that maintaining an optimal dosage will lead to an improvement in SVR rate.

**Treatment of the patient with persistently normal ALT (PNALT)**

In the case of normal, asymptomatic patient with persistently normal ALT (PNALT), the SVR rate was extremely low with conventional treatments using IFN monotherapy, so antiviral therapies were not used actively. However, Zeuzem et al. showed that Peg-IFN/RBV combination therapy could achieve the same therapeutic efficacy as the chronic hepatitis cases. In Japan, too, antiviral treatment guidelines have been established for PNALT cases; those with serum ALT levels of 31 to 40 IU/L are given the same treatment as chronic hepatitis patients, those with serum ALT levels of 30 IU/L or less and the blood platelet count of less than 150,000/μL undergo a liver biopsy, and those with fibrosis of Stage F2 or beyond and necrosis/inflammation of Grade A2 or higher are advised to receive antiviral therapy.

Presently recommended treatment methods that takes the virus response to the treatment into consideration

As mentioned so far, the standard treatment for genotype 1 hepatitis C is Peg-IFN/RBV combination therapy for 48 weeks. However, in LVR cases where HCV-RNA becomes negative between 13 and 24 weeks in the course of treatment, extending the administration to 72 weeks is shown to be effective. Conversely, in cases where HCV-RNA becomes negative within 4 weeks of the course of treatment, it is possible that sufficient therapeutic efficacy will be achieved with only 24 weeks of Peg-IFN/RBV administration. In such cases, depending on the severity of side effects, it may be possible to consider concluding the treatment within 48 weeks.

**New Antiviral Agents**

New pharmaceutical agents for treating hepatitis C currently in development include; new pharmaceutical formulations of IFN aimed at enhancing antiviral activity, RBV pro-drugs, protease inhibitors and polymerase inhibitors that are HCV-selective antiviral agents, and various others aimed at enhancing immunostimulatory activity (Table 1).

**Protease inhibitors**

Protease inhibitors are gaining attention for not only it controls virus proliferation by preventing the excision of HCV nonstructural proteins but also has the potential to enhance host immune responses against virus. Telaprevir alone suppresses viral load to between 1/100 and 1/1,000. Promising results have also been obtained in Phase II clinical trials conducted in the United States and Europe.

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**Table 1 New therapeutic agents for treating hepatitis C**

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<th>1. Agents that enhance antiviral activity</th>
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<td>• New IFN formulations</td>
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<td>• New ribavirin-like pharmaceutical formulations</td>
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<td>• HCV-selective antiviral agents</td>
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<td>Protease inhibitors</td>
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<th>2. Agents that enhance immunostimulatory activity</th>
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<td>• ANA975</td>
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However, there have been reports of emerging mutant viruses at high rates within two weeks of treatment that wanes its antiviral effectiveness, so the monotherapy is not likely to provide the complete clearance of the virus.

The “PROVE-1” trial of telaprevir examined the efficacy in treating previously untreated cases of hepatitis C with genotype 1. In contrast to the SVR rate of 41% for the control group (Peg-IFN/RBV for 48 weeks), the group treated with a combination of telaprevir/Peg-IFN/RBV for 12 weeks plus Peg-IFN/RBV for 12 weeks achieved a significantly higher SVR rate of 61%. Another clinical study, the “PROVE-2” trial, achieved similar results, indicating that the combined use of telaprevir/Peg-IFN/RBV could shorten the Peg-IFN/RBV treatment period to 24 weeks from the current standard of 48 weeks. Furthermore, in the “PROVE-3” trial, which targeted patients who did not have a SVR to Peg-IFN/RBV combination therapy, the SVR rate for the patients who were treated with a combination of telaprevir/Peg-IFN/RBV for 12 weeks plus Peg-IFN/RBV for 12 weeks was 69% among the patients with a previous relapse and 39% among the patients with a previous non-response. These figures were higher than the rates among the patients who were treated with Peg-IFN/RBV for 48 weeks (20% among the patients with a previous relapse, 9% among the patients with a previous non-response).

In the Phase II trials of the protease inhibitor boceprevir, the SVR rate for the control group that received the standard treatment (Peg-IFN/RBV for 48 weeks) was 38%, the group treated with Peg-IFN/RBV for 4 weeks followed with a combination of Peg-IFN/RBV/boceprevir for 44 weeks achieved SVR rate of 74%, and the group treated with a combination of Peg-IFN/RBV/boceprevir for 48 weeks achieved a SVR rate of 66%. Thus, the addition of boceprevir to Peg-IFN/RBV treatments increased therapeutic efficacy. Moreover, daily administration of one dose of TMC435 achieved an effective blood concentration level, and its Phase II trial is currently underway.

These results show that combining protease inhibitors with Peg-IFN/RBV can control the mutant virus that are resistant to protease inhibitors, providing strong antiviral effect. Currently, large-scale clinical trials are underway around the world.

**Polymerase inhibitors**

The crystalline structures of the polymerases that duplicate genes have been revealed, and their inhibitors are being developed. However, there were problems with the polymerase inhibitors that were developed in early days regarding efficacy and side-effects, and their development was often aborted. A first-generation nucleoside polymerase inhibitor currently in development is R7128, which strongly decreases HCV-RNA level at week 4 in combination with Peg-IFN/RBV therapy.

Compared with protease inhibitors, the antiviral activity of these first-generation nucleotide polymerase inhibitors was considerably weak. However, second-generation polymerase inhibitors that can be administered in their triphosphate forms have strong antiviral activity, and seven inhibitors are currently in clinical trials.

**Toll-like receptor (TLR) agonists**

In order to eliminate HCV, innate and acquired immunological responses are required. The persistent HCV infection is thought to result from insufficient immunological responses to HCV, and it is possible to achieve elimination of HCV by using immunity-modifying agents alone or in combination with antiviral agents such as IFN.

Toll-like receptors are receptors that recognize pathogenic agents and are involved in innate immunological responses. Four-week administration of CPG 10101, a TLR9 agonist, has been reported to reduce HCV-RNA level by an average of 1.69 logIU/mL. Seven-day administration of isatoribine, a TLR7 agonist, has been found to reduce HCV-RNA by an average of 0.76 logIU/mL. The use of IFNs combined with these immunity-modifying agents may be developed as new therapeutic methods in the future.

**Conclusion**

Since the days of IFN monotherapy, the treatment of chronic hepatitis C has made a remarkable progress with the emergence of Peg-IFN/RBV combination therapy. However, in approximately half of the genotype 1 cases with high viral load, which are difficult to treat, the virus elimination is unsuccessful and infection remains persistent. In order to improve therapeutic efficacy, rather than using a uniform pattern that depends on the genotype and HCV-RNA level,
administration periods and dosages should be set in accordance with the responsiveness of individual patients to antiviral treatment. Furthermore, protease inhibitors show strong antiviral activity against hepatitis C including genotype 1 cases. The results of large-scale clinical trials on the use of protease inhibitors in combination with Peg-IFN (+ RBV) therapy are anxiously awaited.

References