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TOPIC HIGHLIGHT

2015 Advances in Hepatitis B virus

Antiviral therapy for chronic hepatitis B: Combination of nucleoside analogs and interferon

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Abstract

The ideal goal of chronic hepatitis B (CHB) treatment should be suppression of emergence of hepatocellular carcinoma through the disappearance of hepatitis B s antigen (HBsAg) rather than the control of serum hepatitis B virus-DNA level. For this purpose, various types of combination therapies using nucleoside analogs (NAs) and interferon (IFN) have been conducted. The therapeutic effects of combination of two different kinds of agents are better than those of the monotherapy using NAs or IFN alone, probably because different pharmaceutical properties might act in a coordinated manner. Recently, combination therapies with NAs and IFN and sequential therapies with NAs administration followed by IFN therapy have been routinely employed. We previously reported that combination therapy using entecavir (ETV) and pegylated (PEG)-IFN showed antiviral effects in 71% of CHB patients; the effect of this combination was better than that using lamivudine (LAM) and PEG-IFN. This is partially explained by the better antiviral effects of ETV than those of LAM. In our analysis, the cohort of CHB consisted of the patients who showed a flare-up of hepatitis before antiviral therapy, and their baseline HBsAg levels were relatively low. Therefore, in addition to the combination of the agents, the appropriate selection of patients is critical to achieve a good viral response.

Key words: Hepatitis B virus; Interferon; Sequential therapy; Combination therapy; Nucleoside analog

Core tip: For the suppression of emergence of hepatocellular carcinoma, disappearance of hepatitis B s antigen (HBsAg) is necessary, which is an important goal for the treatment of chronic hepatitis B. In order to achieve HBsAg clearance, combination therapies with nucleoside

analogs (NAs) and interferon (IFN) and sequential therapies with NAs administration followed by IFN therapy have been routinely employed. The combination of antiviral agents, and the appropriate selection of patients are critical to obtain a good response for HBsAg clearance.

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INTRODUCTION

Hepatitis B virus (HBV) is a DNA virus, and it is characterized by reverse transcription for replication in infected hepatocytes[1]. Various nucleoside analogs (NAs) have been employed as antiviral agents for chronic hepatitis B (CHB) patients. Lamivudine (LAM)[2,3], adefovir[4,5], and entecavir (ETV)[6,7] have been used to inhibit HBV replication by blocking DNA chain elongation. However, resistant viruses that appear after long-term administration of NAs[8-10] should be taken into consideration. HBV infects liver cells and forms stable circular double-stranded DNA [covalently closed circular DNA (cccDNA)] using DNA polymerase in the liver cell nuclei, providing a template for viral proliferation[11,12]. NAs do not directly act on cccDNA but inhibit HBV proliferation by blocking reverse transcription. Thus, discontinuing the administration may well cause viral rebound that lead to the reactivation of hepatitis. On the other hand, interferon (IFN) induces natural killer (NK) cell and reduces cccDNA through the elimination of infected liver cells. However, IFN is rarely indicated for the cirrhotic patients with deteriorated liver functions. In addition, it actually exerts a weak inhibitory effect on virus proliferation compared to the NAs[13]. In general, unlike NAs, IFN shows different therapeutic effects depending on the HBV genotypes; patients with the genotypes C and D are more resistant to IFN than those with the genotypes A and B. Instead of IFN, pegylated-IFN, whose metabolism and elimination are suppressed by linear polyethylene glycol (PEG) modification, was developed, achieving stronger antiviral effects[14].

In order to utilize the synergic effects of these agents, NAs have been combined with IFN. Combination therapies with IFN and NAs and so-called "sequential therapies", which are characterized by the NAs administration followed by the IFN therapy, have been routinely employed. In this article, we focus on the recent advancement of antiviral therapy for CHB in the context of combination therapy using NAs and IFNs.

CONCURRENT ADMINISTRATION OF IFN AND NAS AND THEIR COMBINATION

Several randomized large-scale trials have been reported on PEG-IFNα-2a and LAM combination therapy. In hepatitis B e antigen (HBeAg)-negative cases, 48-wk PEG-IFNα-2a monotherapy was compared with 48-wk PEG-IFNα-2a and LAM combination therapy, demonstrating that the combination therapy showed relatively stronger antiviral effects, although no difference was noted at 24 wk after the therapy in terms of viral response (VR rates: 43% *vs* 44%, respectively)[15]. In HBeAg-positive patients, 48-wk PEG-IFNα-2b monotherapy was also compared with 48-wk PEG-IFNα-2b and LAM combination therapy, again demonstrating no difference in the therapeutic effects (VR rates: 32% *vs* 27%, respectively)[16]. Therefore, PEG-IFN monotherapy is recommended as the firs-line treatment because there was no advantage of 48-wk PEG-IFNα-2a and LAM combination in therapeutic effects of CHB[17].

We have conducted another clinical trial wherein we combined ETV that exerted a stronger antiviral effect than LAM, with PEG-IFN for 48 wk[18]. Seventeen CHB patients with genotype C received ETV and PEG-IFNα-2b combination for 48 wk, and were observed for additional 24 wk to know the virological and biochemical response. Our results showed that serum HBV-DNA levels continued to reduce after the 48-wk administration. At 24 wk after the administration, low viral loads were sustained at < 4 log copies/mL in 12 cases (71%). Of 11 HBeAg-positive cases, four (36%) and eight (73%) showed HBeAg seroconversion at the end of the treatment and at 24 wk after the administration, respectively. Hepatitis B s antigen (HBsAg) disappeared in one case. Since only a small number of patients were analyzed in this study, the good antiviral effect of this combination should be confirmed with a larger sample size. However, the virological and biochemical effects observed in this study were superior to those reported in the previous study of HBeAg-positive CHB patients using PEG-IFNα-2a monotherapy or combination therapy with LAM[18]. This is partially explained by the use of ETV that has more potent antiviral effects than LAM. On the other hand, our cohort of CHB consisted of the patients who developed flare-up hepatitis before the treatment with low baseline HBsAg levels. Therefore background condition of hepatitis with active immune response should be an important factor to achieve a good antiviral effect.

A recent report showed randomized control trial of monotherapy *vs* combination therapy: Comparison of the antiviral response between HBeAg-positive patients who received ETV alone for 24 wk *vs* patients treated with PEG-IFN for 24 wk after 24-wk ETV administration[19]. HBeAg loss with an HBV DNA < 200 IU/mL (18% *vs* 32%, respectively, $P = 0.032$) rates were significantly higher in the 24-wk PEG-IFN combination group, and the relapse rate after ETV discontinuation was also lower in the 24-wk PEG-IFN combination group than ETV-monotherapy group. Thus, ETV and PEG-IFN combination may provide favorable outcomes. It is also known that tenofovir (TDF) also exerts a good antiviral effect to HBV. Therefore, TDF and PEG-IFN combination should be conducted in a large-scale study.

SEQUENTIAL THERAPY

Administration of NAs followed by IFN therapy is known as sequential therapy. The results of the treatment with the 20-wk LMV administration, followed by the 4-wk combination of LMV with IFN and subsequent 24-wk IFN monotherapy were reported[20]. Fourteen CHB patients received the therapy, resulting in HBeAg seroconversion in 45% and negative for HBV-DNA in 57%. Thus, this sequential method could be a promising antiviral therapy. However, the majority of the patients examined in this trial had a HBV-genotype A. Therefore, antiviral effect for other genotypes is still unknown.

Other trials were performed using different protocols at many facilities. Sequential therapy was conducted in 36 HBeAg-negative patients using 6-mo LMV monotherapy, followed by 6-mo combination of LAM with IFN, and additional 12-mo IFN monotherapy[21]. At 12 mo after the therapy, biological effects and HBV-DNA-negative rates were not significantly different from those of the age- and sex-matched IFN-alone control group. The antiviral response reported in this study were markedly different from those reported in the previous report[20]. Sequential therapy was also conducted in 24 HBeAg-positive patients using 16 to 32-wk LMV therapy, followed by 4-wk combination with IFN-β and additional 20-wk IFN monotherapy[22]. Virological effects were noted in 29% of the patients, which is also much lower than those reported by Serfaty *et al*[20]. In this trial, the majority of the CHB patients carried genotype C virus that was known as a resistant genotype to IFN therapy. Therefore, these controversial results among the studies may be explained by the difference of the HBV genotype in addition to the differences of sex, and ethnic groups analyzed. In this report, background factor that associated with therapeutic effects were also analyzed: IFN therapy is markedly effective in young patients with low HBV-DNA levels before the therapy[23]. Sequential therapy with ETV and IFNα was also reported, demonstrating no additional therapeutic advantage as compared to those with LMV[24]. However, this therapy is more likely to be effective in patients who achieved clearance of HBeAg during ETV administration. Therefore, the effects of sequential therapy should be enhanced through the appropriate patient selection.

IMMUNE RESPONSE AND THERAPEUTIC EFFECTS

In the early stage of HBV infection, viruses are controlled by natural immunity, mainly consisting of NKT cells, and activated NKT cells activate NK, T, and B cells to ameliorate the HBV infection and eliminate infected hepatocytes[25,26]. Thus, activated NKT cells are essential for viral clearance in acute hepatitis B. On the other hand, attempts have been made to treat chronic hepatitis B by activating NKT cells. In a clinical trial on chronic hepatitis B treatment with α-GalCer, a ligand for type 1 NKT cells, no marked antiviral effects were noted[27]. This should be further investigated in the future.

The expression levels of activation markers in NK cells from the peripheral blood and liver were higher in chronic hepatitis B patients with high alanine transaminase (ALT) levels than in those with low ALT levels, with the degree of activation being correlated with the severity of hepatocyte damage[28]. As described above, IFN exerts antiviral effects through the activation of NK cells[25,26]. Hence, in patients with high ALT levels, antiviral effects may be increased by IFN intervention through the increased activation of NK cells. The marked therapeutic effects of the combination therapy with PEG-IFN and ETV can be explained by the selection of patients with high ALT levels (157 ± 143 IU/L) before the intervention[18]. A high viral load has been reported as an IFN-resistance factor. The combination with ETV may have increased the IFN effects by reducing viruses early. The activities of interleukin 15 and 6 and CD8 were increased by the combination with tenofovir and PEG-IFN as compared to PEG-IFN monotherapy, suggesting that tenofovir improves the immune response to IFN[29]. This should be further examined in the future.

The numbers of NKT cells in chronic hepatitis B patients were lower than those in healthy subjects. However, the numbers of NKT cells were restored in patients successfully treated with telbivudine[30]. In addition, the IFN-γ production capacity of NK cells was improved in patients successfully treated with ETV[31]. Before analog treatment, sequential therapy is conducted to reduce viruses, followed by IFN treatment. IFN intervention may exert effects in patients with the numbers and functions of NKT cells restored by analog treatment.

In both combination therapy with PEG-IFN and analog and sequential therapy, immunocompetent cells, mainly NKT cells, may be associated with the therapeutic effects. From this viewpoint, therapeutic indications and effectiveness should be examined.

CONCLUSION

The concurrent administration of IFN and NAs is intended to enhance the effect of IFN. Baseline viral loads are considered to be associated with IFN resistance, while flare up of hepatitis lead to susceptibility to IFN treatment because active immune response should accelerate the antiviral action of IFN. Thus, IFN exerts maximum effects in a conflicting situation with low HBV-DNA level accompanied by active hepatitis. From this point of view, IFN should be started during an initial decreasing phase of HBV-DNA under the administration of NAs in patients with active hepatitis. To achieve this condition, simultaneous initiation of NAs and IFN should be ideal. Indeed, in addition to the types of combinations of NAs and IFN, various factors, such as ALT, HBV-DNA, and HBsAg levels before the treatment may affect the therapeutic effects.

Sequential therapy is aimed at enhancing thera-

peutic effects and safety discontinuing of the NAs administration. However, it should also induce inactive hepatitis after a long-term administration of NAs, which could affect the effect of IFN. On the other hand, many studies reported the effectiveness of sequential therapy specifically in patients with low serum HBV-DNA levels and negative HBeAg after administration of NA. The factors that predict the effectiveness of sequential therapy should be investigated.

Combination therapy and sequential therapy are based on the different treatment concepts. However, both are basically aimed at drug-free treatment. We should take the advantages as well as the risk of treatment failure into reconsideration for the treatment of CHB.

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