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EDITORIAL

No additive effects of peginterferon on the short-term improvement of liver histology by entecavir monotherapy in chronic hepatitis B patients

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Abbreviations

HBeAg	Hepatitis B virus e antigen
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
ALF	Acute liver failure
ACLF	Acute-on-chronic liver failure
NUCs	Nucleos(t)ide analogues

Hepatitis B virus (HBV) infection represents a serious health problem worldwide, especially in Asian Pacific countries [1]. HBV vaccines are useful to prevent HBV infection, and HBV vaccination programs are conducted in several countries. Pegylated interferon-alpha and nucleos(t)ide analogues (NUCs) are currently used for patients with chronic HBV infection. NUCs could directly inhibit HBV replication and delay clinical progression in HBV-infected patients in advanced liver diseases or cirrhosis by reducing the incidence of hepatic decompensation and the occurrence of hepatocellular carcinoma (HCC) through virological, biochemical and histological responses, although long-term use may cause adverse events to some extent [2, 3].

Interferon therapy decreases the occurrence of HCC in HBV-infected patients with advanced liver fibrosis [4]. Interferon therapy is a significant independent factor for both the survival and development of HCC in HBV-infected individuals. In Japan, pegylated interferon-alpha-2a is currently used as an anti-HBV agent and immunomodulator for HBV-infected patients without cirrhosis, as interferon demonstrates hepatotoxicity as one of the adverse events.

There are several reports regarding combination therapy of NUCs and pegylated interferon-alpha for HBV-infected patients [5]. Previous Japanese pilot study demonstrated that add-on therapy, in which 48 weeks of pegylated interferon-alpha-2a are administered simultaneously with ongoing long-term NUC therapy, is superior to sequential therapy, in which 48 weeks of pegylated interferon-alpha-2a (180 μg/week) are administered from 1 month prior to discontinuation of long-term NUC therapy to 11 months post-discontinuation, for HBV surface antigen (HBsAg) reduction [6].

In this issue of Hepatology International, Chen et al. report that pegylated interferon-alpha-2a add-on therapy does not yield additional hepatic fibrosis regression and virologic response than entecavir alone when they compared liver histology at posttherapy in HBe antigen (HBeAg)-positive or HBeAg-negative HBV-infected patients with mild or moderate hepatic fibrosis (pretherapy biopsy-proven Ishak fibrosis stage 2, 3, or 4) between an entecavir monotherapy group ($n = 47$) and an entecavir-plus-pegylated interferon group ($n = 108$) (Table 1) [7]. However, in general, the effects of pegylated interferon appear after 48 weeks of stopping therapy [5]. Therefore, if possible, further histological evaluation, or elastography which could evaluate liver stiffness measurement, should be performed in the future.

Marcellin et al. demonstrated that the combination therapy with tenofovir disoproxil fumarate and pegylated interferon-alpha-2a for 48 weeks resulted in higher rates of HBsAg loss than those receiving tenofovir disoproxil fumarate or pegylated interferon-alpha-2a only at week 72 [8]. They also observed that the combination therapy with tenofovir disoproxil fumarate and pegylated interferon-alpha-2a for 48 weeks resulted in higher rates of HBeAg loss and anti-HBe seroconversion than those receiving tenofovir disoproxil fumarate only at week 72 [8]. Matsumoto et al.

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Table 1 Effects of pegylated interferon-alpha-2a add-on entecavir, compared with entecavir monotherapy [7]

Items	Add-on group
ALT levels	Similar to entecavir monotherapy group
HBeAg or HBsAg loss or seroconversion rates	Higher without statistical significance
HBV DNA undetectable	Similar to entecavir monotherapy group
LSM	Similar to entecavir monotherapy group
Short-term improvement of liver histology	Similar to entecavir monotherapy group
Safety profiles	One patient with abortion and hospitalization

ALT alanine aminotransferase, *HBV* hepatitis B virus, *HBeAg* HBe antigen, *HBsAg* HBV surface antigen, *LSM* liver stiffness measurement

observed that tenofovir disoproxil fumarate and pegylated interferon-alpha-2a add-on therapy for 48 weeks in Japanese patients with chronic hepatitis B facilitated rapid decreases in HBsAg and HB core-related antigen (HBcrAg) [5].

Chen et al. also demonstrate a similar trend of virologic suppression during the 104-week antiviral therapy in both the groups [7]. Of note, HBeAg or HBsAg loss or seroconversion rates of the entecavir-plus-pegylated interferon group were higher than in the entecavir monotherapy group, with no statistical significance (Table 1). Their results partially support the previous studies which demonstrated no or minimal additive effects for lamivudine on pegylated interferon compared with pegylated interferon monotherapy [9].

At present, as we cannot eliminate HBV's covalently closed circular DNA (cccDNA) residing in hepatocytes, suppression of HBV replication, HBsAg loss or seroconversion from HBsAg-positive to anti-HBs-positive are the current goals of therapy for HBV-infected individuals to prevent the progression to cirrhosis or the occurrence of HCC. In general, the judgement of HBsAg loss or seroconversion from HBsAg-positive to anti-HBs-positive needs careful evaluation for longer periods after stopping pegylated interferon therapy [5].

It was reported that acyclic nucleoside phosphonates, such as adefovir dipivoxil or tenofovir disoproxil fumarate, show additive or synergistic effects on immune responses when combined with pegylated interferon [5]. Although Matsumoto et al. observed that tenofovir disoproxil fumarate and pegylated interferon-alpha-2a add-on therapy in Japanese patients with chronic hepatitis B, whose major HBV genotype was genotype C, facilitated rapid decreases of HBsAg and hepatitis B core-related antigen [5], further studies are needed to improve early HBsAg clearance rate and liver histology in Asian Pacific countries.

Chen et al. revealed that entecavir and pegylated interferon-alpha-2a add-on therapy has no impacts on the short-term improvement of liver histology of patients with chronic hepatitis B in China, where the major HBV genotype was genotype C [7]. Combination therapy may contribute to long-term improvement of liver histology compared with NUC monotherapy [10]. Further investigations regarding the mechanism of interferon signaling pathways and the effects in the combination of pegylated interferon and NUCs on HBsAg loss, suppression of hepatocarcinogenesis, and the longer-term observation of liver histology or elastography should be conducted.

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Declarations

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Informed consent Informed consent is not necessary for this type of study.

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