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【 CASE REPORT 】

Peg-IFNα-2a Contributed to HBs Antigen Seroclearance in a Patient with Chronic Hepatitis B Administered Nucleic Acid Analogs: A Three-year Follow-up

Tomoko Tadokoro, Koji Fujita, Kei Takuma, Mai Nakahara, Kyoko Oura, Shima Mimura, Teppei Sakamoto, Takako Nomura, Joji Tani, Asahiro Morishita, Hirohito Yoneyama, Hideki Kobara, Takashi Himoto and Tsutomu Masaki

Abstract:

We treated a 51-year-old Japanese man with chronic hepatitis B (viral load 7.6 LC/mL, genotype C). Hepatitis B virus DNA and HBe antigen were undetectable during the administration of the nucleic acid analogs (NUCs) lamivudine and adefovir, although the concentration of HBs antigen (HBsAg) was 851.2 IU/mL. The HBsAg levels were reduced 150-fold when pegylated-interferon (Peg-IFN) α-2a was administered weekly for 48 weeks and did not increase during the rest period. Therefore, Peg-IFNα-2a was administered twice each week. During this time, HBsAg reached undetectable concentrations, and HBs antibody was detected and continued to be detectable during the three-year follow-up. These unprecedented findings suggest that IFN may contribute to the seroclearance of HBsAg in patients treated with NUCs.

Key words: case reports, chronic hepatitis B, interferon, HBs antigen, HBs antibody

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Introduction

In chronic hepatitis B, the levels of hepatitis B virus (HBV) DNA and the viral HBs antigen (HBsAg) serve as risk factors for liver carcinogenesis, and increases in their levels are significantly associated with a higher incidence of hepatocellular carcinoma (HCC) (1, 2). Reductions in the levels of HBV DNA are readily achieved when patients are treated with nucleic acid analogs (NUCs). Furthermore, the inhibition of the production of HBV-DNA by NUCs significantly reduces the frequency of HCC (3-6). However, when levels of HBV-DNA are low, the residual levels of HBsAg are significantly associated with the occurrence of HCC (7). As such, the continued detection of HBsAg may be significantly associated with hepatocarcinogenesis. The goal of treating HBV hepatitis is thus the seroclearance of HBsAg (8).

Clearance of HBsAg significantly decreases the risk of HCC for patients with chronic hepatitis (other than those with liver cirrhosis) or patients <50 years old (9). However, specific treatment guidelines for reducing the serum levels of HBsAg are unavailable, and our understanding of the patient characteristics associated with beneficial responses to therapy is insufficient.

Short-term treatment with pegylated-interferon (Peg-IFN) aims to achieve a sustained effect (10). Unlike NUCs, IFN acts by binding to type I IFN receptors on target cell membranes but does not directly inhibit the HBV life cycle (10). IFNα-induced activation of the Janus kinase (JAK)/Signal Transducers and Activator of transcription (STAT) signal transduction pathway leads to increased expression of IFN-stimulated genes, which is required for antiviral activity and closely associated with the efficacy of IFN treatment (11). As described above, the activation of innate or adaptive immunity, or both, of the host may be achieved using IFN but not NUCs.

IFN has been used to treat virus infections in Japan since

Department of Gastroenterology and Neurology, Kagawa University School of Medicine/Graduate School of Medicine, Japan
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Correspondence to Dr. Tsutomu Masaki, tmasaki@med.kagawa-u.ac.jp

Table 1. Laboratory Data before Administering Peg-IFNα-2a Together with NUCs.

Metric	Value	Unit	Reference
TP	7.0	g/dL	6.5-8.2
Alb	4.8	g/dL	3.5-5.5
BUN	11.6	mg/dL	7-20
Cr	0.7	mg/dL	0.5-1
T-bil	1.3	mg/dL	0.1-1.2
D-bil	0.4	mg/dL	0.1-0.6
AST	25	U/L	10-35
ALT	27	U/L	5-40
ALP	196	U/L	100-340
LDH	204	U/L	110-220
γ-GTP	19	U/L	0-30
Na	142	mmol/L	135-146
K	4	mmol/L	3.5-4.6
Cl	106	mmol/L	96-110
WBC	3,530	/μL	4,700-8,700
RBC	494×10⁴	/μL	370-490
Hb	15.9	g/dL	11-15
Ht	45.5	%	35-45
Plt	12.9×10⁴	/μL	15-35
Neut	42	%	38-71.9
Eos	1.7	%	0.2-6.8
Baso	0.3	%	0-1
Lym	51.8	%	26-46.6
Mono	4.2	%	2.3-7.7
PT	100	%	80-100
HBV-DNA	-	LIU/mL	-
HBs Antigen	851.2	IU/mL	0-0.05
HBs Antibody	-	mIU/mL	0-10
HBe Antigen	-	ng/mL	-
HBe Antibody	-		-
HBcr Antigen	4.2	Log U/mL	0-3
AFP	5	ng/mL	
DCP	17	mAU/mL	
Hyaluronic acid	87.8	ng/mL	0-50

1987, and Peg-IFNα-2a has been available since 2011 (8). However, only Peg-IFNα-2a is used to treat hepatitis B in Japan (8).

We herein report a case of HBsAg seroclearance induced by supplemental Peg-IFNα-2a treatment of a patient with chronic hepatitis B who was being concurrently administered NUCs.

Case Report

A 51-year-old Japanese man with a history of chronic hepatitis B had an HBV (genotype C) load of 7.6 log copies (LC)/mL. There was no special mention of this in the patient's or family's medical history. He had been our patient since being admitted to our hospital with chronic hepatitis B in 2001. Lamivudine administration began in October 2001, and resistance was detected in April 2005, at which time combination therapy with adefovir was started. HBV-DNA subsequently reached undetectable levels, although HBsAg tests were positive. Therefore, we started by adding Peg-IFNα-2a to the NUCs (lamivudine and adefovir).

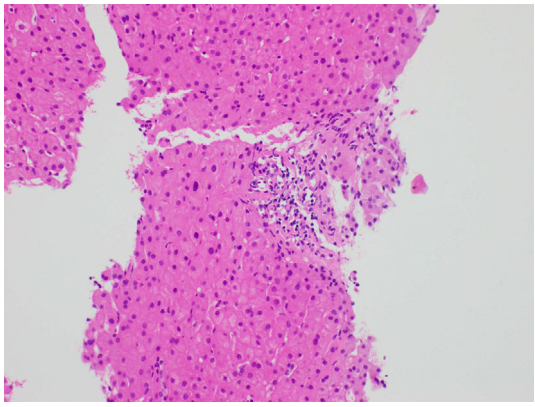

Figure 1. Liver tissue before Peg-IFN treatment. Hematoxylin and Eosin staining, ×20 magnification. In the portal area, there was slight infiltration of inflammatory lymphocytes, piecemeal necrosis was present around the portal area, and fibrosis was present around Gleason's sheath and the central vein (confirmed using azan stain). The histopathological grade of liver tissue was equivalent to A1F1, according to the New Inuyama classification. Peg-IFN: pegylated-interferon

Table 1 shows the laboratory data before Peg-IFNα-2a was administered. The AST and ALT levels were within the normal range, HBV DNA was undetectable, and the HBsAg concentration was 851.2 UI/mL. A liver biopsy was performed before the first Peg-IFNα-2a treatment. The histopathological findings of liver tissue were equivalent to A1F1, according to the New Inuyama classification (12) (Fig. 1). HBV-DNA remained undetectable while NUCs were administered, but seroclearance of HBsAg was not achieved. We informed the patient of the effectiveness of Peg-IFN therapy for seroclearance of HBsAg to reduce the chance of carcinogenesis and explained the potential adverse effects of treatment. The patient then granted his consent for further treatment.

From the start of this modified treatment (Peg-IFNα-2a once weekly for 48 weeks), the HBsAg concentration was markedly reduced from 851.2 IU/mL to 5.64 IU/mL. The ALT levels, which had been mildly elevated during IFN administration, returned to normal upon completion of Peg-IFNα-2a treatment. No serious side effects were observed during treatment.

The HBsAg levels were not elevated during the resting period (Fig. 2). When HBV-DNA or HBsAg is low, HBsAg clearance by IFN can be expected (13). We therefore administered Peg-IFNα-2a biweekly for 24 weeks. HBsAg was subsequently undetectable, and interestingly, anti-HBs antibodies (HBsAbs) were detected 28 months after the start of treatment. When we simultaneously discontinued the administration of NUCs and Peg-IFNα-2a, HBsAg and HBV-DNA were undetectable, and anti-HBsAb was still positive (Fig. 2). Hyaluronic acid levels decreased after treatment, and other fibrotic markers were undetectable at the end of

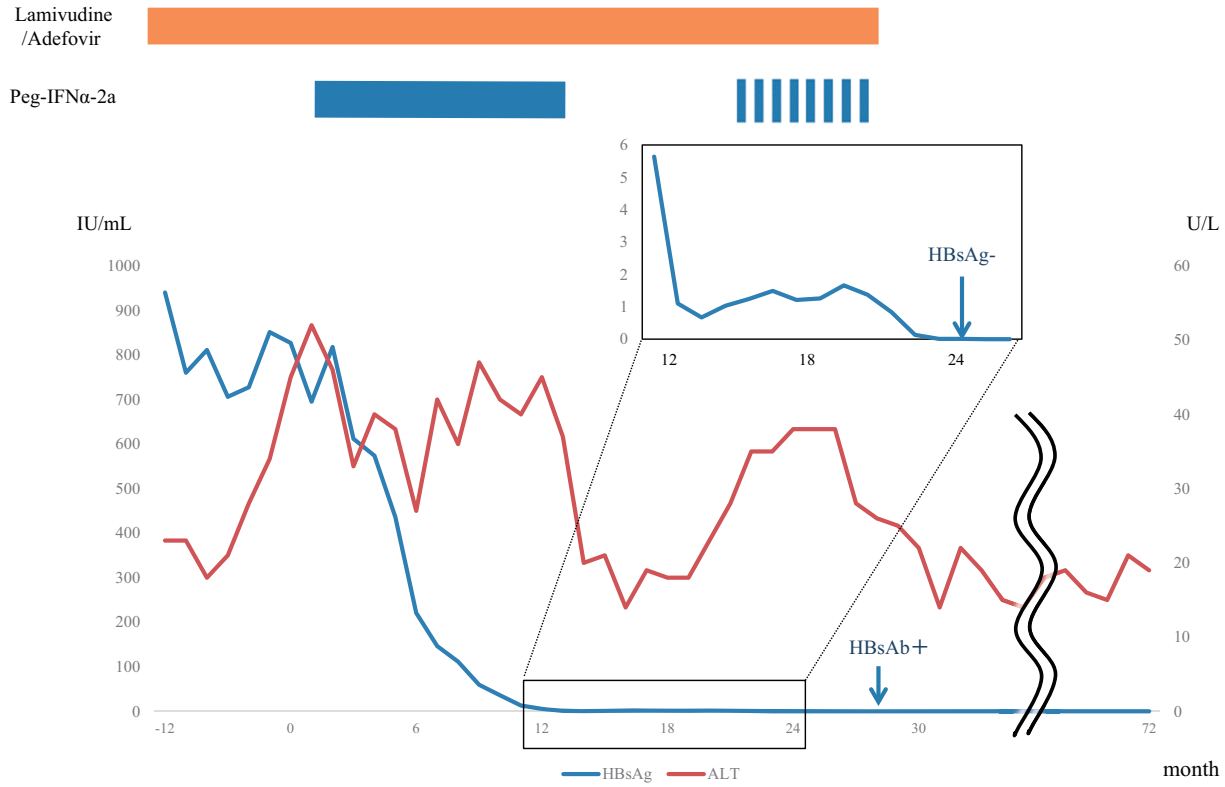

Figure 2. **The patient with chronic hepatitis B infection has been treated with the nucleic acid analogs (NUCs) lamivudine and adefovir since 2000. Although the HBV-DNA levels were undetectable, the test for HBs antigen (HBsAg) was positive. Peg-interferon (IFN) administered once weekly for 48 weeks together with the NUCs reduced the levels of HBsAg from 851.2 to 5.64 IU/mL. Although the HBsAg levels were not reduced during the resting period, resuming biweekly treatment with Peg-IFNα-2a biweekly reduced the levels of HBsAg below the limit of detection, and tests for anti-HBsAbs were positive. Upon completion of Peg-IFNα-2a therapy, the ALT levels normalized.**

treatment. HBe antigen and antibody were unexpectedly undetectable before and after treatment (Table 2).

When this manuscript was submitted, the patient's AST and ALT levels were within normal limits.

Discussion

NUCs are frequently administered to patients with chronic HBV infection to prevent the induction of HCC and the progression of liver fibrosis. However, few cases (0.6-8%) become HBsAg-negative, even after long-term administration of NUCs (9). The incidence of HCC is significantly decreased in patients with undetectable levels of HBsAg. Furthermore, low levels of detected HBsAg at treatment initiation are associated with an increased frequency of a subsequent response (14). When the HBsAg level is low after IFN therapy, it may be possible to consider readministering IFN while paying attention to the adverse as well as therapeutic effects.

The present patient was first treated with NUCs and then subsequently and simultaneously treated with Peg-IFN, which resulted in significant seroclearance of HBsAg. Notably, anti-HBsAbs were detected subsequent to the seroclearance of HBsAg. This finding indicates that, although infrequent (9), Peg-IFN contributes to an immune response against HBV.

We previously reported that reduced serum levels of miR-6126 are associated with a sustained reduction of HBsAg at 48 weeks after the initiation of Peg-IFN therapy (15). MiR-6126 may therefore serve as a marker for selecting patients likely to respond to Peg-IFN therapy, which may reduce the levels of HBsAg (15). However, the present patient exhibited a low miR-6126 signal, similar to the findings in non-responders (15). Although the reason for this is unclear, we hypothesized that it was due to the administration of lamivudine and adefovir. Nucleoside analogs (lamivudine or entecavir) differ from nucleotide analogs (adefovir or tenofovir) in that their mechanism of antiviral activity involves the induction of IFN-λ3 expression (16). However, the potential association with miR-6126 levels requires further study.

Although the present case is rare, our findings suggest that NUCs may be discontinued when Peg-IFN contributes to a reduction in HBsAg levels, which will improve treatment outcomes and thus reduce costs.

The authors state that they have no Conflict of Interest (COI).

Table 2. Laboratory Data for the Patient after Administering Peg-IFNα-2a.

Variable	Value	Unit	Reference
TP	6.8	g/dL	6.5-8.2
Alb	4.4	g/dL	3.5-5.5
A/G	1.83		1-1.8
BUN	17.3	mg/dL	7-20
Cr	0.72	mg/dL	0.5-1
T-bil	0.8	mg/dL	0.1-1.2
D-bil	0.2	mg/dL	0.1-0.6
AST	21	U/L	10-35
ALT	22	U/L	5-40
ALP	219	U/L	100-340
LDH	201	U/L	110-220
γ-GTP	19	U/L	0-30
Na	142	mmol/L	135-146
K	4.1	mmol/L	3.5-4.6
Cl	110	mmol/L	96-110
WBC	5,190	/μL	4,700-8,700
RBC	419×10^4	/μL	370-490
Hb	14	g/dL	11-15
Ht	40.9	%	35-45
Plt	14.7×10^4	/μL	15-35
Neut	53.2	%	38-71.9
Eos	1.7	%	0.2-6.8
Baso	0.6	%	0-1
Lym	39.7	%	26-46.6
Mono	4.8	%	2.3-7.7
PT	100	%	80-100
HBV-DNA	-	LIU/mL	-
HBs Antigen	-	IU/mL	0-0.05
HBs Antibody	49	mIU/mL	0-10
HBe Antigen	-	ng/mL	-
HBe Antibody	-		-
HBcr Antigen	3.1	logU/mL	0-3
AFP	2	ng/mL	
DCP	16	mAU/mL	
M2BPGi	-		-
7S domain of type IV collagen	3.7	ng/mL	0-6
Hyaluronic acid	30.9	ng/mL	0-50

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