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

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Abstract:
We treated a 51-year-old Japanese man with chronic hepatitis B (viral load 7.6 LC/mL, genotype C). HBV 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 Peg-IFNα-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...
Table 1. Laboratory Data before Administering Peg-IFNa-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       |         | 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 | 85.1 U/μL|        | 0.05      |
| HBs Antibody | - mIU/mL|        | 0-10      |
| HBe Antigen | - ng/mL |          | -         |
| HBe Antibody | -       |          | -         |
| HBcAntigen  | 4.2 Log U/μL|    | 0-3       |
| AFP         | 5 ng/mL |          | -         |
| DCP         | 17 mAU/μL|         | -         |
| Hyaluronic acid | 87.8 ng/mL|      | 0-50      |

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

We herein report a case of HBsAg seroclearance induced by supplemental Peg-IFNa-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-IFNa-2a to the NUCs (lamivudine and adefovir).

Table 1 shows the laboratory data before Peg-IFNa-2a was administered. The AST and ALT levels were within the normal range, HBV DNA was undetectable, and the HBsAg concentration was 851.2 IU/mL. A liver biopsy was performed before the first Peg-IFNa-2a treatment. The histopathological findings of liver tissue were equivalent to A1F1, according to the New Inuyama classification.

From the start of this modified treatment (Peg-IFNa-2a therapy). 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 was low, HBsAg clearance by IFN can be expected (13). We therefore administered Peg-IFNa-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-IFNa-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 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.
The present patient was first treated with NUCs and then subsequently and simultaneously treated with Peg-IFNα-2a. HBe antigen and antibody were unexpectedly undetectable before and after treatment (Table 2). We previously reported that reduced serum levels of miR-6126 are associated with a sustained reduction of HBsAg at 61 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).
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