Case Report: Both Mother and Child With Chronic HBV Infection Were Clinically Cured After PEG-IFN Treatment

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Abstract

Background Interferon is significant for chronic hepatitis B patients to get ideal treatment endpoint—functional cure, and is widely used as a first line therapy.

Case presentation We reported two cases of consanguineous patients with chronic hepatitis B. Case 1 was a 36-year-old woman with chronic hepatitis B for 13 years. Case 2 and case 1 were mother-child relationship. At the age of 2, HBsAg and HBeAg of case 2 were found to be positive during physical examination, and they received antiviral therapy together. Both mother and child were treated with Peginterferon (PEG-IFN). Based on antiviral therapy, through prolonged interferon therapy or combined with oral medication of individualized treatment, they both achieved clinical cure.

Conclusion The outcome of the two patients suggests not only the significance of individualized antiviral therapy but also a high correlation between the response to interferon antiviral therapy and genetic background.

Background

Nowadays, there are about 257 million chronic hepatitis B patients worldwide^[1]. Antiviral therapy is the fundamental treatment, which can significantly reduce the incidence of liver cirrhosis and liver cancer^[2]. Peginterferon is one of the first-line treatment drugs. Compared with nucleoside analogs, interferon has antiviral and immunomodulatory effects. However, the response and immune status of different patients varies, so it is necessary to treat different patients individually. At the same time, the efficacy of interferon is affected by genetic factors and many other factors. Some patients do not respond well to interferon, and it is necessary to screen advantage patients. We have reported two cases, which have some enlightenment for the research of individualized interferon therapy and genetic background.

Case Report

Patient 1, female, 36 years old. Hepatitis B virus surface antigen was found positive in 2009. For further diagnosis and treatment, she was admitted to Beijing Ditan Hospital Affiliated to Capital Medical University on August 4, 2010. The results showed that HBsAg, HBeAg and HBV DNA were 5742.92 IU/ml, 3.34 S/CO and 5.30x10³ IU/ml, respectively. Alanine aminotransferase (ALT) 42.0U/L, Aspartate aminotransferase (AST) 47.2U/L, total bilirubin(TBIL)11.8umol/L, direct bilirubin (DBil) 1.8umol/L, gamma-glutamylase (GGT) 30.5U/L, Cholinesterase (CHE) 11126U/L. Creatinine (CR) 51.3umol/L, thyroid hormone 8.22ug/DL. Ultrasound showed that the echo of liver parenchyma was thicker and the thickness of spleen was 38 mm. She was diagnosed as "chronic hepatitis B".

The patient denied the history of trauma, operation and blood transfusion. She had no history of smoking and drinking, no family history of chronic hepatitis B, and denied the history of cancer and heredity. The patient was treated with subcutaneous injection of PEG-IFN α -2a 180 μ g, Qw antiviral therapy in August 2010. After that, the patient was reexamined every 24 weeks. After 72 weeks of treatment, the surface

antigen decreased to 18.71 IU/ml and the e antigen decreased to 3.34 S/CO, HBV DNA level < 20 IU/ml, WBC and PLT decreased slightly during treatment. Continued with 12 weeks of PEG-IFN α -2a treatment, there was no significant decrease in surface antigens, and there was a trend toward an increase. So PEG-IFN α -2a treatment was discontinued for about 12 weeks, and oral entecavir was used to maintain antiviral treatment. After 12 weeks, PEG-IFN α -2a was added and joint with entecavir. After 24 weeks of joint therapy, the surface antigen was reduced to 0.02 IU/ml, e antigen was 0.62 S/CO, and HBV DNA was undetectable. After reaching the clinical cure level, we continued a 24-week consolidation treatment, then the drug was stopped. Regular follow-up was made after that. By June 2021, the surface antigen remained negative, HBV DNA could not be detected, and no hepatitis recurrence was found.

Patient 2, male, 14 years old, had a mother-child relationship with patient 1. In 2012, he was found positive in surface antigen at the same time with his mother. The results were as follows: surface antigen 4742.22 IU/ml, e antigen 149.25 S/CO, e antibody 23.76 S/CO, HBV DNA 5.25×10^5 , ALT 110.2 U/L, AST 114.5 U/L, TBil 6.3 μ mol/L and DBil 2.6 μ mol/L, GGT 45.7 U/L, CHE 10612 U/L, CR 55.7 μ mol/L and thyroid hormone 7.70 UG/DL.

The patient regularly vaccinated with hepatitis B vaccine after birth, so was considered to be vertical transmission from mother to child. After birth, he denied the history of hepatitis and other infectious diseases, trauma and blood transfusion. At the age of 5 years, the patient was treated with subcutaneous injection of PEG-IFN α -2a 135 μ g, Qw antiviral therapy. After 36 weeks of treatment, HBV DNA decreased from 5.25×10^5 to 5.30×10^2 , but had not yet reached negative, so oral entecavir was added. After 48 weeks of treatment, HBV DNA turned negative; after 72 weeks of continuous treatment, e antigen turned negative and reached 0.33 S/CO; after 439 weeks, the surface antigen was negative (0.03 IU/ml). Consolidation continued after about 24 weeks then stopped. By June 2021, the surface antigen remained negative, HBV DNA could not be detected, and no hepatitis recurrence was found.

Discussion & Conclusion

Immune and HBV factors determine the progression and outcome of host liver disease^[3]. Immune cells and cytokines play an important role in the pathogenesis and recovery of chronic HBV infection. In addition, age, gender, compliance will also affect the antiviral response. In this group of case reports, two patients were treated with interferon, and both achieved clinical cure. Both patients were compliant, young, and fit the profile of a good response from existing antiviral efficacy prediction models. Previous studies have shown that human genetic background plays an important role in the disease progression of HBV infection, such as signal transducer and activator of transcription 4 (STAT4) gene polymorphism and other. Some studies have found that there are multiple single nucleotide polymorphisms in human leukocyte antigen (HLA), such as rs9277535, rs7453920 and so on, which are related to the clearance of HBV infection. Genetic background factors play an important role in the onset, progression and outcome of chronic hepatitis B. The response to antiviral therapy in chronic hepatitis B is influenced by many factors such as drug, virus and host. Interferon (IFN) and nucleotide analogues (NA) are the first line drugs for chronic hepatitis B (CHB). In this report, two patients were treated with interferon sequence

therapy and achieved clinical cure. HBV genotyping, viral load and so on are the viral factors that affect the response. HBV DNA load is an indicator of viral replication and infection, and also an independent risk factor for predicting the development of cirrhosis and Hepatocellular Carcinoma (HCC) [4, 5]. At the same time, the patients with lower baseline HBsAg level or earlier decrease of HBsAg were more likely to have HBV DNA negative and HBeAg seroconversion, and then achieved clinical cure. The two patients were HBeAg positive in the early stage of the disease, and after antiviral treatment, they were significantly improved. The two cases reported in this paper were treated with different drugs and had different baseline viral load, but they both achieved ideal antiviral effect. The close relationship between the two patients suggests that host genetic background factors also play an important role in their antiviral response. Genetic testing and other means can be considered for further research and exploration.

In the antiviral treatment of chronic hepatitis B, IFN α can inhibit the replication of virus, decrease the level of serum HBV DNA, HBsAg and HBeAg, and stimulate the specific and non-specific immune response of the body to eliminate the liver cells infected by HBV. In our analysis of ALT, cytokines and antiviral related indicators, HBV DNA, HBsAg and HBeAg levels were found to be associated with elevated ALT [6]. It is suggested that the decrease of HBV DNA, HBeAg and HBsAg levels in patients with chronic hepatitis B during interferon therapy is mainly due to interferon-mediated killing of infected hepatocytes, and the effect of interferon is related to the increase of ALT. In this case, both patients had elevated transaminases before achieving a functional cure. We think that the increase of transaminase level can be used as a indicator of better interferon effect.

In addition, patient 1 had a significant response to interferon antiviral therapy in the first 24 weeks of treatment, but a stagnation of surface antigen decline occurred subsequently. Based on previous studies, interferon can consume CD8 + T cells to affect the efficacy [7], and also failed to work due to the depletion of interferon receptor. Therefore, on the basis of our findings and our clinical experience, we discontinued interferon for 12 weeks and treated the patients with nucleoside analogues only. After recovery of T cell nuclear interferon receptor after 12 week, the combination of interferon and nucleoside analogues was continued and the patient achieved a functional cure. Patient 2 was treated with interferon alone for a period of time, but antiviral effect did not meet expectations. After adding entecavir for combination therapy, the effect was better, which was in line with the team's previous research results: compared with monotherapy, interferon combined with nucleoside analogues had better effect [8]. Our study also shows that in patients treated with nucleoside analogues for viral suppression, a higher rate of surface antigen disappearance can be achieved by combination therapy with interferon [8]. Because of the research which highlighted the importance of extension treatment to the maintenance of HBsAg vanishing in CHB patients [9, 10], we extended the treatment for another 24 weeks after the patient had achieved the disappearance of the surface antigen, in order to better maintain the state of functional healing.

In this case report, the two patients were both treated with interferon therapy, but the choices of method were different. They got functional cure through intermittent treatment and combination therapy

respectively. This suggests that we should choose an individualized treatment plan according to different patients.

Abbreviation

PEG-IFN, Peginterferon; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, total bilirubin; DBil, direct bilirubin; GGT, gamma-glutamyltransferase; CHE, Cholinesterase; CR, Creatinine; STAT4, signal transducer and activator of transcription 4; HLA, leukocyte antigen; IFN, Interferon; NA nucleotide analogues; CHB, chronic hepatitis B; HCC, Hepatocellular Carcinoma

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of Beijing Ditan Hospital. Written informed consent was obtained from all patients.

Consent to publication

Informed consent was obtained from all patients included in the study

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there are no conflicts of interest.

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Authors' contributions

M-HL and YX contributed to the study design. X-YB and ZZ contributed to follow up with the patient. F-FS, Y-JL and LY contributed to data collection. X-YB wrote the first draft of the manuscript. M-HL and YX revised the manuscript and are the guarantors of the article. All authors approved the final version of the manuscript.

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Figures

Figure 1

Changes of HBsAg, HBeAg, ALT, and HBV DNA during antiviral treatment of Patient 1

Figure 2

Changes of HBsAg, HBeAg, ALT, and HBV DNA during antiviral treatment of Patient 2