

論 文 内 容 要 旨

Reduction of hepatitis B surface antigen in sequential versus add-on pegylated-interferon to nucleoside/nucleotide analogue therapy in HBe-antigen-negative chronic hepatitis B patients: a pilot study

(HBe 抗原陰性 B 型慢性肝炎に対するペグインターフェロン・核酸アナログのシークエンシャル療法・アドオン療法における HBs 抗原の低下に関する検討)

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Background: Hepatitis B virus (HBV) infection is a serious global health problem. A lot of people are infected with HBV, and chronically infected individuals often come down with chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Though complete elimination of the virus is difficult, patients are generally treated with interferon or nucleot(s)ide analogue (NA) to suppress viral replication and prevent the progression of liver diseases. On that account Japanese guidelines recommend that the final goal of antiviral therapy should be serum hepatitis B surface antigen (HBsAg) loss but it is difficult to achieve that by long-term treatment with NAs. Recently pegylated-interferon (Peg-IFN) and NAs combination therapy is considered as an option for accelerating HBsAg reduction. However the best approach of Peg-IFN treatment for chronic hepatitis B patients during long term NA therapy has yet to be determined.

Methods: Twenty-one HBe antigen-negative chronic hepatitis B patients whose HBV DNA were suppressed to undetectable levels by NA therapy, and have no evidence of other liver diseases and another viruses infection were administrated Peg-IFNa2a. Sequential therapy, which induced 48weeks of Peg-IFNa2A therapy (180µg/week) beginning one month prior to discontinuation of NA therapy until 11 months after, were underwent for 10 patients, and add-on therapy which induced 48weeks of Peg-IFNa2A that overlapped with NA for 11 patients. Factors associated with HBsAg reduction by Peg-IFN therapy were analyzed.

Results: During Peg-IFN treatment, no patient needed Peg-IFN dose reduction due to side effects. There was no significant difference among clinical factors at the beginning of Peg-IFN therapy between patients treated with sequential therapy and those treated with add-on therapy. During Peg-IFN treatment HBsAg levels were reduced by 0.48 Log IU/ml. More than 1 LogIU/ml of HBsAg reduction was observed in 8 patients (sequential therapy: 6, add-on therapy: 2), and one patient with sequential therapy achieved complete loss of HBsAg. By univariate analysis, sequential therapy was marginally associated with more than 1 LogIU/ml HBsAg reduction during Peg-IFN treatment (P=0.063). Duration of NA treatment, HBsAg, HB core related antigen (HBcrAg), and HBV DNA levels at the beginning of Peg-IFN treatment were not significant. In addition 5 patients (sequential therapy: 5, add-on therapy: 0), including the patient got HBsAg loss, achieved more than 0.5 LogIU/ml of HBsAg reduction by 1 year after Peg-IFN treatment. By univariate analysis, only sequential therapy was significantly associated with HBsAg reduction after Peg-IFN

treatment (P=0.012). ALT and HBsAg levels at the beginning of Peg-IFN therapy were marginally associated with that (P=0.050, P=0.062, respectively). As recently we proposed that upregulation of IL-8 in hepatocyte induced by HBV infection might lead to suppression of interferon responsiveness, we predicted that serum IL-8 levels might be associated with the antiviral effect of Peg-IFN. So we measured serum IL-8 at the beginning and the end of Peg-IFN therapy. Then lower serum IL-8 level at the end of Peg-IFN treatment were significantly associated with HBsAg reduction by 1 year after Peg-IFN treatment (P=0.044). In addition observing the time course of ALT during Peg-IFN therapy, HBsAg reduction levels from the beginning of Peg-IFN therapy to 1 year after the therapy were significantly correlated with the maximum ALT levels during Peg-IFN therapy (P=0.002). In patients whose ALT levels elevates more than 50 U/L during Peg-IFN therapy HBsAg levels were reduced significantly more in 1 year after Peg-IFN therapy than that in patients without ALT elevation (P=0.038). There was no significant association between serum IL-8 at the beginning and end of Peg-IFN therapy and ALT elevation during Peg-IFN therapy (P=0.533, P=0.203, respectively).

Discussion: Marcellin et al. showed the superiority of TDF and Peg-IFN α 2A combination therapy than their monotherapy for inducing HBsAg loss of chronic hepatitis B patients with no history of NA treatment in their study. However it is unclear whether add-on therapy is superior to sequential therapy for HBsAg reduction. In our study sequential therapy brought the reduction of HBsAg not only during the Peg-IFN treatment but also 1 year after the treatment, whereas HBsAg levels in most patients who were treated with add-on therapy were not reduced drastically. We hypothesized that host immune responses might be activated by the cessation of NA therapy and activated immuno response could help bolster the antiviral effects of Peg-IFN leading to reduction of HBsAg. ALT elevation during Peg-IFN therapy and lower IL-8 level at the end of Peg-IFN therapy may support the idea. Although the number of study subjects was small, our results support the need for establishing strategies for inducing HBsAg loss in chronic hepatitis B patients.

(744 words)