Peginterferon Is Superior to Nucleos(t)ide Analogues for Prevention of Hepatocellular Carcinoma in Chronic Hepatitis B

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Abstract

Background. Clinical factors associated with hepatocellular carcinoma (HCC) have been extensively studied in antiviral treatment-naive patients with chronic hepatitis B virus (HBV) infection but not in treatment-experienced patients. Owing to the wide availability of antiviral agents that effectively suppress HBV replication, we investigated HCC risk factors in treatment-experienced patients.

Methods. In a cohort of 330 patients who underwent pretherapeutic liver biopsy, we analyzed the HCC incidence in relationship to clinical parameters. Ultra-deep sequencing of the viral genome was performed on 11 entecavir-treated and pegylated interferon (peginterferon)–treated patients.

Results. Initial univariate/multivariate explorations indicated that cirrhosis and antiviral treatment were independently associated with HCC occurrence. The peginterferon–treated patients had a lower HCC incidence than the nucleos(t)ide analogue–treated patients (P = .011). The peginterferon and entecavir monotherapy groups also differed in HCC incidence (P = .018). Results of analysis of baseline-matched subgroups concurred with cohort analysis (P = .009 for comparison of peginterferon-experienced vs nucleotide analogue–treated patients; P = .022 for comparison of peginterferon- vs entecavir-treated patients). Viral loads of entecavir–treated patients were constantly suppressed to levels lower than those of peginterferon–treated patients (P < .001). Oncogenic surface antigen truncation mutations were detected in entecavir–treated patients with HCC but not in peginterferon–treated patients (P = .015).

Conclusions. Treatment by peginterferon was associated with a lower HCC incidence than nucleos(t)ide-analogue treatment in chronic HBV infection.

Keywords. cohort analysis; pretreatment histology; HBV mutations; ultra-deep sequencing.

The chronic hepatitis B virus (HBV) pandemic affects 350 million patients globally [1]. Life-threatening sequelae such as liver failure and hepatocellular carcinoma (HCC) may develop after decades of uncontrolled hepatitis [2–4]. Interferon and nucleos(t)ide analogues (Nucs) are 2 approved classes of medication with distinct therapeutic rationales. The former modulates the human immune system to restrain viral replication, while the latter directly inhibits viral reverse transcriptase to interrupt the viral life cycle. Both treatments have been shown to reduce viral DNA levels and ameliorate hepatitis activities effectively [5]. They can also reduce the incidence of HCC, as shown in a randomized controlled trial of lamivudine [6], in a longitudinal retrospective study of interferon–treated subjects [7], in patients with compensated liver cirrhosis [8,9], and in subjects receiving interferon prophylaxis after HCC curative therapy [10].

The above evidence pertained to conventional interferon or lamivudine, 2 pioneering drugs of their own classes, which were benchmarked in the initial era of chronic hepatitis B treatments. Following the success of these regimens, antiviral therapies continued to improve alongside the accumulation of real-life clinical experience. Pegylated interferons (peginterferons) have gradually replaced conventional interferons, offering more-sustained effects per each treatment injection [11, 12]. New Nucs, including adefovir, entecavir [13], telbivudine [14–16], and tenofovir [17], have also been approved, showing various degrees of antiviral efficacies, resistance barriers, and effectiveness in HCC preventions [18–20]. Entecavir has been demonstrated to defer HCC occurrence significantly in one study (P = .030) [21] but only marginally in another study (P = .049 for patients with cirrhosis) [22]. When compared with lamivudine, entecavir did not demonstrate a significantly stronger preventive effect [23]. Despite the successful suppression of viral levels, HCC can still occur in a substantial proportion of cirrhotic patients after oral antiviral therapy [18–27]. A recent study from Taiwan also showed that the 5-year cumulative incidence of HCC in cirrhotic patients treated with Nucs was 24.1% [27].

Clinical factors associated with HCC risks in patients with untreated chronic hepatitis B have been extensively studied. However, the clinical usefulness of these data is greatly limited,
owing to the wide availability of effective antiviral treatments. On the other hand, HCC risk factors in treatment-experienced patients have rarely been examined. To address this issue, we set out to investigate clinical factors associated with HCC development in a cohort of patients in whom liver biopsy specimens were collected as part of the pretherapeutic assessment. Intriguingly, initial analysis revealed that patients who received peginterferon treatment had a lower risk of HCC, compared with those who had received only nucleos(t)ide analogues. We carefully examined this factor by comparing the cumulative incidence and assessing viral mutations by ultra-deep sequencing in patients who were treated with these 2 distinct strategies.

**PATIENTS AND METHODS**

**Patients**
Under the approval of the Institutional Review Board, Chang Gung Memorial Hospital, Taiwan, we reviewed a cohort of 372 patients with chronic hepatitis B and without HCC who underwent liver biopsy as part of pretreatment evaluations between 2007 and 2009. Patients who did not receive antiviral treatments because of clinician judgments were excluded from further analysis. The remaining 330 treatment-experienced patients formed the main study cohort (Figure 1). All participants gave written informed consent. Baseline pretreatment evaluations included collection of data on age, sex, liver cirrhosis, and histology activity indexes [28] and measurement of the HBV DNA level, detection of HBV e antigen (HBeAg), quantitation of the HBV surface antigen (HBsAg) level, and measurement of the alanine transaminase (ALT) level, aspartate transaminase (AST) level, bilirubin level, albumin level, gamma-glutamyl transferase level, platelet count, and hemoglobin level. All data were assessed in a College of American Pathologists–accredited laboratory. HBV DNA load was assessed using the COBAS TaqMan HBV test (Roche Molecular Systems, Branchburg, New Jersey). Quantitation of the HBsAg level was assessed using the Elecsys HBsAg II assay (Roche Diagnostics, Indianapolis, Indiana). Diagnosis of HCC was made by liver biopsy or aspiration cytology; if clinical conditions did not allow tissue-based diagnosis, detection of HCC by dynamic computed tomography and by angiography in patients with an alpha-fetoprotein level of >200 ng/mL were used as diagnostic criteria [29, 30]. Patients were followed up for 5 years after the pretreatment biopsy. Losses to follow-up were considered as right-censored data in the survival analysis.

**Antiviral Treatments**
Patients treated with peginterferon alfa-2a (Pegasys, Roche) were considered peginterferon experienced (n = 153), including those treated with peginterferon monotherapy (n = 71) and those also treated with Nucs before, during, or after the peginterferon therapy (n = 82). In HBeAg-positive patients, peginterferon was given for at least 6 months, and in HBeAg-negative patients, peginterferon was given for at least 1 year.

Figure 1. Flowchart of patient stratifications in this study. Study 1 compared pegylated interferon (peginterferon)–experienced and nucleos(t)ide analogue (Nuc)–treated patients. Study 2 compared patients receiving peginterferon monotherapy and patients receiving entecavir monotherapy. Abbreviation: HBV, hepatitis B virus.
RESULTS

Treatment Type and Cirrhosis Were Identified as Independent Factors Associated With HCC Hazards

The study cohort comprised 330 patients with chronic hepatitis B who received antiviral treatments after pretreatment evaluations, including liver biopsy (Figure 1). Baseline characteristics are listed in Table 1. Cirrhosis was diagnosed in 100 patients at baseline (Table 1). The first HCC event occurred 180 days after the biopsy.

An initial univariate analysis revealed that baseline cirrhosis and platelet counts were significantly associated with the hazard of HCC (Table 2). Intriguingly, peginterferon-experienced patients had a lower hazard of HCC than Nuc-treated patients (Table 2). HBV DNA level, ALT level, and other baseline histological activity indexes, nevertheless, showed no such association. In the multivariate analysis, treatment types and cirrhosis remained significantly associated, while platelet count was not (Table 2). This suggested that treatment type and cirrhosis were 2 independent factors associated with HCC.

We then focused on the cumulative HCC incidence with respect to treatment type. Peginterferon-experienced patients had...
| Parameter | Patients, No. | HCC Cases, No. | Mean Days to HCC* | HR (95% CI) | P Value | aHR (95% CI) | P Value |
|-----------|--------------|----------------|-------------------|-------------|---------|-------------|---------|
| Age, y    |              |                |                   |             |         |             |         |
| <46       | 163          | 2              | 1080.50           | . .         | . .     | .           | . .     |
| ≥46       | 167          | 9              | 915.89            | 4.51 (.974–20.872) | .054    |             |         |
| Sex       |              |                |                   |             |         |             |         |
| Female    | 51           | 1              | 276.00            | . .         | . .     | .           | . .     |
| Male      | 279          | 10             | 1012.80           | 1.866 (.239–14.578) | .552    |             |         |
| Cirrhosis |              |                |                   |             |         |             |         |
| No        | 230          | 3              | 762.67            | . .         | . .     | .           | . .     |
| Yes       | 100          | 8              | 1014.50           | 6.485 (1.72–24.446) | .006    | 4.677 (1.200–18.223) | .026    |
| Ishak histology activity index |                |                |                   |             |         |             |         |
| Piecemeal necrosis score | 258 | 6 | 884.50 | . . | . . | . | . . |
| >1 | 72 | 5 | 1019.40 | 2.918 (.891–9.561) | .077    |             |         |
| Confluent necrosis score | 305 | 10 | 923.50 | . . | . . | . | . . |
| >0 | 25 | 1 | 1169.00 | 1.154 (.148–9.015) | .891    |             |         |
| Focal (spotty) lytic necrosis, apoptosis, and focal inflammation score | 260 | 9 | 856.67 | . . | . . | . | . . |
| >2 | 70 | 2 | 1347.00 | 0.808 (.179–3.739) | .785    |             |         |
| Portal inflammation score | 180 | 3 | 897.00 | . . | . . | . | . . |
| >2 | 150 | 8 | 964.13 | 3.104 (.823–11.7) | .094    |             |         |
| HBV DNA load, log10 IU/mL | 164 | 6 | 695.27 | . . | . . | . | . . |
| <6.5 | 166 | 5 | 1246.00 | 0.795 (.243–2.605) | .705    |             |         |
| HBeAg test result | 123 | 3 | 735.00 | . . | . . | . | . . |
| Negative | 125 | 3 | 1249.33 | 0.007 (0.0–4.898) | .331    |             |         |
| Positive | 165 | 3 | 771.00 | 0.38 (.101–1.433) | .153    |             |         |
| HBsAg level, x1000 IU/mL | 164 | 6 | 920.33 | . . | . . | . | . . |
| <2.1 | 165 | 3 | 976.40 | 0.836 (.255–2.74) | .768    |             |         |
| ≥2.1 | 166 | 7 | 1200.75 | 0.556 (.163–1.9) | .349    |             |         |
| ALT level, IU/L | 164 | 6 | 800.14 | . . | . . | . | . . |
| <117 | 165 | 4 | 771.00 | 0.38 (.101–1.433) | .153    |             |         |
| AST level, IU/L | 164 | 6 | 920.33 | . . | . . | . | . . |
| <68.4 | 164 | 5 | 976.40 | 0.836 (.255–2.74) | .768    |             |         |
| Bilirubin level, mg/dL | 133 | 2 | 1379.50 | . . | . . | . | . . |
| <0.9 | 186 | 8 | 764.25 | 2.884 (.612–13.582) | .18     |             |         |
| ≥0.9 | 70 | 3 | 717.33 | . . | . . | . | . . |
| Albumin level, g/dL | 76 | 2 | 727.00 | 0.592 (.099–3.545) | .566    |             |         |
| <4.6 | 83 | 5 | 721.20 | . . | . . | . | . . |
| ≥4.6 | 84 | 2 | 641.50 | 0.389 (.075–2.003) | .259    |             |         |
| GGT level, IU/L | 164 | 9 | 966.00 | . . | . . | . | . . |
| <185 | 166 | 2 | 855.00 | 0.214 (.046–991) | .049    | 0.356 (.074–1.713) | .198    |
| ≥185 | 120 | 4 | 885.25 | . . | . . | . | . . |
| Hemoglobin level, g/dL | 123 | 3 | 1042.33 | 0.732 (.164–3.27) | .683    |             |         |
| <15.3 | 177 | 10 | 923.50 | . . | . . | . | . . |
| ≥15.3 | 153 | 1 | 1169.00 | 0.111 (.014–866) | .036    | 0.126 (.016–987) | .049    |

Abbreviations: aHR, adjusted hazard ratio; ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; GGT, gamma-glutamyl transferase; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus; HR, hazard ratio; Nuc, nucleos(t)ide analogue; peginterferon, pegylated interferon.

* Calculated using subjects with HCC.
a lower cumulative incidence than Nuc-treated patients ($P = .011$; Figure 2A). Since cirrhosis was also an independent factor for HCC, the patients were further stratified by cirrhosis, and the resulting 4 subgroups had a distinct cumulative incidence ($P < .001$; Figure 2B). The highest cumulative incidence was observed in Nuc-treated patients who had cirrhosis backgrounds.

In this study cohort, peginterferon-treated patients might also receive Nuc treatment during the clinical course if hepatitis activities were not under control. Similarly, patients in the Nuc-treated group could be treated with add-on therapies or switched to another Nuc as rescue therapy when virological breakthrough developed. To gain more insight into the beneficial effect of peginterferon in terms of HCC prevention, we compared patients receiving either peginterferon alone (n = 71) or entecavir alone (n = 106), the 2 largest monotherapy groups in this study cohort. Patients treated with entecavir alone include those treated continuously (n = 19; median treatment duration, 1811 days; range, 186–1820 days), those who had sustained viral suppression after the termination of treatment (n = 67; median treatment duration, 1065 days; range, 56–1819 days), and those who stopped treatment, experienced viral relapse, and then received the second entecavir treatment (n = 20; median duration of first treatment, 777.5 days [range, 351–1154 days]; median duration of second treatment, 502 days [range, 152–1393 days]). It was found that patients receiving peginterferon alone showed a lower cumulative incidence, compared with those treated with entecavir alone ($P = .018$; Figure 2C). In fact, no HCC developed in the peginterferon-alone group. The highest cumulative incidence was observed in entecavir-treated patients with baseline cirrhosis (Figure 2D).

Comparison of HCC Incidence With Respect to Treatment Methods in Baseline-Matched Patients

When the cohort was partitioned by treatment method, baseline HBeAg positivity and age were different between the 2 groups (Supplementary Table 1). Hence, we made an additional

**Figure 2.** Cumulative hepatocellular carcinoma (HCC) incidence of antiviral treated subjects. **A**. Comparison between pegylated interferon (peginterferon)–experienced and nucleos(t)ide analogue (NA)–treated patients. **B**. Patients in panel A further stratified by cirrhosis. **C**. Comparison of peginterferon and entecavir (ETV) monotherapy groups. **D**. Patients in panel C further stratified by cirrhosis. $P$ values were calculated by the log-rank test.
comparison in baseline-matched patients. HBeAg positivity was known to correlate with age according to the natural history of HBV [32, 33]. Therefore, we performed an age-matching procedure and selected 120 pairs of age-matched patients whose age difference were <5 years. All clinical factors become statistically insignificant after matching (Supplementary Table 1). Treatment method and cirrhosis remained 2 independent factors of the HCC hazard in baseline-matched patients (Table 3). A lower cumulative HCC incidence was observed in peginterferon-experienced patients than in Nuc-treated patients (P = .009, by the log-rank test; Figure 3A).

In 52 pairs of patients matched on the basis of baseline monotherapy (Supplementary Table 2), a lower cumulative HCC incidence was observed in peginterferon-treated patients than in entecavir-treated patients (P = .022, by the log-rank test; Figure 3B).

HBsAg Truncation Mutations Discovered in Entecavir-Treated Patients by Ultra-Deep Sequencing Methods
We then investigated further to determine the cause of HCC in antiviral treatment–experienced patients. Entecavir was known for its potent viral suppression effects and exceptionally low drug-resistant rates among all Nucs [11]. The average DNA levels dropped from 10 million copies/mL to <1000 copies/mL within the first year in both entecavir-treated and peginterferon-treated patients (Figure 4A). The entecavir-treated group constantly harbored lower HBV DNA levels than the peginterferon-treated group during the observation period (P < .001, by GEE; Figure 4A). The entecavir-treated patients were further partitioned into those who developed and those did not develop HCC during the observational period. The longitudinal HBV DNA levels of these 2 groups showed no significant difference (P = .239, by GEE; Figure 4B).

The viral mutations were then evaluated. We retrospectively retrieved, if available, banked serum samples that, preferably, were collected before the occurrence of HCC. Ultra-deep viral DNA sequencing of the HBV S gene was performed on samples from 5 entecavir-treated HCC patients. Among them, 3 samples were obtained before and 2 obtained after HCC development, owing to availability of banked samples. Samples from 6 peginterferon-treated patients, obtained >1 year after the treatment course, were assayed for comparison. Viral DNA was sequenced with an average depth of 251 912 per each nucleotide base. The high-quality reads (>99% accuracy) have an average depth of 247 074. Surface antigen truncation mutations, such as the oncogenic sW172*, sW182*, and sW196*/rtM204I were detected in 4 of 5 entecavir-treated subjects. No such mutations were detected in the 6 peginterferon-treated patients (P = .015, by the Fisher exact test; Figure 4C).

DISCUSSION
Important predictors for the occurrence of HCC in patients with untreated chronic hepatitis B, including HBV DNA level [34], basal core promoter mutations [35], precore stop codon mutation [36], HBeAg status [34], and genotype [37], and ALT

| Parameter | Subjects, No. | aHR (95% CI) | P Value |
|-----------|---------------|--------------|---------|
| Cirrhosis |               |              |         |
| No        | 175           |              |         |
| Yes       | 65            | 6.96 (1.797–26.961) | .005    |
| Treatment |               |              |         |
| Nuc       | 120           |              |         |
| Peginterferon | 120     | 0.103 (0.013–0.811) | .031    |

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; Nuc, nucleos(t)ide analogue; peginterferon, pegylated interferon.

Figure 3. Cumulative hepatocellular carcinoma (HCC) incidence of baseline-matched patient groups. A, Pegylated interferon (peginterferon)–experienced and nucleos(t)ide analogue–treated patients. B, Peginterferon and entecavir monotherapy groups. P values were calculated by the log-rank test.
level [34], have been reported previously. A risk scale has been developed in patients with untreated nonchronic hepatitis B [34]. However, the clinical usefulness of these data was greatly limited because of the wide availability of effective antiviral therapy. At this time, a great majority of patients with chronic hepatitis B experiencing moderate-to-severe hepatitis-related symptoms received antiviral therapy. Conceivably, the therapeutic factors could strongly affect the predictive value of the clinical and virological factors for HCC development. In this treatment-experienced cohort, HBV DNA and ALT levels were no longer effective predictors. Instead, cirrhosis, platelet count, and treatment method were associated with HCC occurrence in the univariate analysis. A lower platelet count was known to be associated with liver cirrhosis [38]. As such, when a multivariate analysis was performed on the 3 significant variables, the platelet count was no longer an independent factor.

The most interesting finding of our initial exploration was that treatment method (peginterferon vs Nuc) was associated with the hazard for HCC. We then focused on the comparison of these 2 treatment methods, because we believed this could be a very important finding that had never been carefully examined before. In Taiwan, older patients are less likely to be treated with peginterferon because of intolerance of side effects. To compare treatment effects in patients with similar baseline characteristics, we performed an age-matched study. It was not surprising to find that all clinical variables were similar between the 2 treatment groups after age matching (Supplementary Tables 1 and 2). As such, the prognosis could be fairly compared. The result showed that patients in the peginterferon-experienced group had a significantly lower cumulative incidence of HCC.

In this study cohort, the 2 largest monotherapy groups were entecavir- and peginterferon-treated patients. Therefore, we further compared the effects of monotherapy in these 2 groups. It was discovered that the peginterferon-monotherapy subgroup also showed a lower HCC incidence, compared with the entecavir-monotherapy subgroup. An examination of data obtained during receipt of treatment showed that viral DNA levels of patients treated with entecavir alone were constantly kept lower than those treated with peginterferon alone, disproving the prevailing concept implicated in previous HCC risk models that lower viral levels are equated with a lower HCC risk.

Alternatively, ultra-deep sequencing of the HBV surface gene revealed selection pressure on viral mutations, possibly related to

![Figure 4](https://academic.oup.com/jid/article-abstract/213/6/966/2459472/fig4)

**Figure 4.** Hepatitis B virus (HBV) DNA levels and mutations detected in pegylated interferon (peginterferon)– and entecavir-treated patients. A, Longitudinal HBV DNA levels in peginterferon- and entecavir-treated patients (P < .0001, by generalized estimation equations). Vertical bars denote standard deviations. B, Longitudinal HBV DNA levels in entecavir-treated patients with or without hepatocellular carcinoma (HCC). C, Viral surface protein truncation mutations detected in the peripheral blood of 5 entecavir-treated patients by ultra-deep sequencing. The mutation rates were estimated by the ratio of minor base calls to the depth of high-quality calls. For each patient, the highest mutation rate of all the detected mutation sites was presented. No such mutations were found in 6 peginterferon-treated patients. Abbreviation: ETV, entecavir.
drug or immune selection. Known potential oncogenic mutants, including sW196*rtM204I, sW172*, and sW182*/rtV191I [39–41], were detected in entecavir-treated patients (albeit in a small proportion of viral population) but not in peginterferon-treated patients. Proportions of the surface-truncation mutations detected in peripheral blood were in the range of 1%–58% (Figure 4C). Presumably, the truncated surface proteins cause defects in HBV secretion, making the mutated virus highly enriched in hepatocytes but rarely detected in peripheral blood [42].

In the current study cohort, there were patients who were initially treated with entecavir and then had treatment switched to other drugs, including a switch to peginterferon for 6 patients, a switch to tenofovir for 8, a switch to combination entecavir/adefovir for 1, a switch to telbivudine for 2, and a switch to combination telbivudine/adefovir for 2. None of these patients developed HCC during the follow-up period. The data implied that peginterferon might also be considered as one of the rescue therapies when virological breakthrough was identified in Nuc-treated patients.

There has been a long-standing controversy regarding the usefulness of interferon-based anti-HBV therapy in the Chinese population. First, the route of administration (injection) is inconvenient, and the side effects are formidable. Second, after the end of a definite length of treatment, the durability of viral suppression is poor, and virological relapse occurs quite commonly. In contrast, lifelong viral suppression can be achieved by use of either entecavir or tenofovir [43]. Since optimal suppression of HBV DNA is believed to be the key to prevent HCC occurrence, these arguments cast doubts on the protective effect of interferon-based treatment against HCC [43]. The unexpectedly lower HCC incidence among peginterferon-experienced patients in this data set suggests that there are some previously unrecognized beneficial effects of interferon-based treatment, such as those associated with immune modulation.

The lower incidence of HCC in peginterferon-treated patients, compared with that in Nuc-treated patients, was an accidental discovery in a cohort analysis. The convincing nature of this finding was limited by its retrospective nature and sample size. This finding could be confirmed by long-term prognosis analysis in patients enrolled in previous randomized studies comparing therapeutic efficacy between peginterferon and Nucs in chronic hepatitis B.

In summary, in this retrospective study of 330 patients with chronic hepatitis B, peginterferon treatment was associated with a reduced incidence of HCC, compared with Nucs therapy. This finding should be confirmed in a randomized, controlled setting.

**Supplementary Data**

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copublished and are the sole responsibility of the author, so questions or comments should be addressed to the author.

**Notes**

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**Peginterferon Reduces HCC Risk Better Than Nucs • JID 2016:213 (15 March) • 973**
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