Peginterferon Monotherapy versus Peginterferon and Lamivudine Combination Therapy for Chronic Hepatitis B

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Peginterferon Monotherapy versus Peginterferon and Lamivudine Combination Therapy for Chronic Hepatitis B

Abstract
Background: Chronic hepatitis B is a major health problem and may lead to cirrhosis, liver failure, liver cancer, and death if untreated. Interferon is currently better than nucleot(s)ide analogues in sustained seroconversion or loss of HBeAg and HBsAg. Peginterferon prolongs interferon's effects. This review compared benefits and risks of peginterferon monotherapy versus peginterferon with lamivudine therapy in chronic hepatitis B.

Methods: Exhaustive search of medical literature was performed using key words peginterferon, peginterferon alfa-2a, peginterferon alfa-2b, lamivudine, and chronic hepatitis B, on EBMR Multifile, Evidence-Based Resources from the Joanna Briggs Institute, Medline-Ovid, and CINAHL. Qualities of relevant studies were assessed using the GRADE system.

Results: Three randomized controlled trials satisfied inclusion criteria and were included in this review. The first trial compared efficacy and safety between peginterferon alfa-2a alone, with lamivudine and lamivudine alone on 537 patients with HBeAg negative chronic hepatitis B. Regarding the viral suppression and the seroconversion of HBsAg, the groups on peginterferon were better than lamivudine alone; and no significant differences found between the peginterferon alone and the combination group. The second trial used the same three types of therapy groups on 814 patients with HBeAg positive chronic hepatitis B. Results were similar to the first study, plus similar rates of HBeAg loss or seroconversion between the two groups with peginterferon. The third trial used peginterferon alfa-2b alone or with lamivudine on 307 patients with HBeAg positive chronic hepatitis B, but final analysis accounted for 266 patients. Both treatment groups were not significantly different in the rates of responses and safety profile.

Conclusion: Peginterferon alfa-2a or alfa-2b could lead to HBsAg loss or seroconversion and sustained viral suppression in all chronic hepatitis B patients, and HBeAg loss or seroconversion in HBeAg positive patients. Peginterferon alone or with lamivudine showed similar responses and side effects. Peginterferon alfa-2a or alfa-2b were suggested as first line therapy for chronic hepatitis B. Future research is needed to evaluate the long-term responses of chronic hepatitis B to peginterferon alone or with lamivudine, the benefits of combining lamivudine to therapy, and the effects of peginterferon alfa-2b in HBeAg negative chronic hepatitis B patients.

Keywords: peginterferon, peginterferon alfa-2a, peginterferon alfa-2b, lamivudine, chronic hepatitis B.

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Peginterferon Monotherapy versus Peginterferon and Lamivudine Combination Therapy for Chronic Hepatitis B

Thao Van

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
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For the Masters of Science Degree, August 9, 2014.
Faculty Advisor: James Ferguson, PA-C, MS.
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS.
Biography

[Redacted for privacy]
Abstract

Background: Chronic hepatitis B is a major health problem and may lead to cirrhosis, liver failure, liver cancer, and death if untreated. Interferon is currently better than nucleos(t)ide analogues in sustained seroconversion or loss of HBeAg and HBsAg. Peginterferon prolongs interferon’s effects. This review compared benefits and risks of peginterferon monotherapy versus peginterferon with lamivudine therapy in chronic hepatitis B.

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Keywords: peginterferon, peginterferon alfa-2a, peginterferon alfa-2b, lamivudine, chronic hepatitis B.
Acknowledgements

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Table of Contents

Thao Van............................................................................................................................. 1
Biography............................................................................................................................ 2
Abstract ............................................................................................................................... 3
Acknowledgements............................................................................................................. 4
List of Tables ...................................................................................................................... 6
List of Abbreviations .......................................................................................................... 6
BACKGROUND ................................................................................................................ 7
METHODS ......................................................................................................................... 8
RESULTS ........................................................................................................................... 9
DISCUSSION .................................................................................................................... 16
CONCLUSION ................................................................................................................ 18
References ......................................................................................................................... 19

Table I. Characteristics of reviewed studies, GRADE profile, and summary of findings. Peginterferon alone or in combination with lamivudine in chronic hepatitis B treatment. ........................................................................................................................................... 20
List of Tables

Table I: Characteristics of Reviewed Studies, GRADE profile, and Summary of findings. Peginterferon alone or in combination with Lamivudine in Chronic Hepatitis B treatment.

List of Abbreviations

ALT.................................................................................................................................Alanine Aminotransferase
Anti-HBe Ab...........................................................................................................Anti Hepatitis B envelope Antibody
Anti-HBs Ab...........................................................................................................Anti Hepatitis B surface Antibody
CHB..........................................................................................................................Chronic Hepatitis B
CI.............................................................................................................................Confidence Intervals
EBMR....................................................................................................................Evidence-Based Medicine Reviews Multifile
GRADE....................................................................................................................Grading of Recommendations, Assessment, Development and Evaluations
HBV..........................................................................................................................Hepatitis B Virus
HBsAg.....................................................................................................................Hepatitis B surface Antigen
HBeAg....................................................................................................................Hepatitis B envelope Antigen
HCC..........................................................................................................................Hepatocellular Carcinoma
IFN..........................................................................................................................Interferon
LAM..........................................................................................................................Lamivudine
NNT..........................................................................................................................Number Needed to Treat
PegIFN....................................................................................................................Pegylated Interferon
RR............................................................................................................................Risk Ratio or Relative Risk
SQ.............................................................................................................................Subcutaneous injection
WHO.........................................................................................................................World Health Organization
**Peginterferon Monotherapy versus Peginterferon and Lamivudine Combination Therapy for Chronic Hepatitis B**

**BACKGROUND**

Despite the efforts of vaccinations and infection control, hepatitis B still remains a major health problem.\(^1\)\(^,\)\(^2\) There are more than 2 billion people around the world infected with the hepatitis B virus (HBV), among which, about 600 000 people die yearly due to complications of acute or chronic hepatitis B.\(^2\) Chronic hepatitis B (CHB) occurs in about 240 million people worldwide, highest in Sub-Saharan Africa and East Asia, and lowest in North America and Western Europe.\(^1\)

Chronic hepatitis B is defined as the positivity of hepatitis B surface antigen (HBsAg) lasting longer than 6 months with or without the presence of the hepatitis B envelope antigen (HBeAg).\(^1\)\(^-\)\(^3\) HBeAg positivity indicates that the virus is in high replication stage and that the patient's bodily fluids are highly contagious to others.\(^1\)\(^-\)\(^4\) If left untreated, chronic hepatitis B can lead to liver cirrhosis, hepatocellular carcinoma (HCC, a type of liver cancer), liver failure, and death.\(^1\)\(^-\)\(^6\)

Therefore, it is critically important to treat CHB in order to prevent the above complications. Responses to treatment includes virological (HBV DNA suppression), serological (HBsAg seroconversion, plus HBeAg seroconversion if HBeAg positive), biochemical (normalization of ALT –Alanine Aminotransferase), and histological markers (improved inflammation, necrosis, and fibrosis).\(^3\)\(^-\)\(^7\) Currently, there are seven types of medications approved for CHB treatment: interferon (IFN), peginterferon (PegIFN), lamivudine (LAM), adefovir, entecavir, telbivudine, and tenofovir.\(^3\)\(^-\)\(^5\)\(^,\)\(^7\)
Nucleos(t)ide analogues (the latter listed five drugs, with LAM as a classic and most studied drug) are potent antivirals, easier to take (oral form), cheaper to afford, and better to tolerate (less adverse events). Standard interferon can achieve longer post-therapy responses, less drug resistance, and higher HBsAg and HBeAg seroconversion than the nucleos(t)ide analogues. With the addition of the polyethylene glycol group to the IFN structure, PegIFN results in a slower absorption, metabolism, and clearance, thus resulting in a longer half-life than IFN. PegIFN provides more sustained pharmacological activity and allows less frequent dosing than IFN (weekly versus at least three times a week).

Currently, there are two kinds of PegIFN, alfa-2a and alfa-2b, with similar effects. PegIFN alfa-2a is approved worldwide for treating HBeAg negative and HBeAg positive CHB, while PegIFN alfa-2b is only approved in several countries outside the United States.

This systematic review compared the efficacy and safety of peginterferon (alfa-2a or alfa-2b) alone to peginterferon and lamivudine combination. This review wants to investigate if PegIFN monotherapy is as efficacious as the combination therapy, and the benefits of the combined therapy in chronic hepatitis B patients, with HBeAg positive or negative.

**METHODS**

An exhaustive literature search was conducted using the following electronic databases: Evidence-Based Medicine Reviews Multifile, Evidence-Based Resources from the Joanna Briggs Institute, Medline (via Ovid), and CINAHL. Search terms were: peginterferon, peginterferon alfa-2a, peginterferon alfa-2b, lamivudine, and chronic
hepatitis B. The search was then limited to English-language and human studies, but not
to time or location of studies. Inclusion criteria of this search were: studies must be in
adult patients with chronic hepatitis B, who have either HBeAg positive or negative;
studies must contain the two intervention groups, peginterferon alone (alfa-2a or alfa-2b)
and peginterferon combined with lamivudine; study design must be blinded randomized
controlled trials. Exclusion criteria were studies using medications other than
peginterferon and/or lamivudine for chronic hepatitis B, that were open-labeled, or that
were not related to chronic hepatitis B treatment.

After selecting qualified studies for this review, the studies were critically
appraised for the validity, results, and risk of bias. Then the quality of studies was
assessed using the Grading of Recommendations, Assessment, Development and
Evaluation (GRADE) system.8

RESULTS

There were a total of 388 articles found through initial search. After screening
those articles using the search terms and exclusion criteria, 16 relevant articles related to
peginterferon and/or lamivudine therapy in CHB were selected. Out of those 16 studies,
three studies satisfied all the inclusion criteria and were included in this systematic
review. For the purpose of this review, the attention focused on comparing the primary
and important secondary outcomes of the two groups, PegIFN alone and PegIFN with
LAM, even though some studies may have tested LAM monotherapy as well and
monitored additional secondary outcomes. All important outcomes were summarized and
compared in Table 1, Characteristics of reviewed studies, GRADE profile, and summary
of findings—peginterferon alone or in combination with lamivudine in chronic hepatitis B treatment.

"Peg 2a in HBeAg Negative" Study (Marcellin et al)

This study[^9] was a partially double-blinded randomized controlled trial which assessed the efficacy and safety of peginterferon alfa-2a alone, the combination of peginterferon alfa-2a and lamivudine, and lamivudine alone in HBeAg negative chronic hepatitis B patients. Study population was 537 patients, aged 18 to 71 years, enrolled from 54 sites in 13 countries, mostly in Asia and Europe. Eligibility criteria of enrolled patients were: HBeAg negative CHB, anti-HBe Ab and HBsAg positive for at least 6 months, HBV DNA level greater than 100 000copies/ml, serum ALT level between 1 to 10 times the upper limit of the normal range, and liver biopsy within the last 24 months consistent with CHB, with evidence of prominent necro-inflammation.[^9]

The patients were randomly assigned into three groups at the ratio 1:1:1, resulting in 177 patients given 180mcg/week subcutaneously (SQ) PegIFN alfa-2a plus daily oral placebo, 179 patients given 180mcg/week SQ PegIFN alfa-2a plus 100mg/day oral LAM, and 181 patients given 100mg/day oral LAM alone. Treatment length was 48 weeks, then follow-up was an additional 24 weeks. Patients in all study groups were similar in prognostic characteristics at baseline, during, and at the end of treatment. Primary outcomes of efficacy were assessed at the end of follow-up: the normalization of ALT, and the suppression of HBV DNA to below 20 000copies/ml. Secondary outcomes included the HBsAg loss, the HBsAg seroconversion (the loss of HBsAg and the presence of anti-HBs antibody), the histologic response on liver biopsy, and the suppression of HBV DNA to below 400copies/ml. Safety measures of therapy were
monitored at baseline, frequently during treatment, and every 4 weeks during follow-up, including the adverse events, hematologic tests, chemical tests, and vital signs.  

During treatment, ALT flare-up rate was higher in PegIFN-placebo group than in PegIFN-LAM group, but it normalized towards the end of follow-up with similar rates: 59% (95% CI 51.7 to 66.6, P 0.004) in PegIFN-placebo, 60% (95%CI 52.2 to 67.0, P 0.003) in PegIFN-LAM, with RR=1.01, NNT=100. The suppression of HBV DNA levels below 20 000 copies/ml was reached with equal rates in both groups: 43% (95%CI 35.5 to 50.6, P 0.007) in PegIFN-placebo, 44% (95%CI 36.7 to 51.7, P 0.003) in PegIFN-LAM, RR=1.02, NNT=100. These primary outcomes appeared lower in LAM alone group.  

The study also showed that there was a possibility of achieving the ultimate goal of CHB treatment: HBsAg loss and HBsAg seroconversion, which happened in similar rates in both groups that had PegIFN. Liver histologic improvements and the suppression of HBV DNA levels below 400 copies/ml were succeeded at the same percentage of patients in both of the PegIFN-placebo and PegIFN-LAM (Table 1) groups.  

Patients reported adverse events similarly in both of PegIFN groups, and higher than in LAM group, with most common symptoms including pyrexia, fatigue, myalgia, and headache. Serious adverse reactions and discontinuation due to safety problems showed that PegIFN with or without LAM would have similar safety concerns. There were no unexpected adverse effects of the study medications.  

The authors discussed that the study was limited in the length of follow-up, which was not long enough to evaluate the additional benefits of lamivudine in the combination therapy, versus peginterferon monotherapy. They found that there was no significant differences in terms of efficacy and safety between peginterferon alfa-2a alone and
peginterferon alfa-2a with lamivudine therapies, although both regimens did significantly better than lamivudine alone in the suppression of HBV DNA, the loss or seroconversion of HBsAg, and the normalization of ALT levels in HBeAg-negative CHB patients. They suggested peginterferon alfa-2a as first line therapy for HBeAg negative chronic hepatitis B patients due to the possibilities of HBsAg loss or seroconversion.9

“Peg 2a in HBeAg Positive” Study (Lau et al)

The goal of this partially double-blinded randomized controlled trial10 was to evaluate the efficacy and safety of peginterferon alfa-2a alone, combination of peginterferon alfa-2a and lamivudine, and lamivudine alone in HBeAg positive chronic hepatitis B. The study enrolled 814 patients, aged 17 to 77 years, from 67 sites in 16 countries in Asia, Australia, Europe, North and South America. Inclusion criteria for selected patients were: HBsAg positive for at least 6 months, anti-HBs Ab negative, HBeAg positive, HBV DNA level greater than 500 000 copies/ml, serum ALT level between 1 and 10 times the upper limit of the normal range, and liver biopsy within the previous 12 months consistent with chronic hepatitis B.10

All patients were randomly assigned at the ratio of 1:1:1 into three groups: 271 patients received SQ PegIFN plus oral placebo, 271 patients received SQ PegIFN plus oral LAM, and 272 patients received oral LAM only. Dosage of PegIFN alfa-2a was 180mcg/week and of LAM was 100mg/day. Treatment was conducted for 48 weeks, and follow-up was for another 24 weeks. Patient characteristics were similar at baseline, and prognostic balance was maintained among three groups during and at the end of treatment. Primary outcomes at the end of follow-up were the HBeAg seroconversion (the loss of HBeAg and the presence of anti-HBe Ab), and the suppression of HBV DNA
levels to below 100,000 copies/ml. Secondary outcomes were also recorded at end of follow-up, including the combined response (the HBeAg seroconversion, the normalization of ALT levels, and the suppression of HBV DNA levels to lower than 100,000 copies/ml), the HBsAg seroconversion (the loss of HBsAg and the presence of anti-HBs antibody), and the histologic response on liver biopsy. The study monitored safety of therapies closely at baseline, during treatment and follow-up, including the adverse events, hematologic tests, clinical chemical tests, and vital signs.10

As the results, primary outcomes did not show significant heterogeneity between PegIFN-placebo and PegIFN-LAM groups. HBeAg seroconversion was slightly higher, although not significant, in PegIFN-placebo group than in PegIFN-LAM group [32% (95%CI 26.6 -38.0, P <0.001) versus 27% (95%CI 22.1 to 33.0, P 0.02), with RR=0.84, NNT=20]. The suppression of HBV DNA levels to below 100,000 copies/ml was 32% (95%CI 26.2 to 37.6, P 0.01) in PegIFN-placebo group, and 34% (95%CI 28.0 to 39.5, P 0.003) in PegIFN-LAM group, RR=1.06, NNT=50. These primary outcomes were lower in LAM alone group. The recorded combined response of serological, biochemical, and virological markers was 23% in PegIFN-placebo group, and 21% in PegIFN-LAM group. The rates of HBsAg seroconversion and liver histologic improvement in PegIFN-placebo and PegIFN-LAM group were very much the same (Table 1).10

Adverse events were also monitored closely in the study. The most common symptoms were pyrexia, fatigue, myalgia, and headache. All adverse events were as expected and were reported similarly in both PegIFN treatment groups, including serious adverse events and therapy discontinuation due to safety reason.10
Similar to the first study, this study's authors did not find any relevant differences in benefits or risks between peginterferon alfa-2a alone and peginterferon alfa-2a with lamivudine combination. Both treatment regimens showed more benefits than lamivudine alone in seroconverting HBeAg and HBsAg, in suppressing HBV DNA levels, and in normalizing ALT levels in patients with HBeAg positive CHB. Overall, they suggested peginterferon alfa-2a as first line therapy for HBeAg positive chronic hepatitis B, due to the possibility of having HBsAg and HBeAg seroconversion, the highest goals of treatment for this group of hepatitis B. However, the authors did not discuss limitations of the study.10

“Peg 2b in HBeAg Positive” Study (Janssen et al)

The authors of this double-blinded randomized controlled trial11 wanted to know if the combination of lamivudine with peginterferon alfa-2b would increase the rate of sustained response in HBeAg positive chronic hepatitis B, as compared to peginterferon alfa-2b alone. They enrolled 307 patients, aged 16 years and older, from 42 centers in 15 countries in Europe, East Asia, and North America. Patients must have all of the following eligibility criteria to join the study: HBsAg positive for longer than 6 months, HBeAg positive on two occasions within the previous 8 weeks before the randomization, two episodes of elevated ALT twice the upper limit of normal range within the previous 8 weeks before the start of the study.11

All patients were randomly allocated into two groups, at 1:1 ratio, 155 patients assigned to receive SQ PegIFN alfa-2b plus daily oral placebo, and 152 patients assigned to receive SQ PegIFN alfa-2b plus 100mg/day oral LAM. Dosage of PegIFN alfa-2b changed from 100mcg weekly for the first 31 weeks to 50mcg weekly for the last 21
weeks, and was adjusted to weight if patients weighed 55 kilogram or less. Treatment was 52-week long, with 26-week follow-up post-therapy.

However, the final analyses included a total of 266 patients, 136 patients in the PegIFN-placebo group, and 130 patients in the PegIFN-LAM group, after 41 patients were excluded from the study (due to misconduct, lost HBeAg before the study started, or did not receive study medications). The withdrawal distributed equally among treatment groups. Patient characteristics in both study groups were similar at baseline, and the prognostic balance was maintained during treatment and at the study's completion.

Primary end point at the end of follow-up was the loss of HBeAg. Secondary end points included the suppression of HBV DNA levels to below 200 000 copies/ml, the HBV DNA level undetectable (less than 400 copies/ml), the normalization of ALT concentrations, HBsAg loss or seroconversion, liver histologic response. This study also assessed the HBV genotype and mutation, which are not the focus of this systematic review.

At the end of follow-up, the primary end point was homogenous across two study groups. The HBeAg loss was at 35% of the PegIFN-LAM group, at 36% of the PegIFN-placebo group, and not statistically significant between two groups (p = 0.91, α=0.05). The HBeAg seroconversion was also similar in both groups (29% in each group, RR =1, p=0.92). The rates of suppression of HBV DNA levels to below 200 000 copies/ml, the HBsAg seroconversion, the HBsAg loss, the undetected HBV DNA levels (below 400 copies/ml), the ALT normalization, and the liver histologic improvements of two treatment groups did not reveal relevant differences or statistical significance (all p values greater than the significant level α).
Adverse events were expected and similar in PegIFN alone and PegIFN with LAM groups. Most common side effects were flu-like symptoms: pyrexia, fatigue, myalgia, and headache. All adverse events were reversible after stopping therapy. There was not concerning differences of serious adverse effects and therapy discontinuation between the two study groups.¹¹

The study found that peginterferon alfa-2b could cause HBeAg loss and reduction of HBV DNA suppression in HBeAg positive chronic hepatitis B patients. However, combination peginterferon alfa-2b with lamivudine was not more beneficial than peginterferon alfa-2b monotherapy, as all results were not statistically significant between treatment groups (p values of all outcomes at end of follow-up were greater than 0.05). The authors warned the readers to interpret the liver biopsy results carefully, since the biopsy was optional for the patients at the end of therapy, and the pool of patients who had biopsies may have also been selected.¹¹

DISCUSSION

Through the three trials⁹-¹¹ reviewed above, peginterferon alfa-2a and alfa-2b were proven effective in treating chronic hepatitis B, regardless of HBeAg negative or positive CHB. These peginterferon forms were found to cause HBsAg loss or seroconversion and sustained HBV DNA suppression in both HBeAg positive and negative chronic hepatitis B patients,⁹-¹¹ as well as HBeAg loss or seroconversion¹⁰,¹¹ if patients have HBeAg positive. On the other hand, these studies did not find additional benefits of adding lamivudine to peginterferon therapy. The study results actually showed that the peginterferon monotherapy had some outcomes at slightly higher rates and some adverse
events at slightly lower rates than did the combination therapy, although those differences were not significant.\textsuperscript{9-11}

However, as we look into the studies closely, there were limitations in these studies. There was likely publication bias in all studies. The studies were sponsored and/or designed by Roche\textsuperscript{9,10} or Schering-Plough International and GlaxoSmithKline Research and Development.\textsuperscript{11} The study publications could have been altered by these drug companies for their commercial benefits without the authors’ knowledge. However, all authors\textsuperscript{9-11} stated that they had full access to study data and actively performed the studies from data collection, analysis, data interpretation, writing the reports, and making final decisions for publication. These statements made the bias less severe and the results still reliable and useful. Due to this suspected bias, quality of all studies was downgraded one level, using the GRADE system (Table 1).

There was possible selection bias, as mentioned in the result section above, in post-therapy liver biopsy in the study of Janssen et al.\textsuperscript{11} The biopsy occurred at the end of the treatment phase and was not a form of treatment, so it did not alter the primary and other secondary outcomes, besides the histologic outcome. In this regard, this bias was localized within a subset of secondary outcomes, so it did not affect the overall quality of this study. Thus, the quality of this study was not downgraded further due to this limitation.

In these three studies,\textsuperscript{9-11} follow-up lasted from 24 to 26 weeks, which may be sufficient for reevaluating the CHB condition and retesting the HBV status once or twice, but may be not long enough to fully evaluate the long-term responses of HBV, HBsAg, HBeAg, ALT, and liver histology to peginterferon alone or with lamivudine. One study’s
authors, Marcellin et al, admitted this fact and suggested longer length of follow-up to evaluate the sustained responses to peginterferon alfa-2a. Due to this limitation, quality of all studies was downgraded one level, using the GRADE system (Table 1).

**CONCLUSION**

It has been proven that peginterferon alfa-2a or alfa-2b could lead to HBsAg loss or seroconversion and sustained viral suppression in all patients with chronic hepatitis B, as well as HBeAg loss or seroconversion if patient has HBeAg positive.\(^9\)\(^-\)\(^11\) However, it is not clear about the benefits of adding lamivudine to peginterferon therapy, since peginterferon alone or with lamivudine showed similar responses and side effects. These studies suggested peginterferon alfa-2a or alfa-2b as first line therapy for CHB, but none of them recommended whether peginterferon should be used alone or with lamivudine. Based on the GRADE criteria, the quality of all studies are low, as discussed above and described in Table 1.

More randomized controlled trials with longer length of follow-up are needed to evaluate the long-term responses of Hepatitis B virus to peginterferon (alfa-2a or alfa-2b) alone or with lamivudine, as well as the effects of adding lamivudine to peginterferon for treating CHB. Future randomized controlled trials investigating the efficacy and safety of peginterferon alfa-2b in HBeAg negative chronic hepatitis B would also be important for clinical practice and patient outcomes.
References

Table I. Characteristics of reviewed studies, GRADE profile, and summary of findings. Peginterferon alone or in combination with lamivudine in chronic hepatitis B treatment.
Table I: Characteristics of reviewed studies, GRADE profile, and summary of findings. Peginterferon alone or in combination with lamivudine in chronic hepatitis B treatment.

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a Length of follow-up was not sufficient (24 to 26 weeks)

b All studies were sponsored or funded by pharmaceutical companies, but authors stated that they had full access to data and actively involved in all steps of study from patients selection to manuscript of reports.