Higher Risk of Hepatocellular Carcinoma Progression in the Population of Untreated Immune-Tolerant Phase Chronic Hepatitis B Patients: An Evidence Based

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ABSTRACT

Aim: *This evidence-based case report is meant to comprehensively review the effect of antiviral treatment in IT-phase CHB patients from available studies.*

Method: *Pubmed, ProQuest, Cochrane, Scopus, Sciencedirect and EBSCOhost were comprehensively searched for systematic review and cohort prognostic researches studying the impact of anti-virals treatment for CHB patients in IT-phase. Three studies were selected and critically appraised. Data were then summarized descriptively.*

Results: *The three studies included in this study were retrospective cohort studies. One study stated that the treated IT-phase group had significantly reduced risk for HCC (HR = 0.234; log-rank p = 0.046), compared to the untreated IT-phase group. One study found that untreated IT phase is asscociated with significantly higher risk of HCC (HR = 2.54; 95% CI: 1.54 to 4.18; p < 0.001) compared to the treated immune-active (IA) phase group. The last study stated a higher adjusted hazard ratio (aHR) of the UIT in predicting HCC risk was 2.327 (95% CI 0.475–11.391; p = 0.297), if compared to the IA group.*

Conclusion: *While studies shows apparent results regarding the treatment of CHB patients in the IT-phase and its benefit in reducing cumulative incidence of HCC, its clinical advantage is soon to be discovered. The results were inconclusive, and the initiation of treatment in CHB patients within the IT-phase cannot yet be recommended until further research.*

Keywords: 'Hepatitis B', 'chronic hepatitis B', 'immune-tolerance phase', 'anti-viral', 'hepatocelullar carcinoma'

ABSTRAK

Tujuan: *Laporan kasus berbasis bukti ini dimaksudkan untuk meninjau secara komprehensif dampak dari pengobatan antivirus pada pasien HBK dalam fase IT berdasarkan penelitian yang telah ada.*

Metode: *Kami menelusuri Pubmed, ProQuest, Cochrane, Scopus, Sciencedirect dan EBSCOhost secara komprehensif untuk mencari meta-analisis dan penelitian prognostik yang mempelajari dampak pengobatan anti-virus untuk pasien CHB pada fase IT. Tiga studi dipilih dan dinilai secara kritis. Data kemudian dirangkum secara deskriptif.*

Hasil: *Tiga studi kohort retrospektif dianalisa dalam studi ini. Satu studi menyatakan bahwa kelompok fase-IT yang diterapi memiliki risiko lebih rendah terhadap KSH (HR, 0,234; log-rank P = 0,046), bila dibandingkan*

dengan yang tidak diobati. Satu studi menemukan bahwa fase IT yang tidak diobati berhubungan dengan risiko KSH yang lebih tinggi (HR = 2,54; 95% CI: 1,54-4,18; p < 0,001) dibandingkan dengan kelompok fase immune-active (IA) yang diobati. Studi terakhir menyatakan rasio hazard yang disesuaikan lebih tinggi (aHR) dari UIT dalam memprediksi risiko HCC adalah 2,327 (95% CI: 0,475-11,391; p = 0,297), jika dibandingkan dengan kelompok IA.

Simpulan: *Penelitian telah menunjukkan hasil yang jelas mengenai dampak pengobatan pasien HBK dalam fase IT terhadap penurunan kejadian kumulatif dari KSH, namun keputusan pelaksanaan terapi tersebut secara klinis masih harus dipertimbangkan, sehingga pengobatan pasien HBK dalam fase IT belum dapat direkomendasikan sampai penelitian lebih lanjut.*

Kata kunci: *'Hepatitis B', 'Hepatitis B kronik', 'immune-tolerance', 'anti-viral', 'karsinoma sel hati'*

INTRODUCTION

Hepatitis B infection (HBV) is a major health problem worldwide, currently occurring in 350-400 millions of people. In Indonesia, HBV currently infects 4.0-20.3% of the country's healthy population. If not treated properly, hepatitis B infection may progess into chronic hepatitis B (CHB)—which is marked by the persistence of HBsAg for at least 6 months or more—and may develop into a more chronic liver condicion such as cirrhosis and/or hepatocellular carcinoma (HCC).[1] HCC, the most common type of liver cancer, is one of the leading cause of cancer-related death worldwide and is known for its very poor prognosis. In Indonesia, the average life of expectancy of HCC patients is less than three months with most patients being in an advanced stage—in which the survival rate is very low.[2]

HBV infection itself is a dynamic process involving close interaction of both virus replication and host immune response which can be divided into four phases. The immune-tolerant (IT) phase, the immune active (IA) phase, the inactive phase, and in many cases the reactivation phase. Among all four, the IT phase is the least most understood.[3] IT phase, as defined by the American Association for the Study of Liver Diseases (AASLD), is a phase marked by positive serum HBeAg, high level of HBV DNA, and persistently normal serum alanine aminotransferase (ALT).[4] According to studies, there are minimal or no necroinflammatic activity or fibrosis in this phase, hence a lower risk in the development of more chronic liver disease state. This explained why antiviral therapy is not recommended in this phase.[5]

Recent studies however, has challenged our current understanding regarding the need of treatment in the IT phase by showing that there are apparently histological activity and immune specific response findings towards HBV in the IT phase. Moreover, with the high level of chromosomal HBV DNA integration into the host's genome and clonal expansion of the hepatitis, have brought us closer in questioning whether IT phase is actually the first phase which chronic liver disease firstly developed.[6-8] Thus, treatment in the IT phase may be beneficial to minimilize hepatocyte imparement. Current studies shed light in answering these questions, by showing the possibility of lowering HCC progression risk in CHB patients by treating IT-phase patients. Nevertheless, antiviral treatment in CHB patients has not yet been routinely recommended by consensus.[3,5,9] Questions regarding the need of starting treatment earlier in CHB patients is intriguing—yet there is no evidence based case report which studied the lower risk of HCC development in CHB patients treated with antivirals. This evidence-based case report is meant to comprehensively review the effect of antiviral treatment in IT-phase CHB patients from available studies.

CASE ILLUSTRATION

A 52 years old Man came to the Hepatology procedure ward in the Cipto Mangunkusumo National Referal Hospital for his routine check-up and fibroscan procedure. The patient had been diagnosed with Chronic Hepatitis B since 4 months ago. Currently, he has no complaints. Any signs of fatigue, nausea, vomiting, jaundice, fever and abdominal pain were denied. Four months ago, patient came to the hospital with the complaints of yellowing of the skin and fatigue. He denied any pain in the chest, shortness of breath and abdominal pain. The patient then went to Tangerang Regional Public Hospital and got tested for HBsAg, where he received positive results. The patient was then referred to Cipto Mangunkusumo National General Hospital for further evaluation. Lab test showed normal AST and ALT, positive HBD DNA of 9.4×10^4, with elevated total and direct bilirubin.

The result of fibroscan was F0 and ultrasound showed chronic liver disease. The patients was then assessed with chronic hepatitis B within the immune-tolerance phase and did not receive antivirals. Patients routinely perform fibroscan and ultrasound each month. Patient have no history of transfusion, drug injections, tattoos or piercings, changing sexual partners, alcohol and smoking. Patients do not have a history of hypertension, diabetes, allergies, asthma, and vomiting of blood.

CLINICAL QUESTION

Based on the case illustration, we formed two clinical questions: (1) Do IT-phase CHB patients non-treated with antiviral have lower cumulative incidence of HCC if compared with treated Immune-active (IA) phase CHB patients?; (2) Does starting anti-viral therapy in CHB patients currently in the IT-phase may lower the risk of the progression towards HCC?

Table 1. Clinical Question Formulation 1

Population	Non-treated hepatitis B chronic patients in immune-tolerant phase (Positive HBeAg, normal ALT, HBV DNA > 200.000 IU/mL, minimal necroinflammation in histological findings)
Exposure	Not treated with anti-virals
Comparison	Treated hepatitis B chronic patients in immune-active phase (Positive HBeAg, elevated ALT, HBV DNA > 2000 IU/mL, necroinflammation in histological findings)
Outcome	Risk of Developing Hepatocellular carcinoma
Type of question	Prognostic
Type of relevant studies	Systematic Review-Meta Analysis of Cohort Studies and Cohort Studies

Table 2. Clinical Question Formulation 2

Population	Hepatitis B chronic patients in immune-tolerant phase
Exposure	Treated with anti-virals
Comparison	Non-treated hepatitis B chronic patients in immune-active phase
Outcome	Risk of Developing Hepatocellular carcinoma
Type of question	Prognostic
Type of relevant studies	Systematic Review-Meta Analysis of Cohort Studies and Cohort Studies

METHOD

Literature searching was conducted in April 2019 using the keywords shown in Table 2 from six different journal databases of which are Pubmed, ProQuest, Cochrane, Scopus, Sciencedirect and EBSCOhost. The studies obtained from the search were screened though their title and abstract and then filtered according to the inclusion criteria of prognostic studies design (cohort, systematic review, and meta-analysis). Relevant articles were then further studied by reading their full article. Articles not in accordance with the objective of this study are excluded. Searching strategy, searching results, inclusion and exclusion criteria are shown in Figure 1.

Table 3. Searching strategy

Database	Keywords	Findings	Selected Findings
Pubmed	(((((tolerant OR immune tolerant)) OR hbeag-positive) AND chronic hepatitis b) AND (antiviral OR therapy)) AND hepatocellular carcinoma	164	2
Cochrane	"Chronic hepatitis B" AND "Immune tolerant" AND (antiviral OR therapy OR treatment) AND "Hepatocellular carcinoma"	21	0
EBSCO	"Chronic hepatitis B" AND "Immune tolerant" AND “Antiviral”	64	2
Sciencedirect	"Chronic hepatitis B" AND "Immune tolerant" AND (antiviral OR therapy OR treatment) AND "Hepatocellular carcinoma"	345	0
PROquest	"Chronic hepatitis B" AND "Immune tolerant" AND (antiviral OR therapy OR treatment) AND "Hepatocellular carcinoma"	417	2
Scopus	"Chronic hepatitis B" AND "Immune tolerant" AND (antiviral OR therapy OR treatment) AND "Hepatocellular carcinoma	28	2

RESULTS

Based on the selection of articles, 3 relevant studies were collected and analyzed in our evidence-based case report. The studies consist of three cohort studies.

CRITICAL APPRAISAL

We criticaly appraise the articles studies in this paper. All of the studies were critically appraise according to the The Centre for Evidence-Based Medicine appraisal tools for retrospective cohort studies (Table 4).

THE STUDY OF LEE HW, ET AL (2019)[3]

The validity of the study was defined by four aspects, a representative sample assembled at a common point of the disease, sufficient follow-up period, objective of

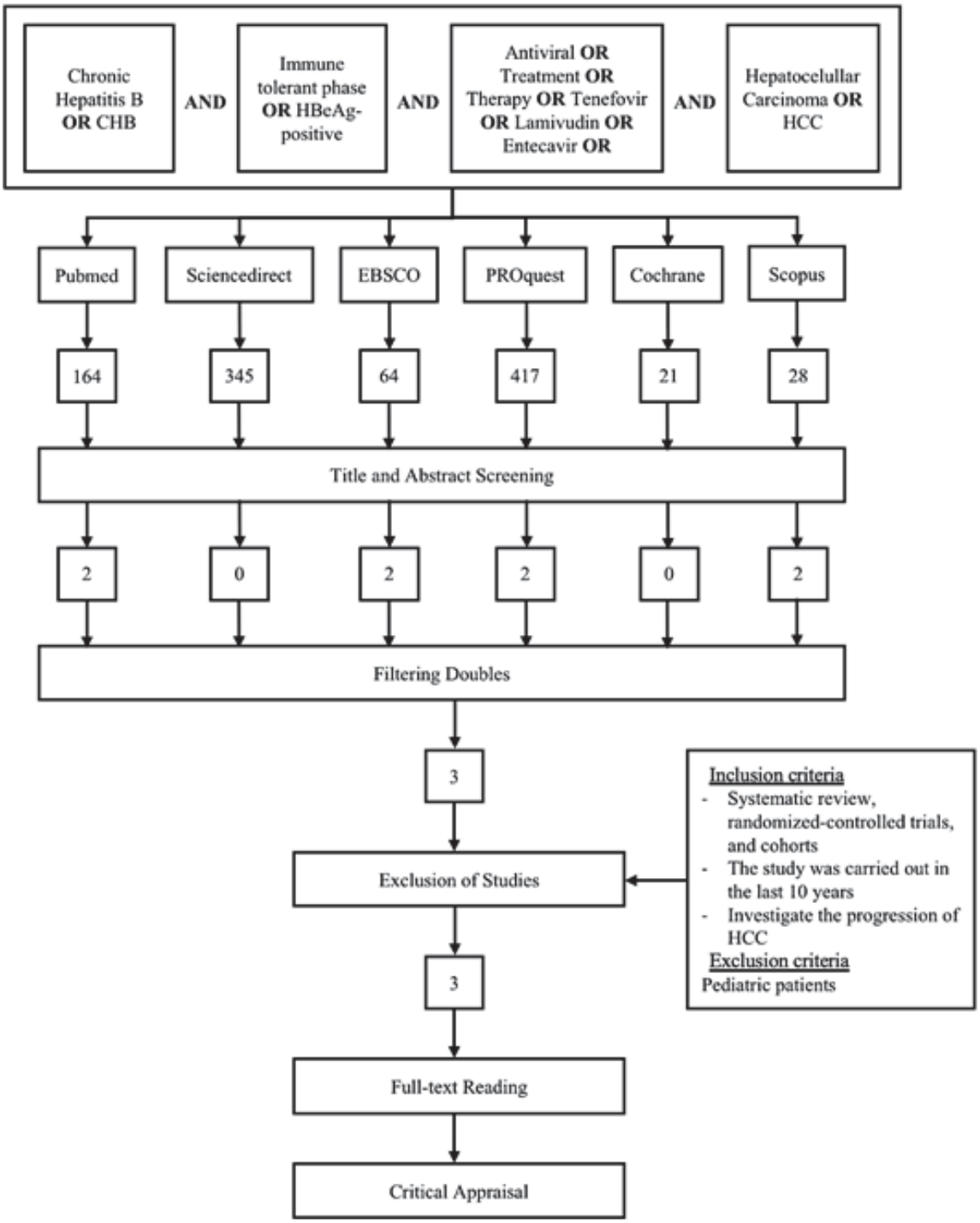

Figure 1. Literature searching procedure

Table 4. Summary of studies

Author, Year	City, Country	Materials and Method			Outcome	
		Type, Recruitment	Allocation	Measurement	Subjects Characteristics	Clinical Outcomes
Lee HW, et al (2019)	Seoul, Korea	**Retrospective cohort** **Inclusion criteria** 1) Positive serum HBsAg test for at least 6 months, 2) age ≥20 years old, 3) reliable liver stiffness (LS) value by transient elastography, and 4) follow-up duration of at least 1 year. **Exclusion criteria** 1) history of HCC or liver cirrhosis at the enrollment, 2) co-infection with other viral hepatitis or presence of other liver diseases, 3) current use of immunosuppressive agents, 4) HCC, hepatic decompensation or death within 6 months of enrollment and 5) other significant medical illness.	**Consecutive sampling of CHB patients** into two groups (from 767 patients): **UTI Group (Untreated-Immune tolerant phase)** Patients with: 1) serum HBV-DNA levels of ≥20,000 IU/mL 2) positive HBeAg, 3) persistently normal serum ALT level during the follow-up (ULN at 40 U/mL) (n = 126) **VR Group (Treated-Immune active phase)** IA Patients who achieved serum HBV-DNA < 2,000 IU/mL by antiviral therapy with Nucleos(t)ide analogues (NUCs) (n = 641)	**Outcome of Interest** The development of HCC or comprehensive liver related events (LRE), which included HCC, decompensation (hepatic encephalopathy, ascites, variceal bleeding, spontaneous bacterial peritonitis, or hepatorenal syndrome) or liver-related mortality. **Diagnosis of HCC** Based on histological evidence or radiological findings determined by dynamic computed tomography and/or magnetic resonance imaging (nodule >1 cm with arterial hyper-vascularity and portal/delayed-phase washout)	**Mean Age** **UTI Group** was 47.7 ± 11.1 years **VR Group** was 53.5 ± 10.7 years **Gender** **UTI Group** 50.8% was female **VR Group** (Treated-Immune active phase) 63.8% was male **Mean Serum HBV DNA** **UTI Group** was 6.9 ± 0.2 $\log_{10}$ IU/mL **VR Group** was 2.7 ± 0.9 $\log_{10}$ IU/mL **Mean Serum ALT** **UTI Group** was 23.4 ± 7.8 U/mL **VR Group** was 24.9 ± 10.2 U/mL	**Hepatocelullar carcinoma** UIT group had similar 10-year cumulative risks of HCC (2.7% vs. 2.9%, p = 0.704), compared to VR group After adjusting well-known prognostic variables (i.e. age, gender, presence of diabetes and LS values), adjusted hazard ratio (HR) of the UIT group (vs. the VR group) to predict HCC risk was 2.327 (95% CI 0.475–11.391; p = 0.297) **Liver-related events** Similar 10-year cumulative risks of liver-related events (4.6% vs. 6.1%, p = 0.903) development, compared to VR group. After adjusting well-known prognostic variables (i.e. age, gender, presence of diabetes and LS values), adjusted HR of the UIT group (vs. the VR group) to predict LRE risk was 1.341 (95% CI 0.457–3.933; p = 0.593).
Kim GA, et al (2017)	Seoul, Korea	**Retrospective cohort** **Inclusion criteria** 1) Serum HBV DNA levels of ≥20.000 IU/mL 2) HBeAg positive at baseline. 3) no evidence of cirrhosis, 4) no history of cancer or organ transplantation 5) followed for at least 1 year. **Exclusion criteria** 1) Positive serology for HCV, HIV or other hepatotrophic viruses 2) prior anti-viral treatment or current treatment with immunosuppressive agents 3) transition from the immune-tolerant (IT) to immune active (IA) phase 4) no initiation of oral NUC treatment in the IA phase 5) transition from the MA to IA phase.	**Consecutive sampling of CHB patients** into two groups (from 1910 patients): **IT Group** Patients with: 1) serum HBV-DNA levels of ≥20,000 IU/mL 2) positive HBeAg, 3) ALT level less than the upper limit of normal (ULN) of <19 U/L for females and <30 U/L for males according to AASLD (n = 413) **IA Group** Patients with ALT level more than 2× ULN treated with nucleos(t)ide analogues (n = 1497)	**Outcome of Interest** The occurrence of HCC and death or liver transplantation. **Diagnosis of HCC** Based on histological examination and/or typical features (nodule >1 cm with arterial hypervascularity and portal/delayed-phase washout) determined through dynamic CT and/or MRI.	**Mean Age** **IT Group** was 38±11 years **IA Group** was 40±11 years **Gender** **IT Group** 66.8% was male **IA Group** 65.0% was male **Median Serum HBV DNA** **IT Group** was 8.0 (7.0–8.4) $\log_{10}$ IU/mL **Group IA** was 7.7 (6.9–8.3) $\log_{10}$ IU/mL **Median Serum ALT:** **IT Group** was 19 (16–25) U/mL **IA Group** was 156 (95–308) U/mL	**Hepatocelullar carcinoma** The 10-year estimated cumulative incidences of HCC (12.7% vs 6.1%; p=0.001) were significantly higher in the IT group than the IA group In multivariable analyses, the IT group showed a significantly higher risk of HCC (HR 2.54; 95% CI 1.54 to 4.18) than the IA group **Liver-related events** The 10-year estimated cumulative incidences of death/transplantation (9.7% vs 3.4%; p<0.001) were significantly higher in the IT group than the IA group. In multivariable analyses, the IT group showed a significantly higher risk of death/transplantation (HR 3.38; 95% CI 1.85 to 6.16) than the IA group.

Author, Year	City, Country	Materials and Method			Outcome	
		Type, Recruitment	Allocation	Measurement	Subjects Characteristics	Clinical Outcomes
Chang Y, et al (2017)	Seoul, Korea	**Inclusion criteria** Patients that tested positive for HBeAg with an HBV DNA >20,000 IU/mL, ALT <40 IU/L, no evidence of cirrhosis, no history of cancer or organ transplantation, and were followed for at least 1 year. **Exclusion criteria** Confirmed LC diagnosis, prior diagnosis of any malignancy including HCC, previously exposed to NA or interferon therapy, presence of antibodies to hepatitis C or D viruses, or received prophylactic NA therapy because they were immunosuppressed	**Consecutive sampling of CHB patients** into two groups (from 1928 patients): **Treatment Group** 87 patients that received NA therapy immediately after diagnosis of HBeAg-positive chronic HBV infection with the upper limit of the normal range of ALT values as approximately 40 IU/L **Control Group** 397 patients who did not receive NA therapy, rather they were followed regularly after being diagnosed with HBeAg-positive chronic HBV infection with the upper limit of the normal range of ALT values as approximately 40 IU/L	The primary endpoint was the development of HCC, and the secondary endpoint was the development of LC. HCC was diagnosed according to the European Association for the Study of the Liver guidelines. If there was no clear radiological diagnosis of HCC, we performed a liver biopsy for histological diagnosis.	**Mean Age** **Treatment Group** was 43.2±13.0years **Control Group** was 41.5±12.5 years **Gender** **Treatment Group** 52.9% was female **Control Group** 50.9% was male **Mean Serum HBV DNA** **Treatment Group** was 7.3±1.3 $\log_{10}$ IU/mL **Control Group** was 7.4±1.2 $\log_{10}$ IU/mL **Median Serum ALT:** **Treatment Group** was 26.9±7.9 U/mL **Control Group** was 26.8±8.0U/mL	**Hepatocelullar carcinoma** After using multivariate analysis to adjust for several confounders that were significant risk factors for HCC development, the treatment group had a lower risk of developing HCC than the control group; however, the statistical significance was marginal (adjusted hazard ratio [aHR]=0.188, 95% confidence interval [CI]=0.030–1.186, *P*=0.075). After PS matching, the treatment group showed significantly lower risk of HCC (HR=0.234, 95% CI=0.050–1.104, log-rank P=0.046) **Liver Cirrhosis** The treatment group appeared to have a decreased risk of liver cirrhosis, but the difference between the two groups was not statistically significant (aHR=0.382, 95% CI=0.081–1.804, P=0.225). The treatment group showed significantly lower risk of LC (HR=0.235, 95% CI=0.066–0.833, log-rank P=0.015; Figure 1B) than the matched control group.

Table 5. Critical appraisal for cohort studies

Appraised Aspects		Studies		
		Lee HW, et al (2019)	Kim GA, et al (2017)	Chang Y, et al (2017)
Validity	A defined, representative sample of patients was assembled at a common point in the course of the disease	+	+	-
	Patient follow-up was sufficiently long and complete	+	+	+
	Objective outcome criteria were applied in a "blind" fashion	-	-	-
	There was adjustment for important prognostic factors, if subgroups with different prognoses are identified	+	+	+
Importance	Likely outcome	10-year cumulative risk of HCC (2.7% vs 2.9 %; p = 0.704) compared to the IA group	10-year cumulative risk of HCC (12.7% vs. 6.1%; p = 0.001) compared to the IA group	Reduced risk for HCC (HR = 0.234, log-rank P = 0.046) compared with the control group
	Precise prognostic estimation	95% Confidence Interval = p +/ 1.96 x SE = 1.69% +/- 0.004%	95% Confidence Interval = p +/ 1.96 x SE = 5.8% +/- 0.013%	-
Applicability	Patients of the study were similar	+	+	+
	This evidence will make a clinically important impact	+	+	+

+= stated in the article; - = not stated in the article

outcome through "blind" fashion, and the adjustment of important prognostic factors in different subgroups. In the study of Lee HW, et al patients were assembled under the same institution. The incusion and exclusion criteria were set before the recruitment of subjects and the inisiation of treatment in this study was based on the treatment guidelines and patients in the untreated IT-phase (UIT group) at Severance Hospital, Yonsei University College of Medicine and also the guidelines developed by the Korean Association for the Study of the Liver and the reimbursement guidelines of the national health insurance program of the Republic of Korea. By hence, we consider this research included a representative sample for the study. Follow-up of patients was done with a median of 8 years, which was relatively short to determine the development of HCC, but is considered adequate for the study. The study did not stated any blinded method for the examiner. There were also adjusted hazard ratio for well-known prognostic variables (i.e. age, gender, presence of diabetes and LS values). Overall, we consider the study conducted by Lee HW, et al is valid.

The importance of the study was defined by two aspects, how likely are the outcomes over time and how precise is this prognostic estimate. The study calculated both the 5-years and the 10-years cumulative risk of HCC if compared with the VR group. We calculated the standard of Error (SE) and the confidence interval. SE was $\sqrt{(0.0169 \times (1-0.0169) / 767)} = 0.0021\%$ while calculations of CI (95%) was 1.69% +/- 0.004%.

The applicability of the study in clinical settings was defined by two aspects, of which whether the subjects of the study are similar with our patient and will it make any clinically important impact. Patients in this study were similar with our patients and the study is believed to be able to impact important clinical judgement for our patient.

The Study of Kim GA, et al (2017)[5]

Patients were assembled at the same baseline characteristic, of which are HBsAg-positive, treatment-naïve, non-cirrhotic and adults. All of the patients were enrolled at the same institution. Patients were then followed up, and excluded if found to have positive serology for HCV or HIV or had received prior anti-viral treatment of immunosuppressive agents. The sample was considered representative. Patients included in this study was from January 2000 to Decemer 2013, with the last follow-up was May 2016. The follow-up period was relatively short for predicting HCC outcome, but still considered adequate for this study. This study used inversed probability treatment weighting (IPTW) and propensity score-matching analysis to reduce the effect of selection bias and potential confounders between groups. Variables inputted to derive propensity scores were age; sex; serum levels of HBV DNA, albumin and total bilirubin; platelet count; diabetes mellitus and hypertension. The study did not stated any blinded method for the examiner. To conclude, we considered the study of Kim GA, et al was valid. The study also stated both the 5-years and the 10-years cumulative risk of HCC if compared with the IA group. The precise prognostic estimations was 95% Confidence Interval = p +/ 1.96 x SE = 5.8% +/- 0.013%. Patients in this study were similar with our patients and the study is believed to

be able to impact important clinical judgement for our patient.

The Study of Chang Y, et al (2017)[9]

Patients were enrolled at one of eight tertiary hospitals in Korea: Seoul National University Hospital, Konkuk University Hospital, Samsung Seoul Medical Center, Kyung Hee University Medical Center, Severance Hospital, Hanyang University Seoul Hospital, and Kyungpook National University Hospital, and Asan Medical Center. The inisiation of NAs treatment in patients was largely determined by the physicians considering various factors such as age, medical condition, economical condition, family history of HCC, occupational requirements, and the patients' preferences, making the baseline characteristics of the two groups to be disparate. The study then adjusted or balanced those variables using three different statistical methods (i.e., multivariate Cox regression analysis, PS matching, and IPW) in parallel. Median follow-up duration was 66.5 months (interquartile range [IQR], 23–80): 71 months (IQR, 24–82) for the control group and 50 months (IQR, 42–66) for the treatment group. The median time to follow up was relatively short to determine the development of HCC but is enough to be used for this study. Blinding methods when data were extracted is not stated in the study. This study also did subgroup analysis on ALT level, FIB-4 index, age, and HBV DNA level. To conclude, we considered the study of Chang Y, et al was valid. The study also stated both the 5-years and the 10-years cumulative risk of HCC if compared with the treated-IT group. The precise prognostic estimations cannot be calculated as we are not able to find the number of subjects who developed HCC in the untreated IT group. Patients in this study were similar with our patients and the study is believed to be able to impact important clinical judgement for our patient.

DISCUSSION

Current Management of Chronic Hepatitis B in the Immune-Tolerant Phase

The condition of chronic Hepatitis B (CHB) is marked by positive HBV seromarker findings in two different examination carried out in a minimum of 6 months interval. Worldwide, there are currently up to 400 million HBV infected people and the majority of them reside in the Asia-Pacific region, where HBV infections is considered endemic.[1] *American Association for the Study of Liver Diseases* (AASLD) in the year of 2016 defined IT phase as a state if patients have normal ALT (<30 U/L for men and <19 U/L for women), elevated HBV DNA (commonly over 1 million IU/mL), positive HBeAg, and minimal inflamation and fibrosis histologically.[4] Indication for the treatment of IT-patients in the *Asian Pacific Association for the Study of the Liver* (APASL) is defined by HBeAg positivity, persistently normal serum ALT levels, and serum HBV DNA >2 x 10^7 IU/ml with minimal histological changes. [11] The management of patients in IT-phase in both AASLD and APASL guidelines is recommended only if there are evidence of moderate to severe inflammation or significant fibrosis found during routine assessment. The same recommendation was also stated in the National Guidelines for the Management and Treatment of Hepatitis B Patients published by the Indonesian Asscociation for the Study of Liver in the year of 2017.[1]

The European Association for the Study of the Liver (EASL) 2017 clinical practice guidelines suggest that patients with HBeAg-positive chronic HBV infection, persistent normal ALT and high HBV DNA levels may be treated if they are older than 30 years, regardless of the severity of liver histological lesions, or if they have a family history of HCC or cirrhosis. However, the evidence level was quite low ("III", "weaker" recommendation), hence indication a more definite answer.[11]

Table 6. Treatment of choice for CHB, comparison of interferon and NAs[1]

	Interferon	Nucleotide analog
Duration	Given with the maximun of 48 weeks	Lifetime use
Route	Subcutaneous	Per oral, once a day
For Decompensated Cirrhosis	Not given	Given
Side Effects	More	Less
Suppresion of HBV	Slightly lower	Slightly higher
Seroconversion Rate	Higher	Lower
Biochemistry Response	Equal	Equal
Histopathological Response	Equal	Equal
Resistance	Not found	Higher, in some type
Long-term Response	Tends to improve when the therapeutic target is reached	May relapse if treatment is not continued

Progression Towards HCC in the IT-Phase: Lesser Risk if Treated?

Study conducted by Chang Y et al. included IT patitents, and compare the outcome of HCC risk of those who were treated (n = 87) and those who were

not (n = 397) as control. Baseline liver function was more favorable for the control group, and matching for propensity score was done. The antiviral treatment group had a significantly reduced risk for HCC (HR, 0.234; log-rank *P* = 0.046), compared to the control group. Inverse probability weighting was done to balance the baseline characteristics of the patients, and antiviral therapy was found to significantly reduced the risk of HCC (HR, 0.189; log-rank *P* = 0.004).

Study conducted by Kim GA, et al. included untreated IT patients (n = 413) and treated IA patients (n = 1497). Stated in the study was among all patients (n = 1910), 78 (4.1%) developed HCC during the 6.3 years of median follow-up period. The annual incidence in the IT group was higher than the IA group, accounting for 1.05% vs 0.51%; p=0.001, respectively. Cumulative incidence of HCC was also found to be higher in the IT group, with the 5 years- and 10 years-cumulative incidence of HCC in the IT vs IA groups was 4.2% vs 1.6% and 12.7% and 6.1% (p = 0.001), respectively. IT group was also found to be asscociated with significantly higher risk of HCC (HR = 2.54; 95% CI 1.54 to 4.18; p < 0.001) compared to the IA group. To reduce the effect of selection bias and potential confounders between the groups, IPTW was employed using propensity scores of patients at baseline. In this analysis, the IT group had a significantly higher risk of both HCC (HR 2.69; 95%CI 1.63 to 4.45; p<0.001) and death/ transplantation (HR 3.34; 95% CI 1.83 to 6.11; p < 0.001) than the IA group

Similar to the study conducted by Lee HW, et al included untreated IT patients (n = 126) and treated IA patients (n = 641). Among the populations, 13 (4.4%) developed HCC during the 99.6 months of median follow-up period. Similar cumulative risks of HCC was found between both groups (1.1% and 2.7% vs 1.0% and 2.9%) at 5- and 10-years, respectively; p=0.704. After the adjustment of well-known prognostic variables, of which include age, gender, presence of diabetes and LS values, adjusted hazard ratio (aHR) of the UIT group (vs. the VR group) to predict HCC risk was 2.327 (95% CI 0.475–11.391; p = 0.297).

There is continued debate whether there is an undergoing liver damage and disease progression in the IT phase, and the aforementioned studies has shed light towards answering this question by showing that clinically, there may be disease progression towards a more chronic liver condition. There are three explanations explaining how liver damage may occur in the IT phase, of which are due to (1) immunologic and histologic response and changes, (2) genetic damage as the results of HBV DNA integration to host's DNA and (3) hepatocyte clonal expansion.[12]

There is apparently mild liver immunologic and histologic changes in studies of IT patients. A prior, small scale, study of liver biopsies and sera from 18 neonatally infected HBsAg positive children in Taiwan (aged 4–9 years) showed that all of the children underwent liver abnormalities.[13] Moreover

A study For example, an early, small scale study of liver biopsies and sera from 18 neonatally infected HBsAg(+) children in Taiwan (aged 4–9 years), all 18 children were found to have liver abnormalities.[13] Morever, the presence of mild hepatitis and fibrosis in IT patients also indicate immune mediated liver damage and the destruction of hepatocytes.[6] In addition to immunologic and histological changes during the IT-phase, there is also evidence regarding genetic damage to the hepatocycte and its possibility to initiate oncogenesis. Studies shows that HBV DNA integration into hepatocyte DNA at a sufficient frequency can mutate any host gene's hence reflecting the possibility of host DNA damage within the hepatocyte—which may initiate the progression of HCC. Moreover, clonal expansion of these hepatocytes, which from the studies quantified by the integrated HBV DNA as a cell lineage marker, were found to greatly expands and exceeds the prediction of the hepatocyte model regeneration based on the current consensus on the nature of normal liver.[6,14,15]

Viral Load and HCC Progression in Hepatitis B Infected Patients

The level of HBV DNA has been regarded as a major risk factor for the progression towards HCC in patients infected with hepatitis B. Others include tumor status (tumor number, expansion, presense of vascular invasion), serum AFP level, albumin and the presence of cirrhosis—which all of these are irreversible factors. HBV DNA, on the other hand, is correctable and may serve as a potential preventive factor towards the progression into HCC.[16] The study by Zhou JY, et al.[17] has suggested an increased risk of HCC in HBV-infected patients with high HBV DNA level (>10^4 IU/ml). The study by Chen, et al.[17] also found that HBV-infected patients with HBV levels greater than 1 million copies/mL were 10-fold more likely to develop HCC than patients with the viral load of 300 copies/mL.[18] This is understandable as there are higher chances of mutations due to HBV DNA integration into the host genome which may lead to the proposed molecular mechanisms of hepatocarcinogenesis, which is explained thoroughly in the study by An P, et al[19] that there are at least three

prevailing mechanism for the development of HCC in patients infected with HBV, of which include chronic inflammation that may lead to the accumulation of genetic disruption, the integration of HBV DNA to the host genome that may lead to hepatocarcinogenesis, and HBV proteins that may promote cell proliferation. A large prospective study conducted by Chen CJ, et al[20] also shows an increased risk of HCC and hence it was suggested that HBV DNA may be an indication for antiviral therapy. Hereafter, the pivotal role of anti-viral to suppress the HBV DNA is analysed.

Anti-viral in the Treatment of CHB in the Immune-Tolerant Phase

In the Study of Lee HW, et al[3], all patients in the VR group continued NUC therapy even after the achievement of VR. NUCs initially administered for the VR group comprised lamivudine (n = 269, 42.0%), entecavir (n = 217, 33.9%), adefovir (n = 77, 12.0%), telbivudine (n = 38, 5.9%), tenofovir (n = 24, 3.7%), and clevudine (n = 16, 2.5%). Stated in the Study of Kim GA, et al, with the availability of potent and safe oral NUCs, such as tenofovir and entecavir, the suppression of HBV DNA replication is achievable in most patients without the risk of drug resistance, while the treatment of immunotolerant patients with an even less potent, low genetic barrier drug (lamivudine) was suggested to be highly cost-effective in preventing HCC and cirrhosis.

Several concerns related to the inisiation of NA therapy in CHB patients with low-level inflammation stage as it is considered insufficient when given to patients with normal ALT levels. However, the study conducted by Chang Y, et al[9] showed adequate HBV suppression after a long-term follow up period. Most patients received entecavir or tenofovir, which are known for its high genetic barrier hence there are no viral resistance observed in the treated-IT group. Cost-effectiveness of long-term NA treatment was also discussed in the study. Stated in the study was an additional treatment cost of NA, but the reduction of HCC and liver cirrhosis incidence (5.9% and 15.0%, respectively) over the 120 month study period. The cost-effectiveness of long-term NA therapy was considered quite reasonable, but age should be considered as HCC and LC are rare in young age groups.

Age as an Important Factor of HCC Progression in IT-phase CHB Patients

An interesting topic regarding the consideration of treatment inisiation by taking into account of the patient's age should be discussed. WHO's Recommendation Algorithm on the Management of Persons with Chronic Hepatitis B Infection[16] included age as an important approach for the treatment inisiation conderation. Patients with HBsAg, with no evidence of cirrhosis, with the age above 30 years old, persistently abnormal ALT, with HBV DNA > 20.000 IU/ml are recommended to start NA therapy. While this group of patients are not included in the IT-phase, age is potrayed to be an important prognostic factor in the development of HCC. The EASL clinical practice guidelines 2017[11], as stated above, also suggest that patients with HBeAg-positive chronic HBV infection, persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years, regardless of the severity of liver histological lesions, or if they have a family history of HCC or cirrhosis. Study conducted by Lee HW, et al found no occurance of HCC in the subgroup analysis according to the age ≤ 40 years old. The study also found that patients with the age >40 years old showed the trend towards the higher risk of HCC (1.6% vs 0.0%; p=0.379) at 7-years, compared to the subgroup of the age ≤ 40 years old, although this results was not statistically significant.

CONCLUSION

While there are studies showing apparent results regarding the treatment of CHB patients in the IT-phase and its benefit in reducing cumulative incidence of HCC, its clinical advantage is soon to be discovered. The results were inconclusive, and the initiation of treatment in CHB patients within the IT-phase cannot yet be recommended until further research. Even so, CHB patients in the IT phase patients who are young with ALT/AST normal may be treated if they are older than 30 years. Starting the treatment at 20s, would not be beneficial as they won't reach seroconversion. If choose to be treated, then treatment with NAs is recommended.

All of the available studies were conducted in Korea, with most (>98%) CHB patients were infected with genotype C HBV through vertical transmission. Such condition may not be similar in other countries, hence we encourage studies to be conducted in other countries. Multi-centers studies with longer follow-up span are more encourage to overcome small event numbers and produce adequate development period for HCC. Questions surrounding cost-effectiveness of the treatment using NAs should also be studied.

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