財團法人明日醫學基金會補助專題研究計畫

☑成果報告 ☐期中進度報告

計畫名稱：

慢性 B 型肝炎抗病毒治療使用不足與肝臟相關罹病與死亡風險的關聯性
Association between underutilization of antiviral treatment for chronic hepatitis B and risks of liver-related mortality and morbidity

計畫類別：☑ 個別型計畫　　☐ 整合型計畫

執行期間： 110 年 1 月 1 日起 至 110 年 12 月 31 日止

計畫主持人： **許耀峻**
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計畫參與人員：

成果報告類型：☑精簡報告 ☐完整報告

處理方式：☐可公開查詢

執行單位：義守大學醫學系及義大醫院肝病中心

Association between underutilization of antiviral treatment for chronic hepatitis B and risks of liver-related mortality and morbidity

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Background: Chronic hepatitis B (CHB) is the leading cause of liver-related disease and death worldwide. Antiviral treatment for CHB includes interferon-alpha and nucleoside (acid) analogues (NAs). Previous studies have confirmed that antiviral therapy can effectively reduce the risks of clinical events such as developing hepatocellular carcinoma (HCC). However, it remained unclear how seriously antiviral therapy was underutilized in clinical practice.

Aim: We aimed to quantify the association of liver-related morbidity and mortality due to underutilization of antiviral therapy in patients with CHB in Taiwan

Methods: This is a retrospective cohort study of adult patients with CHB based on analysis of the electronic healthcare record (EHR) of the E-Da hospital, Kaohsiung, Taiwan. Eligibility criteria for inclusion included age >18 years, CHB defined by seropositivity of HBsAg for longer than 6 months, and liver-related morbidity that includes HCC (certified by the cancer registry), complications from hepatic decompensation such as hepatic encephalopathy, variceal bleeding, refractory ascites, or acute on chronic liver failure, and liver-related mortality (certified by the death registry). Patients with hepatitis C virus or human immunodeficiency virus infection were excluded.

Results: Between April 1, 2004 and December 31, 2012, there were more than

30,000 adult patients diagnosed with CHB (positive HBsAg for 6 months or longer) in the E-Da Hospital and 2,236 patients in this CHB cohort developed HCC during the study period, which was certified by the cancer registry. Among them, 174 patients could not be further categorized because of missing or erroneous data, 351 patients had been treated with antiviral therapy prior to HCC diagnosis, 839 patients received antiviral therapy after HCC diagnosis, and 1046 patients were never treated for their CHB throughout the study period.

Conclusions: Antiviral therapy for CHB was underutilized in Taiwan. Most of the CHB patients who developed HCC did not receive antiviral therapy before the diagnosis of HCC and approximately half of them were never treated for CHB.

Keywords: chronic viral hepatitis B; antiviral therapy; linkage to care

INTRODUCTION

Consistent data from randomized controlled trials, real-world cohort studies, and laboratory experiments have demonstrated that antiviral therapy is effective to improve outcomes in patients with chronic hepatitis B (CHB).1, 2 Nonetheless, several lines of evidence suggest that antiviral treatment for CHB is currently underutilized in Taiwan where hepatocellular carcinoma (HCC) and hepatic failure remain the major causes of death.3 For instance, hepatitis B virus (HBV) infection has continued to be the leading etiology of HCC without changes in trend over time after antiviral treatment for CHB was reimbursed for by the national health insurance since 2003. The number of HBV-related HCCs remained invariably high with more than 3,500 new cases diagnosed every year in recent statistics update although the age-adjusted incidence might appear to decline.

Moreover, among the 2 million patients with CHB in Taiwan, less than one tenth (n=138,261 as of August 09, 2020 according to the bureau of national health insurance) are currently treated with antiviral therapy. In clinical practice, it is not uncommon to find CHB patients who progress to HCC, hepatic decompensation with clinical complications, or even liver-related death without having received antiviral therapy which could have prevented the progression.

The magnitude of underutilization, however, remains unclear in Taiwan. Furthermore, it needs to be clarified how the underutilization of CHB treatment is associated with excessive risks of liver-related mortality and morbidity at a population level. These findings will reveal gaps in the current practice where the opportunities to prevent adverse outcomes were missed and may thus inform healthcare policymaking to improve the linkage to care.

Hypothesis

Antiviral therapy for chronic hepatitis B is underutilized and is associated with excessive risks of liver-related morbidity and mortality in Taiwan

Primary aim

To quantify the "missed opportunities" in preventing liver-related mortality and morbidity in Taiwan because of underutilization of antiviral treatment for CHB

Secondary aims

- To clarify the major causes for not having received antiviral therapy before CHB patients develop clinical complications

- To model how many events (HCC, hepatic decompensation, deaths) might have been prevented if a certain portion (a tuning parameter) of these patients had been given antiviral treatment

Methods and Materials

This is a retrospective cohort study based on the HER databases that include demographic data, cancer registry, death certificate, vital statistics, laboratory data such as serum liver enzymes, viral serology (e.g., hepatitis B surface antigen, i.e., HBsAg, status), and measurements of viremia.

To achieve our goals, first we will identify all patients who develop HCC, encounter the first episode of clinical complications as result of decompensated cirrhosis, first admission for acute on chronic liver failure, and liver-related mortality every year from 2004 to 2018 (the most updated data). Then these patients were classified as having CHB or not, which will be defined by HBsAg status (if available), enrollment in the surveillance program for chronic viral hepatitis, registry in the reimbursement list for antiviral therapy, or specific diagnostic code for CHB. For those patients who had not been tested for HBsAg status and was not diagnosed with HBV infection until occurrence of the aforementioned clinical events, we assume these patients had

CHB because the vast majority of Taiwanese patients with CHB acquire HBV infection through vertical transmission or in infancy.

Among these CHB patients with late clinical events, we will identify those who had never received antiviral therapy until one month prior to the clinical event. Patients who receive antiviral therapy within one month prior to the event will not be excluded because the treatment could be given as a result of the event and a therapy shorter than one month is insufficient to prevent a late event. We will then calculate the number of these patients, characterize them in details, and examined the chronological changes over years.

Statistical analysis

There are about 2,000,000 Taiwanese residents with chronic hepatitis B. Each year, 3,500 people develop HCC and the number remains stable in the past 10 years. Nearly half of them (40~45%) are related to HBV infection. In short, we should be able to identify more than 15,000 CHB patients who developed HCC for our analysis. Taking into consideration the scenarios where CHB patients may progress to hepatic decompensation or pass away without developing HCC first, we are confident to identify at least 20,000 patients eligible for analysis.

Continuous data were summarized with median and interquartile range (IQR), whereas categorical data were presented with the exact number and proportion. The cumulative incidences of non-fatal events were estimated by semi-parametric analyses adjusted for competing mortality with the method developed by Gray. The incidence rate of each event was calculated by event occurrences per person-time for a specified time interval, and the trend over time was examined using Poisson regression for statistical significance.

Potential risk factors for underutilization of antiviral therapy were explored by logistic regression. Regardless of statistical significance in the univariable analysis, all variables were examined by a stepwise approach in the multivariable regression that retained statistically significant (prespecified as a $P < 0.05$) variables in the final model. The analyses will be based on available information in the database without data imputation. Observations with missing data are thought to occur randomly and not included in the regression. Commercial software programs Stata (version 13.0, Stata Corp, College Station, TX, USA) and SAS (version 9.4, SAS Institute, Cary, NC, USA) will be used to manage and analyze the data. We computed all point estimates along with their 95% confidence intervals (CIs). All tests were two-sided

with statistical significance defined as a P value <0.05.

Preliminary results

The data has been extracted from the database and has been analyzed. Only preliminary results are available now because the huge amount of data in need of data pruning. Finally, we found there were more than 30,000 adult patients diagnosed with CHB (positive HBsAg for 6 months or longer) in the E-Da Hospital between April 1, 2004 and December 31, 2012. In this retrospective cohort with CHB, 2,236 patients developed HCC during the study period, which was certified by the cancer registry. Among them, 174 patients could not be further categorized because of missing or erroneous data, 351 patients had been treated with antiviral therapy prior to HCC diagnosis, 839 patients received antiviral therapy after HCC diagnosis, and 1046 patients were never treated for CHB throughout the study period (Figure 1).

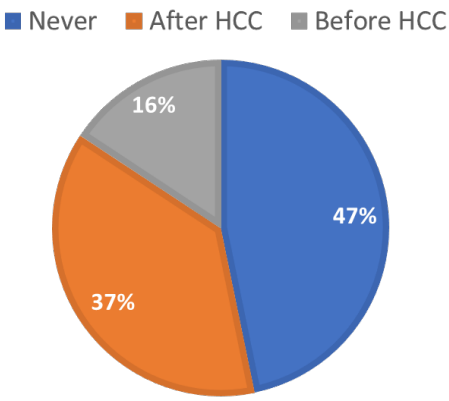

Figure 1. Proportions of patients treated with antiviral therapy according to the timing in reference to the diagnosis of HCC: Antiviral therapy was never used, used prior to HCC diagnosis, and used only after HCC diagnosis in 1046, 351, and 839 patients, respectively.

We'll go on to analyze potential causes for not having been treated with antiviral therapy in these patients. The causes may be classified along the chain all the way from the diagnosis of CHB (e.g. never examined for HBsAg until the occurrence of a late event) to the national policy of antiviral therapy (e.g., patients with an established diagnosis of CHB and regularly followed up at specialists who could not initiate antiviral therapy because he or she did not fulfill the reimbursement criteria until occurrence of the late event).

Finally, we'll estimate how many late events could have been prevented with administration of antiviral therapy by referencing studies which reported the effectiveness for reducing the risk of incident HCC, complications of decompensated cirrhosis, and liver-related mortality. As a more conservative approach, we assume at least 3 years of antiviral therapy will be needed to be effective.

REFERENCES:

1. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. Journal of hepatology 2012;57:167-85.

2. Polaris Observatory C. Global prevalence, treatment, and prevention of hepatitis B

161 virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol
162 2018;3:383-403.
163 3. Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and
164 treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology
165 2018;67:1560-99.
166 4. European Association for the Study of the Liver. Electronic address eee, European
167 Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the
168 management of hepatitis B virus infection. Journal of hepatology 2017;67:370-98.
169 5. Sarin S, Kumar M, Lau G, et al. Asian-Pacific clinical practice guidelines on the
170 management of hepatitis B: a 2015 update. Hepatology international 2016;10:1-98.
171 6. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with
172 tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up
173 study. Lancet 2013;381:468-75.
174 7. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the
175 reversal of fibrosis/cirrhosis and continued histological improvement in patients with
176 chronic hepatitis B. Hepatology 2010;52:886-93.
177 8. Lok AS, McMahon BJ, Brown RS, Jr., et al. Antiviral therapy for chronic hepatitis
178 B viral infection in adults: A systematic review and meta-analysis. Hepatology
179 2016;63:284-306.