**財團法人明日醫學基金會研究計畫申請書**

|  |  |
| --- | --- |
| 計畫名稱 | （中文）慢性B型肝炎患者停止類核苷(酸)藥物後發生肝臟衰竭及死亡風險的真實世界分析 |
| （英文）A real-world analysis for the risks of liver failure and mortality after cessation of nucleos(t)ide analogs in patients with chronic hepatitis B |
| 計畫類別 | 🗹個別型 | 🞎整合型 |
| 計畫歸屬 | 🞎基礎醫學🞎生物醫學🗹臨床醫學🞎資訊系統🞎醫院管理🞎整合性醫學研究 |
| 計畫主持人 | 姓名：許耀峻Yao-Chun Hsu | 機關：**輔大醫院** |
| 職稱：**醫研部主任** | 單位：**醫學研究部** |
| 通訊地址 | **新北市新莊區中正路510號** |
| 聯絡電話 | **(02)29053405, 0988687726** |
| 計畫執行期限 | 自 **108** 年 1 月 **1** 日起至 **108** 年 **12** 月 **31** 日止 |
| 共同主持人（一） | 姓名：  | 機關：  |
| 職稱： | 單位：  |
| 共同主持人（二） | 姓名： | 機關： |
| 職稱： | 單位： |
| 共同主持人（三） | 姓名： | 機關： |
| 職稱： | 單位： |
| 共同主持人（四） | 姓名： | 機關： |
| 職稱： | 單位： |

**研究計畫摘要**

**研究主題:** 類核苷(酸)藥物治療慢性B型肝炎需停藥的策略面臨的臨床風險評估

**ㄧ、試驗目的：**

１. 本研究將釐清慢性Ｂ型肝炎患者停止口服類核苷(酸)藥物後發生猛爆性肝炎、肝臟衰竭與因肝病死亡的發生率

2. 進一步探討上述發生猛爆性肝炎、肝衰竭與因肝病死亡的病人特徵

3. 藉由上述得到的量化資料，建立計量模型估計停藥政策的風險效益分析

**二、研究背景：**

慢性B型肝炎是國人肝硬化、肝衰竭和肝癌的主要病因，使用口服類核苷(酸)藥物可有效抑制B肝病毒複製，是國內外醫學會建議的第一線治療藥物，已被廣泛使用。口服抗病毒藥物治療期間B型肝炎會進入緩解(remission)狀態，然而停止治療後多數病人B肝病毒會再度大量複製，可能又會復發活動性肝炎，甚至導致嚴重急性發作；雖然停止治療可能有助於恢復對抗病毒的免疫反應，甚至增加表面抗原清除的機會，但是在真實世界日常診療中，Ｂ型肝炎患者停止類核苷(酸)藥物所造成的可能效益與潛在風險尚未被釐清。

**三、研究方法：**

本計畫為本國多中心回溯世代研究，將經由分析醫院電子病歷資料(electronic health record)，整合國內義大醫院、義大癌治療醫院、台中榮民總醫院、台北榮民總醫院、嘉義基督教醫院、宜蘭羅東博愛醫院、台大雲林分院和市立台南醫院等各院的資料，研究對象為慢性Ｂ型肝炎(定義為慢性感染表面抗原陽性超過６個月)成年(滿20歲)患者，使用類核苷(酸)藥物至少12個月後停止藥物至少１個月，並排除非首次抗病毒療程者（曾使用過類核苷酸或干擾素藥物超過１個月），罹患任何癌症或曾接受器官移植的病人，或者停藥時已呈現肝機能代償不全的情形。符合條件的病人自停止抗病毒治療後，追蹤肝臟發炎與機能指標的異常狀況，並計算發生下列事件的發生率：急性肝炎發作定義為血清轉胺酶上升超過正常上限值5倍或10倍(200或400 U/L)，急性併慢性肝衰竭（Acute on Chronic Liver Failure），以及因肝病死亡(Liver-related Death)。

**關鍵詞:**慢性B性肝炎；類核苷酸藥物；風險效益分析；醫療政策

**研究計畫目的及背景說明**

Antiviral therapy with nucleos(t)ide analog (NA) has become the cornerstone in the management of chronic hepatitis B virus (HBV) infection 1-3. Through potent inhibition of viral replication, NA ameliorates hepatic inflammation, prevents liver fibrosis, and may improve clinical outcomes in patients with chronic hepatitis B (CHB) 4-6. However, NAs exerts little effects on the viral covalently closed circular DNA (cccDNA) in the nucleus, and treatment cessation almost always leads to loss of viral remission 7-9. Following viral relapse in patients who discontinue NAs, clinical hepatitis frequently ensues and can rapidly deteriorate into liver failure with fatal consequences 10,11.

Currently, hepatitis B surface antigen (HBsAg) loss is the most widely accepted endpoint to guide cessation of NA treatment 12-14. However, as HBsAg loss is an infrequent event, this strategy entails an indefinite therapeutic duration that could be lifelong for the vast majority of NA-treated patients 15. Intriguingly, recent studies suggested that discontinuation of NA therapy could be associated with a higher chance of HBsAg loss 16-18. Berg and colleagues demonstrated in a randomized trial that a substantial proportion of patients who were allocated to stop tenofovir achieved HBsAg clearance and maintained viral suppression with HBV DNA <2,000 IU/mL 16. Jeng and colleagues also reported a higher incidence of HBsAg loss after NA cessation than that during therapy 18.

However, a strategy of finite NA therapy needs to balance the risk of clinical flare and the chance of HBsAg clearance. Therefore, it is controversial whether patients with CHB may stop NAs before loss of HBsAg. The risks of serious outcomes have not been quantified in the real world. Bridging this knowledge gap is essential to inform the healthcare policy in weighting the pros and cons of stopping NA in CHB patients.

**研究目標:**

1. To quantify the incidences of liver failure and liver-related death after NA cessation
2. To characterize individuals at distinct risks of serious clinical outcomes
3. To calculate healthcare expenditure in the clinical events incurred by NA cessation

**研究方法及步驟：**

***Study design and setting***

This is a retrospective cohort study based on analysis of the electronic healthcare database of 8 hospitals (E-Da Hospital, E-Da Cancer Hospital, Lotung Poh-Ai Hospital, National Taiwan University Hospital-Yunlin, Veterans General Hospital-Taichung and Taipei, Tainan Municipal Hospital, and Chia-Yi Christian Hospital) in Taiwan. We will screen all previously untreated CHB patients who stopped NA therapy after at least 12 months on therapy for eligibility.

***Patient population***

Included patients must fulfill all of the following criteria: adult patients aged 20 years or older with a diagnosis of chronic hepatitis B virus, defined as HBsAg positive for 6 months or longer who completed antiviral therapy using any NA for a minimum of one year and discontinuation of the treatment for at least one month. They were excluded if any of the following condition exists: ever exposure to any NA or interferon for more than one month, any malignant disease or organ transplantation, or manifestation of hepatic decompensation when the antiviral therapy was discontinued.

***Data collection and patient follow-up***

After identifying the eligible patients from the computerized database, we will record pertinent information including demographics, blood chemistry, hemogram, viral serology, and relevant data such as health-related behavior Accuracy of the abstracted information will be audited by the investigators, who will also ascertain the outcome of each enrolled subject. Those with cirrhosis remain eligible for analysis because the reimbursement is finite in Taiwan in the absence of splenomegaly, esophagogastric varices, or pretreatment viremia >2,000 IU/mL. Eligible patients will be followed up for the outcomes listed below until death or data censoring:

***Longitudinal follow-up and outcome measure***

The primary study outcome was the development of acute on chronic liver failure (ACLF), as defined by the Asian-Pacific Association for the Study of Liver Diseases. The secondary outcomes are mortality resulting from ACLF, acute exacerbation (AE) of CHB defined as ALT>200 U/L with viremia >2,000 IU/mL, hepatic decompensation defined as serum bilirubin >5 mg/dL and INR >1.5, hospitalizations/ICU admission due to AE of CHB or hepatic decompensation, and hepatocellular carcinoma (HCC). Generally, the frequency of surveillance was every 6 months in patients without cirrhosis and 3 months in those with cirrhosis. Patients were censored at loss to follow-up, death, or the last follow-up date on June 01, 2019.

***Statistical analysis***

Continuous variables are expressed with mean and standard deviation, and categorical variables with proportions. Death occurring prior to the non-fatal events may be considered as a competing risk event. The modified Kaplan-Meier method and the Gray's method were used to calculate the cumulative incidences. Factors that are associated with the events are analyzed by the modified Cox proportional hazard model adjusted for competing risks and multiple covariates. The hazard ratio (HR) along with its 95% confidence interval (CI) will be reported. Data was managed and analyzed by the commercially available software (Stata, version 13.0; Stata Corp, College Station, TX, USA). The competing risk analyses were performed using the R software with the “cmprsk\_2.1-4” package. A p value <0.05 defined statistical significance.

**References:**

1. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int.* 2016;10(1):1-98.

2. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67(2):370-398.

3. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology.* 2018;67(4):1560-1599.

4. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology.* 2010;52(3):886-893.

5. Wu CY, Lin JT, Ho HJ, et al. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. *Gastroenterology.* 2014;147(1):143-151 e145.

6. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet.* 2013;381(9865):468-475.

7. Seto WK, Hui AJ, Wong VW, et al. Treatment cessation of entecavir in Asian patients with hepatitis B e antigen negative chronic hepatitis B: a multicentre prospective study. *Gut.* 2015;64(4):667-672.

8. Hsu YC, Mo LR, Chang CY, et al. Association Between Serum Level of Hepatitis B Surface Antigen at End of Entecavir Therapy and Risk of Relapse in E Antigen-Negative Patients. *Clin Gastroenterol Hepatol.* 2016;14(10):1490-1498 e1493.

9. Chen CH, Hsu YC, Lu SN, et al. The incidence and predictors of HBV relapse after cessation of tenofovir therapy in chronic hepatitis B patients. *J Viral Hepat.* 2017.

10. Hsu YC, Mo LR, Chang CY, et al. Serum viral load at the virological relapse predicts subsequent clinical flares in chronic hepatitis B patients off entecavir therapy. *J Gastroenterol Hepatol.* 2017;32(8):1512-1519.

11. Van Hees S, Bourgeois S, Van Vlierberghe H, et al. Stopping nucleos(t)ide analogue treatment in Caucasian hepatitis B patients after HBeAg seroconversion is associated with high relapse rates and fatal outcomes. *Aliment Pharmacol Ther.* 2018;47(8):1170-1180.

12. Kim GA, Lim YS, An J, et al. HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability. *Gut.* 2014;63(8):1325-1332.

13. Yip TC, Wong GL, Wong VW, et al. Durability of hepatitis B surface antigen seroclearance in untreated and nucleos(t)ide analogue-treated patients. *J Hepatol.* 2017.

14. Seto WK, Cheung KS, Wong DK, et al. Hepatitis B surface antigen seroclearance during nucleoside analogue therapy: surface antigen kinetics, outcomes, and durability. *J Gastroenterol.* 2016;51(5):487-495.

15. Chevaliez S, Hezode C, Bahrami S, Grare M, Pawlotsky JM. Long-term hepatitis B surface antigen (HBsAg) kinetics during nucleoside/nucleotide analogue therapy: finite treatment duration unlikely. *J Hepatol.* 2013;58(4):676-683.

16. Berg T, Simon KG, Mauss S, et al. Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients - FINITE study. *J Hepatol.* 2017;67(5):918-924.

17. Hung CH, Wang JH, Lu SN, Hu TH, Lee CM, Chen CH. Hepatitis B surface antigen loss and clinical outcomes between HBeAg-negative cirrhosis patients who discontinued or continued nucleoside analogue therapy. *J Viral Hepat.* 2017;24(7):599-607.

18. Jeng WJ, Chen YC, Chien RN, Sheen IS, Liaw YF. Incidence and predictors of HBsAg seroclearance after cessation of nucleos(t)ide analogue therapy in HBeAg negative chronic hepatitis B. *Hepatology.* 2017.

19. Chen CH, Hung CH, Hu TH, et al. Association Between Level of Hepatitis B Surface Antigen and Relapse After Entecavir Therapy for Chronic Hepatitis B Virus Infection. *Clin Gastroenterol Hepatol.* 2015;13(11):1984-1992 e1981.

20. Chen CH, Lu SN, Hung CH, et al. The role of hepatitis B surface antigen quantification in predicting HBsAg loss and HBV relapse after discontinuation of lamivudine treatment. *J Hepatol.* 2014;61(3):515-522.