**財團法人明日醫學基金會研究計畫申請書**

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| 計畫名稱 | （中文）停止類核苷(酸)藥物治療後急性肝炎發作與B型肝炎表面抗原血清清除發生率的關聯 | |
| （英文）Association of Acute Hepatitis Flares with Incidence of HBsAg Seroclearance after Cessation of Nucleos(t)ide Analogues | |
| 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 | |
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**研究計畫摘要**

**ㄧ、試驗目的：**

1. 釐清慢性B型肝炎患者停止類核苷(酸)藥物治療後若發作急性肝炎，是否會影響B型肝炎表面抗原血清清除發生率

**二、研究背景：**

患有慢性B型肝炎病毒感染的病人在停止使用核苷(酸)類似物治療後經常會經歷急性肝炎發作。這些肝炎發作可能會導致肝功能衰竭，但也被認為可以促進B型肝炎表面抗原(HBsAg)的血清清除，這是停止使用核苷(酸)類似物的主要理由之一。我們的目的是評估和釐清在慢性B型肝炎患者中，核苷(酸)類似物停藥後急性肝炎發作與隨後的HBsAg血清清除之間的關聯。

**三、研究方法：**

這是一項多中心的回溯世代研究，我們將系統性分析義大醫療體系中接受核苷(酸)類似物治療的所有慢性B型肝炎患者。我們將納入在2004年4月1日至2022年5月24日之間停止核苷(酸)類似物藥物，且在停藥前至少已經連續治療一年的成人，惡性腫瘤、肝功能不全(經由黃疸和凝血功能障礙定義)或其他病毒共感染的患者將被排除。急性肝炎發作的定義是血清丙氨酸轉氨酶(ALT)上升超過正常上限(ULN; 40 U/L)5倍，主要研究結果事件是核苷(酸)類似物停藥期間的HBsAg血清清除發生率。我們將使用競爭風險分析估計HBsAg血清清除的發生率，並考慮死亡或再次治療作為非隨機的資料設限，對結果估計的影響，並且在多變項調整的次分佈風險回歸(sub-distribution hazard)模型中，將急性ALT發作作為一個隨時間而變動的變數。

**關鍵詞:**慢性B性肝炎；核苷(酸)類似物抗病毒治療；有限療程；B型肝炎血清表面抗原清除

**研究計畫目的及背景說明**

Chronic hepatitis B virus (HBV) infection remains a primary contributor to liver-related morbidity and mortality globally, especially in Asian regions including Taiwan. The care of individuals with chronic hepatitis B (CHB) has evolved to include antiviral treatments, primarily interferon alpha and nucleos(t)ide analogs (NAs). By effectively suppressing viral replication, NAs not only decrease viremia and mitigate liver inflammation but also hold potential in halting or even reversing liver scarring. Numerous studies validate the efficacy of NAs in enhancing patient outcomes. Yet, maintaining the therapeutic benefits often proves challenging after discontinuation of NA therapy.

Because of high off-therapy relapse rates, major international guidelines currently recommend an indefinite prolongation of NA therapy, possibly until loss of hepatitis B surface antigen (HBsAg) with or without appearance of accompanying antibodies. However, this strategy entails life-long treatment for most treated patients. Recently, intense research has been carried out to clarify predictors of off-therapy relapse and identify patients who can maintain remission without resuming medication. One of the unresolved issues is whether acute hepatitis flares off NA therapy is associated with a higher chance of HBsAg seroclearance. In an observational study, patients who experienced clinical relapse and remained untreated demonstrated a notably higher incidence of HBsAg seroclearance compared to clinical relapsers who underwent retreatment. However,

In this study, we aim to clarify whether acute hepatitis flares in patients with chronic hepatitis B, after discontinuation of nucleos(t)ide analog therapy, affect the incidence rate of hepatitis B surface antigen seroclearance.

**Methods and Materials:**

***Design and setting***

We will retrospectively screen the electronic healthcare records (EHRs) of all patients who received any NA regimen for CHB in the E-Da Hospital, E-Da Cancer Hospital, and E-Da Dachang Hospital (all in Kaohsiung, Taiwan). All patients were managed as appropriate according to the practice standard in Taiwan. Demographic data, laboratory results, diagnostic codes, pharmacy prescription claims, and vital statistics data were extracted from the EDA Healthcare System EHR database and complimented by manual chart review as needed.

The study is carried out in compliance with the Declaration of Helsinki and the protocol was approved by the institutional review board of the E-Da Healthcare System.

***Study patients***

Patients eligible for analysis are adults (aged 20 years or older) with CHB as defined by having a specific diagnosis code or positive HBsAg for at least 6 months, who were previously untreated and initiated on a NA regimen including lamivudine, adefovir, telbivudine, entecavir, or tenofovir for a minimum of one year prior to treatment cessation. Patients are excluded for any of the following criteria: seroclearance of HBsAg during the NA treatment, positive serology of HBeAg at treatment cessation, co-infection with hepatitis C virus (HCV), organ transplantation, malignant disease including hepatocellular carcinoma (HCC), or any severe comorbidity that was certified in the registry of catastrophic illness patient database. The study baseline was set at the day of treatment cessation, as confirmed by pharmacy records. The definition of cirrhosis was based upon a clinical diagnosis, usually made according to clinical assessment including liver images mainly by sonography. Hepatic insufficiency was defined by laboratory measurements of serum bilirubin >2mg/dL or prolongation of prothrombin time >3 seconds because this operational definition indicated reimbursement for antiviral treatment according to the national health insurance in Taiwan.

***Criteria for initiation and discontinuation of antiviral treatment***

Antiviral therapy for HBV infection is covered by the Taiwan national health insurance, which is universal and compulsory, since October 1, 2003,6 but is strictly regulated with criteria specifying indications and therapeutic durations. In brief, NA treatment was indicated in patients with manifestations of hepatic insufficiency (operationally defined as serum bilirubin rising >2mg/dL or prolongation of prothrombin time >3 seconds). Except for a special condition such as organ transplantation or malignancy that required antiviral prophylaxis, the indications were generally determined by high viral load (>2,000 IU/mL) and persistent ALT elevation (>2 folds the upper limits of normal [ULN] for at least 3 months), with the details separated by HBeAg status. For the indication of cirrhosis, a prerequisite of HBV DNA >2,000 IU/mL was required during the study period.

The reimbursement of antiviral therapy is finite in principle and generally 3 years at most, with particular maximum duration of coverage specified. After July 1, 2010, indefinite coverage was granted for the indication of cirrhosis but required evidence of portal hypertension (i.e., splenomegaly or esophagogastric varices) in addition to imaging characteristics of cirrhosis if pathological proof is absent. Moreover, HBV DNA >2,000 IU/mL is a prerequisite. Thus, throughout the study period, patients with a clinical diagnosis of cirrhosis but without viremia of at least 2,000 IU/mL or without overt features of portal hypertension were ineligible for indefinite treatment.

***Criteria for retreatment, off-therapy observation, and outcome measurement***

The criteria for antiviral retreatment were also tightly regulated by the healthcare system. Reimbursement for retreatment was indicated for occurrence of hyperbilirubinemia (serum bilirubin > 2mg/dL), coagulopathy (prolonged prothrombin time > 3 seconds), or persistent hepatitis flares (ALT >2 x ULN for > 3 months). Retreatment was not indicated for virological relapse alone or transient (<3 months) ALT elevation, regardless of the level of serum HBV DNA or ALT.

***Study outcomes***

The primary outcome is seroclearance of HBsAg that occurred during the off-therapy period. HBV reactivation is defined with reoccurrence of HBV DNA >2000 IU/mL.

The observation for occurrence of study outcome starts after the day of treatment cessation and is censored at death, the last EHR encounter, or 6 months following antiviral re-treatment. The effect of retreatment on the outcome observation is further analyzed.

***Statistical analyses***

Data of continuous variables were summarized by medians along with interquartile ranges (IQRs) and those of categorical values were shown in numbers together with percentages. We applied the Kaplan Meier method to estimate the cumulative incidence rates of clinical events and examined the differences between patient subgroups by the log rank test. The incidence rates of study outcomes were calculated by event per person-time, and the statistical significance for a chronological trend was examined using Poisson regression. As missing data were expected in this retrospective real-world analysis, we only summarized data that were available in more than 90% of the study population. Without data imputation, observations with missing data were regarded as random occurrences and not included in the regression analyses. A sensitivity test was performed to include only patients who received either entecavir or tenofovir.

For a study outcome with more than 10 event occurrences, the Cox proportional hazard model was performed to explore risk factors. We carried out the multivariable analysis in a stepwise manner to remove variables that were not statistically significant. Point estimates were reported along with 95% confidence intervals (CIs). All statistical examinations were two-sided. Statistical significance was set at a P value <0.05. All analyses were performed using the commercially available software SAS (version 9.4, SAS Institute, Cary, NC, USA).

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