# 財團法人明日醫學基金會研究計畫申請書

	(中文) 慢性 B 型肝炎患者停止類核苷(酸) 藥物後再接受抗病毒	
計畫名稱	治療與表面抗原血清清除之間的關聯	
	(英文) Association Between Retreatment and Hepatitis B Surface Antigen Seroclearance in Patients with Clinical Relapses Following	
	Withdrawal of Nucleos(t)ide Analogues	
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# 研究計畫摘要

一、試驗目的:

本研究目的在釐清停止核苷(酸)類似物治療後出現臨床復發的患者中,再治療與B型肝炎表面抗原血清清除之間的關聯

二、研究背景:

使用核苷(酸)類似物治療慢性B型肝炎的最佳療程仍存在爭議,其中停藥策 略被認為可以誘導B型肝炎表面抗原(HBsAg)的血清清除。然而,停藥常常 導致臨床肝炎復發,而臨床復發通常意味著需要再治療。目前尚不清楚再治療 對於B型肝炎表面抗原血清清除的影響。

三、研究方法:

這是一項回溯性、多中心世代研究,我們將系統地檢視義大醫療體系中,所有接 受第一線核苷(酸)類似物,亦即恩替卡韋(entecavir)或替諾福韋(tenofovir),治 療的慢性 B 型肝炎患者,並且找出隨後停止治療的人。符合條件的患者在停止治 療前必須確認 B 型肝炎 e 抗原(HBeAg)為陰性,並且具有檢測不到 B 型肝炎 病毒 DNA 的紀錄。我們將排除患有惡性腫瘤、接受器官移植或病毒合併感染的 患者。臨床肝炎復發的定義是停止治療後血清丙氨酸氨基轉移酶(ALT)升高到 正常上限的兩倍以上。主要結果是臨床復發後 B 型肝炎表面抗原(HBsAg)的血 清清除。恢復核苷(酸)類似物治療被分析為一個時變變量,並對潛在的干擾因 素進行調整,以闡明其與 B 型肝炎表面抗原血清清除的關聯。

**關鍵詞:**B性肝炎病毒;抗病毒藥物;有限療程;功能性痊癒

## 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 the impact of resuming antiviral treatment on HBsAg seroclearance in patients who experience relapse after discontinuing NA therapy.

In this study, we aim to investigate whether resumption of antiviral treatment is associated with seroclearance of hepatitis B surface antigen in patients with chronic hepatitis B who experience relapse after discontinuation of nucleos(t)ide analog therapy. This research will provide valuable insights into the long-term management of CHB patients and potentially inform decisions regarding retreatment strategies

#### Methods and Materials:

#### Design and setting

This retrospective study will analyze electronic health records (EHRs) of patients who received nucleos(t)ide analog (NA) treatment for chronic hepatitis B (CHB) at E-Da Hospital, E-Da Cancer Hospital, and E-Da Dachang Hospital in Kaohsiung, Taiwan. Data extraction will include demographic information, laboratory results, diagnostic codes, pharmacy prescription claims, and vital statistics from the EDA Healthcare System EHR database, supplemented by manual chart review when necessary. The study adheres to the Declaration of Helsinki and has been approved by the E-Da Healthcare System's institutional review board.

## Study patients

Eligible participants will be adults ( $\geq$ 20 years) with CHB, defined by a specific diagnosis code or positive HBsAg for at least 6 months. Inclusion criteria include: 1) Previously untreated patients, 2) initiated on NA regimen (lamivudine, adefovir, telbivudine, entecavir, or tenofovir), 3) minimum one year of NA treatment prior to 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

NA treatment initiation followed Taiwan's national health insurance guidelines, which generally required high viral load (>2,000 IU/mL) and persistent ALT elevation (>2x ULN for  $\geq$ 3 months), with specific criteria based on HBeAg status. For cirrhotic patients, HBV DNA >2,000 IU/mL was required.

Treatment duration was typically limited to 3 years, with exceptions for certain cirrhotic patients meeting specific criteria after July 1, 2010. The indefinite coverage for cirrhosis required 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 also followed the national health insurance in general. Retreatment was indicated for hyperbilirubinemia (serum bilirubin >2mg/dL), coagulopathy (prolonged prothrombin time >3 seconds), and persistent hepatitis flares (ALT >2x ULN for >3 months). Retreatment was not indicated for virological relapse alone or transient (<3 months) ALT elevation.

#### 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, and clinical relapse is defined by elevation of serum ALT above two times the upper limit of normal. 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.

#### Statistical analyses

Descriptive statistics will be used to summarize the data. Continuous variables will be presented as medians with interquartile ranges (IQRs), while categorical variables will be expressed as numbers and percentages. The cumulative incidence rates of clinical events will be estimated using the Kaplan-Meier method. Differences between patient subgroups will be examined using the log-rank test. Incidence rates of study outcomes will be calculated as events per person-time, and Poisson regression will be used to assess chronological trends for statistical significance.

For study outcomes with more than 10 event occurrences, we will employ the Cox proportional hazard model to explore risk factors. Multivariable analysis will be conducted in a stepwise manner, removing variables that are not statistically significant. Point estimates will be reported with 95% confidence intervals (CIs). A sensitivity analysis will be performed, including only patients who received either entecavir or tenofovir. All statistical tests will be two-sided, with statistical significance set at a P value <0.05. Analyses will be conducted using SAS software (version 9.4, SAS Institute, Cary, NC, USA).

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