**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） 慢性B型肝炎E抗原陰性患者在終止類核苷(酸)藥物治療因而發生病毒學復發的臨床後果 |
| （英文）Clinical Outcomes following Virological Relapse after Discontinuation of Nucleos(t)ide Analogues in Chronic Hepatitis B E Antigen-negative Patients  |
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| 計畫執行期限 | 自 **105** 年 1 月 **1** 日起至 **105** 年 **12** 月 **31** 日止 |
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**研究計畫摘要**

**研究主題:** 慢性B型肝炎E抗原陰性患者在終止類核苷(酸)治療後若發生病毒學復發，其臨床後果為何

**ㄧ、試驗目的：**

已知使用類核苷(酸)抗病毒藥物的慢性B型肝炎病人，停藥後病毒學復發機率很高，本研究將進一步釐清病毒學復發後的臨床結果

**二、研究背景：**

 慢性B型肝炎是全世界的重要公共衛生問題，是肝硬化，肝衰竭，以及肝癌的主要病因，目前台灣成年人口仍有約15%罹患慢性B型肝炎，也是國人肝病的最大元凶，因此如何改善患者預後仍是我國首要臨床議題之一。

 類核苷(酸)藥物是現今第一線抗B肝病毒藥物。雖然在口服抗病毒藥物治療期間，B型肝炎會進入不活動狀態，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。

 我們以往的研究已經發現停藥後發生病毒學復發的機率很高，E抗原陽性患者若未能清除E抗原即停藥，幾乎都會遇到病毒學和臨床肝炎復發，根本不應停藥。E抗原陰性患者停藥後仍有相當比率復發，然而病毒學復發後是否應立即再使用藥物治療，則仍存在爭議。本計畫擬從以往研究進一步深入探討發生病毒學復發後的臨床結果，以瞭解再治療的必要性與立即性。

**三、研究方法：**

　　本計畫為前瞻世代(prospective cohort)研究，建立在2011年7月起從義大醫院，羅東博愛醫院，以及台大雲林分院收集的慢性B型肝炎病人臨床資料與血液檢體。所有患者皆接受類核苷酸藥物治療至少三年，停藥時血中已經檢測不到B肝病毒，停藥後每三個月回診追蹤，接受臨床，生化，血清，和病毒學方面的檢測，一直追蹤到患者再度使用藥物或退出研究為止。患者停藥後若血中B肝病毒超過2000 IU/mL，則定義為發生病毒學復發。

 我們將分析患者發生病毒學復發後的臨床後果，包括死亡，肝臟衰竭，B型肝炎急性發作，臨床肝炎等，此外，我們也將分析病毒學復發後表面抗原濃度的變化。

**關鍵詞:**慢性B性肝炎；類核苷酸藥物；表面抗原

**研究計畫目的及背景說明**

 Hepatitis B virus (HBV) infection ranks among the top global health priorities. Chronic hepatitis B (CHB), which usually persists throughout life in individuals who perinatally acquired the infection, is the leading cause of end-stage liver disease and hepatocellular carcinoma (HCC) around the around. It is endemic in Asia, particularly in China and Taiwan where most of the patients were infected perinatally or in childhood. How to improve clinical outcomes of infected patients is an urgent but unresolved issue in Taiwan.

 Nucleoside and nucleotide analogues (NAs) effectively inhibit DNA polymerase of hepatitis B virus (HBV) and potently suppress viral replication. Consistent evidence from randomized placebo-controlled trials has established the efficacy of NAs in inducing HBeAg seroconversion. However, the off-treatment durability of antiviral therapy with NA remains unsatisfactory. There has been a large body of evidence indicating that substantial viral replication may resume with recurrence of active hepatitis after discontinuation of NA. We have previously demonstrated a high risk of relapse in end-of-therapy HBeAg-positive patients, who should not discontinue medication at all. Among those with negative HBeAg, there is ongoing controversy surrounding whether they should resume NAs following virological relapse.

 On the basis of our previous research, we proposed in this study to investigate the clinical consequences of virological relapse in HBeAg-negative patients after discontinuation of NAs, in order to clarify if immediate retreatment is indicated.

**研究方法及步驟：**

(一)受試者選擇標準（Patient eligibility）

This is a cohort study based on analysis of consecutive CHB patients treated with NA in E-Da Hospital, Lotung Poh-Ai Hospital, and National Taiwan University Hospital Yun-lin Branch, of which were teaching hospitals in Taiwan. The study protocol has been approved by the institutional review board.

From July, 2011 to December, 2014, consecutive CHB patients who were about to discontinue NA therapy were screened for eligibility. The inclusion criteria were age more than 20 years, a diagnosis of CHB for longer than 6 months before treatment commencement, use of NA (lamivudine, adefovir, telbivudine, entecavir, tenofovir) for a minimum of 3 years, and undetectable viral DNA in serum at the time of stopping NA therapy. The exclusion criteria were co-infection with human immunodeficiency virus or hepatitis C virus, malignant disease including HCC, cirrhosis, history of hepatic encephalopathy, variceal hemorrhage, organ transplantation, prior exposure to interferon alpha for more than one month, and use of cytotoxic or immunosuppressive agent.

**(二)試驗設計與流程：**

Enrolled participants were evaluated for demographic information, biochemical tests, serological markers (HBsAg, HBeAg, anti-HBs, anti-HBe), and HBV DNA at the cessation of NA treatment, at which time point the study baseline was set. Thereafter, they were followed up every 3 months for physical checkup and liver function measurement. Abdominal ultrasound and serum alpha-fetoprotein were examined every 6 months in general, and at a shorter interval if clinically indicated. At each visit, serum samples were collected and then sent to a central laboratory in the Taipei Pathology Institutes (Taipei, Taiwan) for quantification of HBsAg and viral DNA. Serum HBsAg was quantified by the automated micro-particle immunoassay (Abbott Architect i2000, Abbott Park, IL, USA; automatic range 0.05~250 IU/mL), in conjunction with dilution method for samples with a concentration exceeding 250 IU/mL. Serum HBV DNA was quantified by the commercialized polymerase chain reaction method (COBAS TaqMan HBV Test, version 2.0, Roche Molecular Systems, Inc., USA) with a detection range from 20 to 1.7 x 108 IU/mL.

We closely observed clinical outcomes including death, hepatic decompensation, severe acute exacerbation of CHB, clinical hepatitis after occurrence of virological relapse. We also measured change in serum concentration of hepatitis B surface antigen following virological relapse.

（三）資料之蒐集處理評估及統計分析方法:

Continuous variables are expressed with median and interquartile range (IQR) and analyzed by Wilcoxon rank sum test, whereas categorical variables expressed with proportion and examined by Fisher’s exact test. Patients are classified according to whether they use older or newer generation of NAs. Those who mixed different NAs are excluded from analysis. Multivariate logistic regression analysis for outcomes will be performed to adjust for potential confounding factors that included underlying comorbidity, drinking habit, choices of antiviral therapy, and the baseline viral load (HBV DNA). Hazard ratios are computed with an estimation of 95% confidence interval (CI). Statistical analyses are conducted using commercially available software (Stata, version 9.1; Stata Corp, College Station, TX, USA). All tests are two-sided with significance set at p value less than 0.05

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**預期貢獻:**

本研究將闡明慢性B型肝炎E抗原陰性患者停止抗病毒治療後，若病毒再度大量複製，所可能發生的臨床後果，以瞭解病毒學復發是否須立即再治療，若能達成此目標，將可解決現今對B肝患者停藥後處置上的爭議。本研究不預期對參與的個別患者有直接效益。