**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）建立慢性B型肝炎患者停止類核苷(酸)治療的風險預測模型 |
| （英文）Development of risk prediction model for cessation of nucleos(t)ide analogues 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 |
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| 計畫執行期限 | 自 **106** 年 1 月 **1** 日起至 **106** 年 **12** 月 **31** 日止 |
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**研究計畫摘要**

**研究主題:** 建立評估慢性B型肝炎患者停止類核苷(酸)治療的風險預測模型

**ㄧ、試驗目的：**

1. 分析慢性B型肝炎患者停止類核甘(酸)治療後復發的危險因子

2. 綜合已知危險因子建立風險預測模型

**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，雖然類核苷(酸)口服抗病毒藥物可以有效抑制病毒複製，讓B型肝炎進入不活動狀態，然而停止治療後，多數病人體內B肝病毒會再度活躍，可能又會復發活動性肝炎，甚至導致嚴重急性發作。

 我們以往研究已發現表現抗原濃度，病毒學復發時病毒量，年紀，與血清轉安酶濃度是停藥後復發的獨立危險因子，目前仍在檢驗B型肝炎核心相關抗原(Hepatitis B core-related Antigen, HBcAg)可否預測類核苷(酸)藥物停藥後反應；但是尚未能建立完整的風險預測模型，本研究擬持續既有成果，發展並驗證可以準確預測安全停藥的風險模型。

**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。參與本研究必須符合下列條件: 年滿20歲，表面抗原(HBsAg)血清陽性達６個月以上者，服用口服類核苷(酸)抗病毒藥物三年後將停藥者，停藥時血清e抗原為陰性且血中已偵測不到病毒；患者不能合併Ｃ型肝炎或人類免疫不全病毒(HIV)感染，已診斷任何癌症(包括肝癌)，患有肝硬化，曾有肝腦病變或胃食道靜脈瘤出血，器官移植，曾使用干擾素抗病毒製劑超過一個月者，或者在使用化療或免疫抑制劑者。

 我們將分析患者血中核心相關抗原的濃度，並對應臨床後果 (包括死亡，肝臟衰竭，B型肝炎急性發作，臨床肝炎)，以探討是否可藉由核心抗原濃度預測病程變化。

**關鍵詞:**慢性B性肝炎；類核苷酸藥物；B肝核心相關抗原；世代研究

**研究計畫目的及背景說明**

 Chronic infection with hepatitis B virus (HBV) is a major health problem worldwide, infecting approximately 350 million people globally. It is endemic in Asia, particularly in China and Taiwan where most of the patients were infected perinatally or in childhood. Chronic hepatitis B (CHB) is associated with serious morbidity and mortality in that severe complications including hepatic failure, liver cirrhosis, and hepatocellular carcinoma (HCC) may occur in 15~40 % of the infected patients during their lifetime. Although HBV generally is not cytopathic in itself, immune responses to chronic infection may lead to persistent hepatic necro-inflammation and over time result in fibrosis. The clinical outcome of CHB is the consequence of a complex interaction among viral, host, and environmental factors.1

 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.2 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, whether the patients are hepatitis e antigen (HBeAg) positive or negative.3-6 How to predict the off-therapy response in patients treated with NA, nonetheless, remains unknown.7-12

 Recently, a new enzyme immunoassay was developed to detect another serological marker of another hepatitis B virus. This chemiluminescence enzyme immunoassay measures serum levels of hepatitis B core antigen (HBcAg), HBeAg and empty particle (p22). The monoclonal antibodies is able to recognize the common epitopes of these three proteins.13 Therefore, this assay actually quantifies hepatitis B core-related antigen (HBcrAg).14-15 We are now evaluating whether serum level of HBcrAg correlates the risk of relapse after discontinuation of NA therapy.

In the present study, we will integrate all the risk factors identified by our and others research to develop a risk prediction model that can accurately predicts a safe strategy for NUC cessation in patients with CHB.

**研究方法及步驟：**

***Study setting and patient eligibility***

This study is based on analysis of serum samples collected from participants in a prospective study entitled “Can serum level of hepatitis B surface antigen predict off-therapy outcomes in chronic hepatitis B patients treated with nucleos(t)ide analogue” which has been approved by the IRB of E-Da Hospital (EMRP100-049). Participants who consent to donate their residual blood samples for further hepatitis research (as specified on the written informed consent form of EMRP100-049) are screened for eligibility for the current study project.

***Antiviral treatment and off-therapy follow-up***

From 2011 August, all adult patients with CHB who receive NA will be screened for eligibility. CHB patients treated with NA regimen in this hospital are followed up with the frequency of 3 months. At each follow-up visit, in addition to physical evaluation, serum alanine aminotransferase (ALT), serological and virological markers are measured. Serological markers are determined by enzyme-linked immunoassay and HBV DNA by quantitative polymerase chain reaction method.

Serum levels of HBsAg and viral DNA are measured in participants at the time point of discontinuing NA therapy. After discontinuation of NA therapy, biochemical, quantiity of anti-HBc along with conventional serological (HBsAg, HBeAg, anti-HBs, anti-HBe) markers and HBV DNA will be observed every 3 months until endpoints occurred or the study ended. Recurrence of active hepatitis was defined as HBV DNA of more than 2,000 IU/mL in addition to serum ALT of more than 80 IU/L (2 folds of upper normal range). Virological relapse was HBV DNA > 2,000IU/mL with or without accompanying elevation of serum ALT.

***Statistical analysis***

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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**Expected results and contributions**

 Before the availability of a novel treatment that can completely eradicate hepatitis B virus (most difficultly the cccDNA in the nucleus), NUC will continue to be the mainstay of antiviral therapy for chronic hepatitis B. Therefore, how to safely discontinue NUCs in patients with chronic hepatitis B remains a practical issue in clinical practice, particularly in Taiwan where there is a strict regulation on the reimbursement for NUC. Exploration of biomarkers that can predict off-therapy outcomes is necessary. Taking the advantage of our established cohort with sufficient follow-up, the current project is expected to develop an off-therapy management algorithm for safe cessation of NUC.