# 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 型肝炎病人停止新一代類核苷(酸)治療後臨床及病毒學反應 | |
| | （英文）Clinical and virological outcomes in chronic hepatitis B patients after discontinuing new generations of nucleos(t)ide analogues | |
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# 研究計畫摘要

**研究主題:** 慢性 B 型肝炎病人停止類核苷(酸)治療後臨床及病毒學反應

**一、試驗目的：**

探討使用口服類核甘(酸)抗病毒藥物治療的慢性 B 型肝炎病人在停止服藥後的臨床及病毒學結果

**二、研究背景：**

慢性 B 型肝炎是國人罹患肝硬化，肝衰竭，以及肝癌的主要病因，雖然自 1986 年台灣實施新生兒全面預防接種 B 肝疫苗後，國內兒童的 B 肝帶原率已下降至 1-2%，但是成年人口仍有 15-20%罹患慢性 B 型肝炎，因此如何改善 B 肝患者的預後仍是台灣最重要的臨床議題之一。

口服類核苷(酸)藥物可有效抑制 B 肝病毒複製，進而改善肝臟發炎與纖維化，已被廣泛應用於慢性 B 型肝炎的治療，因為具有抗病毒能力強以及抗藥性低的優點，是現今國內外肝臟醫學會建議的第一線抗 B 肝病毒藥物。雖然絕大部分病人在口服抗病毒藥物治療期間 B 型肝炎會進入不活動狀態，然而以往的研究顯示停止治療後，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。但是，目前慢性 B 型肝炎病人使用新一代口服抗病毒藥物治療停藥後的反應仍未十分清楚。

**三、研究方法：**

本研究為世代(cohort)研究，建立在從 2011 年八月即開始前瞻收集的慢性 B 型肝炎病人臨床資料與血液檢體。所有在義大醫院服用抗病毒藥的病人皆被評估是否可被收案，符合條件而同意加入研究者從停藥時起每三個月回診追蹤，接受臨床，生化，血清，和病毒學方面的檢測，一直追蹤到慢性 B 型肝炎急性發作定義為 ALT 超過 80 IU/L (正常上限值的兩倍)合併 B 型肝炎病毒超過 2,000IU/mL。病毒學上的復發定義為病毒超過 2,000IU/mL 但沒有合併肝發炎指數上升。

本研究將比較服用新一代抗病毒藥包括貝樂克(entecavir)和惠力妥(tenofovir)，以及早期藥物包括干安能(lamivudine)和喜必福(telbivudine)，在停藥後反應上有無差異。

**關鍵詞:**慢性 B 性肝炎，貝樂克，惠力妥

**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.

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. However, whether the choice of NA therapy affects the probability of viral recurrence remains undetermined.

We conduct this study with the primary aim first to elucidate clinical and virological outcomes of CHB patients after NA discontinuation, and then to compare patients receiving newer generations of NA (i.e. entecavir and tenofovir) and those treated with earlier medication (i.e. lamivudine and telbivudine) in terms of off-therapy response.

**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, a regional teaching hospital in southern Taiwan. The study protocol has been approved by the institutional review board.

From 2011 August to 2014 December, all adult patients with CHB who receive NA will be screened for eligibility. The inclusion criteria are age > 20 years, serum HBsAg positivity > 6 months before the start of therapy, and NA regimen (lamivudine, adefovir, telbivudine, entecavir, tenofovir) for at least one year. The exclusion criteria are co-infection with human immunodeficiency virus, hepatitis C virus or hepatitis D virus, active malignant disease (including hepatocellular carcinoma), presence of cirrhosis, history of hepatic encephalopathy or variceal hemorrhage, organ transplantation, prior use of interferon-based antiviral therapy > 1 month, and receiving chemotherapy or immunosuppressive agent.

**(二)試驗設計與流程：**

CHB patients treated with NA regimen are followed up every 3 months in principal. 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, serological (HBsAg, HBeAg, anti-HBs, anti-HBe), and virological markers (HBV DNA) will be observed every 3 months until study endpoint, i.e. recurrence of active hepatitis, occurs or for two years off therapy or the end of the scheduled study period. Change of serological markers such as surface and e antigen are also measured.

Primary end point of this study is recurrence of active hepatitis defined as elevated serum ALT of more than 80 IU/L (2 folds of upper normal range) accompanied with HBV DNA of more than 2,000IU/mL, and virological relapse as

HBV DNA > 2,000IU/mL without accompanying elevation of serum ALT. HBeAg seroreversion is defined as reappearance of serum HBeAg on consecutive serum samples.

（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

**REFERENCES:**


1. Chen C-J, Wang L-Y, Yu M-W. Epidemiology of hepatitis B virus infection in the Asia-Pacifi c region. J Gastroenterol Hepatol 2000; 15: 3–6.
2. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65–73
3. Tsai WL, Chung RT. Viral hepatocarcinogenesis. Oncogene 2010;29:2309-24.
4. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N Engl J Med.* Jul 18 2002;347(3):168-174.
5. Hsu YS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous

HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology.* Jun 2002;35(6):1522-1527.

6. Lai CL, Chien RN, Leung NW, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med.* Jul 9 1998;339(2):61-68.

7. Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med.* Feb 27 2003;348(9):808-816.

8. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med.* Mar 9 2006;354(10):1001-1010.

9. Chan HL, Heathcote EJ, Marcellin P, et al. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial. *Ann Intern Med.* Dec 4 2007;147(11):745-754.

10. Lai CL, Gane E, Liaw YF, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med.* Dec 20 2007;357(25):2576-2588.

11. Liaw YF, Leung NW, Chang TT, et al. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *Gastroenterology.* Jul 2000;119(1):172-180.

12. Harrington LE, Hatton RD, Mangan PR et al. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol 2005; 6: 1123–32

13. Park H, Li Z, Yang XO et al. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol 2005; 6: 1133–41.

14. Wilson NJ, Boniface K, Chan JR et al. Development, cytokine profile and function of human interleukin 17-producing helper T cells. Nat Immunol 2007; 8:

950–7.

15. Sallusto F, Lanzavecchia A. Human Th17 cells in infection and autoimmunity. Microbes Infect 2009; 11: 620–4.

16. Afzali B, Lombardi G, Lechler RI, Lord GM. The role of T helper 17 (Th17) and regulatory T cells (Treg) in human organ transplantation and autoimmune disease. Clin Exp Immunol 2007;148:32-46.

17. Hsu HC, Yang P, Wang J, Wu Q, Myers R, Chen J, Yi J, Guentert T, Tousson A, Stanus AL, Le TV, Lorenz RG, Xu H, Kolls JK, Carter RH, Chaplin DD, Williams RW, Mountz JD. Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. Nat Immunol 2008;9:166-75.

18. Zhang JY, Zhang Z, Lin F, Zou ZS, Xu RN, Jin L, Fu JL, Shi F, Shi M, Wang HF, Wang FS. Interleukin-17-producing CD4(+) T cells increase with severity of liver damage in patients with chronic hepatitis B. Hepatology 2010;51:81-91.

19. Chang Q, Wang YK, Zhao Q, Wang CZ, Hu YZ, Wu BY. Th17 cells are increased with severity of liver inflammation in patients with chronic hepatitis C. J Gastroenterol Hepatol 2012;27:273-8.

20. Zhang JP, Yan J, Xu J, Pang XH, Chen MS, Li L, Wu C, Li SP, Zheng L. Increased intratumoral IL-17-producing cells correlate with poor survival in hepatocellular carcinoma patients. J Hepatol 2009;50:980-9.

**預期貢獻:**

本研究預期瞭解慢性Ｂ型肝炎患者停止抗病毒治療後的復發情形，以及和使用的類核苷藥物種類是否相關。若能達成此目標，吾人應可了解在現行抗病毒治療的限制，哪些患者需特別密切追蹤，以及進一步推測宿主免疫反應，病毒活性，和藥物種類對感染後果的影響。本研究不預期對參與的個別患者有直接效益。