財團法人明日醫學基金會研究計畫申請書

計畫名稱	（中文）以干擾素或者不含干擾素抗病毒藥物廓清 C 型肝炎病毒和血中自體免疫抗體的關聯性	
	（英文）Association between Circulatory Autoantibodies and Eradication of Hepatitis C Virus by Antiviral Therapy with or without Interferon	
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 **109** 年 1 月 **1** 日起至 **109** 年 **12** 月 **31** 日止	
共同主持人（一）	姓名：	機關：
	職稱：	單位：
共同主持人（二）	姓名：	機關：
	職稱：	單位：
共同主持人（三）	姓名：	機關：
	職稱：	單位：
共同主持人（四）	姓名：	機關：
	職稱：	單位：

研究計畫摘要

研究主題: 釐清廓清 C 型肝炎病毒感染和血中自體免疫抗體產生是否有關，且與抗病毒藥物包括干擾素與否的關聯性

一、試驗目的：

1. 研究 C 型肝炎病毒清除與自體免疫抗體產生之間的關係
2. 探討上述關聯和抗病毒藥物使用干擾素與否有無不同
3. 釐清 C 型肝炎、病毒清除，與自體免疫疾病的風險

二、研究背景：

C 型肝炎是一種全身感染性疾病，可導致多種肝外表現，其中包括自體免疫病因疾病。然而，以往用於治療 C 型肝炎感染的聚乙二醇化干擾素（Peg-IFN）治療，藥物本身也可能誘發自體免疫或加重已有的自體免疫疾病。先前有關研究尚未能釐清 C 型肝炎病毒廓清與自體免疫性疾病風險降低，和不同抗病毒治療之間是否存在顯著關聯。

三、研究方法：

本計畫為本國單一中心回溯世代研究，將經由分析電子病歷資料(electronic health record)，整合義大醫院與義大癌治療醫院 300 位先前接受抗病毒治療的慢性 C 型肝炎患者。患者在療程開始前、療程中與治療結束後收集血清檢體並保存。我們將定量血清中自體免疫抗體例如 antinuclear antibody (ANA), rheumatic factor (RF) 等的濃度，分析在不同時間點的變化，並釐清和病毒清除與抗病毒藥物間關係。

關鍵詞:慢性 C 性肝炎；自體免疫抗體；干擾素治療；直接抗病毒藥物

研究計畫目的及背景說明

Chronic infection with hepatitis C virus (HCV) is associated with substantial morbidity and mortality. In addition to hepatic complications, it also predisposes infected patients to several extra-hepatic disorders that include mixed cryoglobulinemia, membranous glomerulous nephritis, autoimmune thyroiditis, and other autoimmune diseases.[1] A growing body of evidence indicates that there is a causal association between CHC and induction of autoimmunity. However, it remains unclear whether viral clearance may ameliorate induction of autoantibodies and prevent occurrence of autoimmune disease.

Our previous work using the national health insurance research database (NHIRD) did not find there was an association between antiviral therapy using interferon and incidence of catastrophic autoimmune diseases. A recent study based on multicenter cohorts from Taiwan also found treatment for HCV infection using all-oral regimens of direct antiviral agent (DAA) was not associated with occurrence of rheumatic diseases. Findings from these studies thus questioned the effectiveness of HCV clearance in preventing autoimmune diseases. Nevertheless, prior studies were limited to linkage to insurance claims databases without laboratory confirmation and the statistical power might be compromised because of the few occurrences of autoimmune clinical disorders.

In order to elucidate whether or how HCV clearance may impact the induction of autoantibodies and thus influence the pathogenesis of autoimmunity, it is prudent to directly measure the production of autoantibodies in response to viral eradication. Moreover, because interferon treatment for HCV infection may induce autoimmune manifestations, data from patients treated with DAA are needed but currently lacking.

研究目標:

1. Investigate if the association of viral eradication with production of autoantibodies differ according to the antiviral therapy using interferon or DAA.
2. Determine if eradication of HCV decreases the risk of developing an autoimmune disease by lowering autoantibodies
3. Determine the number of patients in this cohort who develop an autoimmune disease and correlate with their autoantibody profile
4. Explore the relationship between HCV and autoimmunity

研究方法及步驟：

Study design and setting

This is a retrospective cohort study based on analysis of the electronic healthcare database and repurposed utilization of archived serum samples from HCV-infected patients who were treated with antiviral therapy in the E-Da Hospital or E-Da Cancer Hospital.

Patient population

Patients are considered eligible if they are aged more than 20 years, seropositive for HCV antibody for more than 6 months, had detectable HCV RNA in serum and elevated serum alanine aminotransferase. Those who meet any of the following exclusion criteria are not enrolled: co-infection with human immunodeficiency virus

or hepatitis B virus, seropositivity for anti-smooth muscle or anti-mitochondria antibody, presence of other concomitant liver diseases (e.g. hemochromatosis, Wilson disease, drug-related hepatitis, or alpha-1 antitrypsin deficiency), pregnant or lactating women.

Antiviral therapy

All patients enrolled in the prospective translational research are treated with antiviral therapy using either interferon-based regimen or all-oral DAA agents. The duration of therapy follows regulations of the national health insurance. The definitions of treatment responses are based on the sensitive polymerase chain reaction (PCR)-based assay (COBAS Taqman/AmpliPrep, Roche) in accordance with international guidelines: end-of-treatment response (EotVR) was defined as HCV RNA negativity when treatment was completed and sustained viral response SVR12 as undetectable HCV RNA at 12 weeks after completion of therapy respectively. After cessation of therapy, those who do not achieve SVR are classified as non-responders (detectable HCV RNA at the end of therapy) or relapsers (once clearance but reappearance of HCV RNA after cession of therapy).

Data collection and patient follow-up

After identifying the eligible patients from the computerized database, we will record pertinent information including demographics, blood chemistry, hemogram, viral

serology, and relevant data such as health-related behavior Accuracy of the abstracted information will be audited by the investigators, who will also ascertain the outcome of each enrolled subject. Eligible patients will be followed up for the outcomes listed below until death or data censoring:

Statistical analysis

For univariate comparison of continuous variables, paired t test is used for values collected at different time points in the same patient, and independent t test for group comparison. Fisher's exact test is used for analysis of proportions. We'll conduct multivariate regression analysis with stepwise method to evaluate independent risk factors associated with the primary and secondary outcomes. We'll compare change of autoantibodies between patients with and without SVR after adjusting for probable confounders by calculating propensity score for SVR. All statistical analyses are two-tailed and are accomplished with use of commercial software package (Stata, version 9.0; Stata Corp, College Station, TX, USA). P value of less than 0.05 is the threshold for statistical significance.

REFERENCES:

1. Zignego AL, Ferri C, Pileri SA, Caini P, Bianchi FB. Extrahepatic manifestations of Hepatitis C Virus infection: a general overview and guidelines for a clinical

approach. Dig Liver Dis 2007;39:2-17.
2. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009;49:1335-74.
3. Farrell GC. New hepatitis C guidelines for the Asia-Pacific region: APASL consensus statements on the diagnosis, management and treatment of hepatitis C virus infection. J Gastroenterol Hepatol 2007;22:607-10.
4. Yu ML, Chuang WL. Treatment of chronic hepatitis C in Asia: when East meets West. J Gastroenterol Hepatol 2009;24:336-45.
5. Simmonds P, Holmes EC, Cha TA, et al. Classification of hepatitis C virus into six major genotypes and a series of subtypes by phylogenetic analysis of the NS-5 region. J Gen Virol 1993;74 (Pt 11):2391-9.
6. Shaheen AA, Myers RP. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis C-related fibrosis: a systematic review. Hepatology 2007;46:912-21.
7. Hsu YC, Ho HJ, Huang YT, Wang HH, Wu MS, Lin JT, Wu CY. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. Gut. 2015 Mar;64(3):495-503.
8. Hsu WF, Chen CY, Tseng KC, Lai HC, Kuo HT, Hung CH, Tung SY, Wang JH, Chen JJ, Lee PL, Chien RN, Lin CY, Yang CC, Lo GH, Tai CM, Lin CW, Kao JH, Liu CJ, Liu CH, Yan SL, Bair MJ, Su WW, Chu CH, Chen CJ, Lo CC, Cheng PN, Chiu YC, Wang CC, Cheng JS, Tsai WL, Lin HC, Huang YH, Tsai PC, Huang JF, Dai CY, Chuang WL, Yu ML, Peng CY. Sustained virological response to hepatitis C therapy does not decrease the incidence of systemic lupus erythematosus or rheumatoid arthritis. Sci Rep. 2020 Mar 25;10(1):5372.