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IL28B基因多形性對於慢性C型肝炎感染之再次治療結果的預測價值

Predictive Value of IL28B Gene Polymorphisms on Retreatment Outcome of Chronic Hepatitis C

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目錄

圖表目錄

國立臺灣大學碩士學位論文
口試委員會審定書

IL28B 基因多形性對於慢性 C 型肝炎感染之

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本論文係陳明堯君（學號 P99421005）在國立臺灣大學臨床醫學研究所完成之碩士學位論文，於民國 101 年 7 月 19 日承下列考試委員審查通過及口試及格，特此證明

口試委員：高嘉宏（簽名）

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楊宏志

系主任、所長 高嘉宏（簽名）

（是否須簽章依各院系所規定）

誌謝

從踏入實驗室至今已有 3 個年頭，終於完成了碩士學業與論文寫作。臨床上，面對肝病這個艱難的疾病，尤其是肝炎病毒方面，愧為消化內科的年輕主治醫師，經常面臨到「該不該治療?」、「何時治療?」、「如何治療?」以及「如何監測?」的困境，有幸能有高嘉宏教授與劉俊人教授的悉心教導，他們總能繁徵博引，讓人驚嘆的聽著他們講述各家的起源、發展與異同；卻又能化繁為簡，剖析治療的精髓，讓吾人可領悟其中的奧妙並適用於其他患者的準則。在研究上，舉煩研究的題目、案例收集與進行的時程，總是不厭其煩的提點，在我怠惰不前時又即時提供溫馨的鼓舞。對我的指導老師–劉教授，更是感謝他啟發性的教誨，無論是醫學研究倫理的個案申請、各式的研究報告、還是論文寫作，總是十足耐心的鼓勵著慢如龜步的我，一有進展，又能即以旋風式的速度加以修改回應。同時感謝陳祈玲老師提供了許多統計上的幫忙與建議。還有楊宏志醫師在論文口試上所提出令人啟發的建議。

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中文摘要

慢性 C 型肝炎感染(chronic hepatitis C, CHC)是造成失償性肝硬化以及肝細胞癌的主要原因之一。為期 48 週的長效干擾素合併依體重調整的雷巴威林是亞太地區當今治療第一型慢性 C 型肝炎的標準治療，然而，約只有 60-70%患者可以達成持續病毒學反應(SVR)。在從未治療過的患者中，IL28B 附近的單一核苷酸多形性(SNP)與是否會自發性痊癒或者經治療而清除病毒有關。但是對於台灣人之慢性 C 型肝炎的復發者(relapser)而言，當今標準治療的效果以及 IL28B SNP 的影響均不明瞭。

在台灣，吾人從 2009 年收錄了 103 位慢性 C 型肝炎的復發者。吾人進行 48 週的長效干擾素及雷巴威林的合併治療，評估 IL28B SNP 以及治療過程中的病毒動力學變化以及生化反應。其中僅納入 75 位(73%)的第一基因型慢性 C 型肝炎患者進行分析研究。整體而言，治療中的病毒動力學變化針對快速病毒學反應(RVR)、治療結束病毒反應(EOT-VR)與 SVR 而論，分別為 37%、73%與 52%。復發率則為 29%。若能達成 RVR，則有較高的機率可以達成 SVR (P<0.0001) 以及較低的復發率(P=0.0034)。與 GT IL28B 基因型相比，TT 的患者有較高的 RVR (P=0.0002)、EOT-VR (P=0.0001)以及 SVR (P<0.0001)的機會。若合併第四週病毒轉陰化(week 4 viral negativity，即 RVR)與 IL28B 基因型，則判別 SVR 的陽性與陰性預測值(PPV, NPV)與第 12 週時的病毒轉陰化效果相當。

運用當今標準治療來醫治台灣的第一基因型慢性 C 型肝炎復發者，約有半數可以達成持續病毒學反應。IL28B SNP 會影響再次治療中的病毒動力學變化，SVR 以及復發率。將來若能依據 IL28B SNP 以及 RVR 的變化，或許可進行個人化的治療，甚至可以當成早期停藥的指標。

關鍵詞：慢性 C 型肝炎，長效型干擾素，IL28B，再治療

英文摘要

Chronic hepatitis C infection (CHC) is a leading cause of decompensated cirrhosis and hepatocellular carcinoma. Forty-eight-weekly pegylated interferon (PEG-IFN)plus weight-based ribavirin (RBV) has been the current standard of care (SOC) for CHC genotype 1 in Asia-Pacific region and can only achieve an overall sustained virologic response (SVR) of 60-70%.The single nucleotide polymorphism (SNP) near the interleukin-28B (IL28B) is associated with spontaneous or treatment-induced viral clearance in untreated patients. It remains unclear for the efficacy of current SOC and influence of IL28B SNP in re-treating Taiwan CHC relapsers.

In Taiwan, since November 2009, we consecutively enrolled 103 CHC relapsers into this study. We evaluated the IL28B SNPs, virologic kinetics, and biochemical responses of CHC patients receiving 48-weekPEG-IFN plus RBV. Only 75 CHC genotype 1 relapsers (73%) were included for analysis. The overall viral kinetics was 37%,73% and 52% in rapid virologic response (RVR), end-of-treatment viral response (EOT-VR) and SVR respectively. Relapse rate was 29%.Patient with TT IL28B had higher rate of RVR (P=0.0002), EOT-VR (P=0.0001) and SVR (P<0.0001) in comparison with GT. Achieving a RVR ensured a higher SVR rate (P<0.0001) and lower relapse rate (P=0.0034). In combination of week 4 viral negativity (i.e. RVR) with IL28B genotype, a high positive and negative predictive value of SVR achieved as equally good as week 12 viral negativity.

About half of the CHC relapsers in Taiwan would achieve SVR under current SOC. IL28B SNP would influence the on-treatment viral kinetics, SVR and relapse rate in retreatment. There might be the individualized therapy according to the IL28B SNP and RVR in the future, especially the early stopping rule.

Keywords: chronic hepatitis C, pegylated interferon, IL28B, retreatment

第一章　緒論 (Introduction)

1.1 背景(Background)

慢性 C 型肝炎(chronic hepatitis C, CHC)感染是造成慢性肝病的重要原因之一，亦為影響全球健康的重要議題。粗估全球約有一億七千萬人受到慢性 C 型肝炎病毒的感染[2,3]。在亞太地區，受到 C 型肝炎病毒感染的盛行率有很大的區域性差異，從 0.3%至 12%均有學者報導過[4]。受到 C 型肝炎病毒(hepatitis C virus, HCV)感染後，在無症狀者，估計有高達 60~80%的病人無法自發性的清除病毒而成為慢性帶原者[1]。因此，得到慢性 C 型肝炎後，會造成程度不一的肝細胞傷害，因此是失償性肝硬化、肝細胞癌與肝臟移植的主要原因之一。所以，應及早治療慢性 C 型肝炎與防治病毒的傳染，進而減低肝因性的罹病率與死亡率。

1.2 慢性 C 型肝炎感染的初次治療之當代標準 (Current standard of care [SOC] for treatment-naïve CHC infection)

近二十年來，慢性 C 型肝炎的臨床照護已有重大的改革，而且各種臨床治療指引已經有多版的修定。慢性 C 型肝炎治療的最主要目標在於消除血液循環中的 C 型肝炎病毒，希望能達成持續的病毒學反應(sustained virologic response, SVR)，亦即在停止治療的六個月後仍無法測得病毒，此種狀態被認定為病毒學上的治癒狀態。隨著美國食品及藥物管理局(FDA)於 2001 年同意長效型干擾素(pegylated interferon, PEG-IFN)上市之後，每週施打長效干擾素合併依體重計量的雷巴威林(weight-based ribavirin)已然成為廣泛使用的處方，並且是當今治療慢性 C 型肝炎患者的治療標準。然而，即便使用此種標準化的治療處方，再加上依照病毒基因型(viral genotype)或治療中的病毒動力學變化(on-treatment viral kinetics)為導向的治療方式，受到 HCV genotype 1 感染的患者在接受 48 週的治療後，在西方國家僅約可達 40~50%的持續病毒學反應(SVR)，在亞太地區約為 60-70%的 SVR；而受 HCV genotype 2 感染患者在接受 24 週的治療後則可達成 80%以上的持續病毒學反應[5-8]。

在合併使用長效干擾素與雷巴威林的治療下，患者須忍受相當多的副作用，例如類感冒症狀、嚴重的疲倦、憂鬱、焦躁不安、睡眠障礙、皮膚過敏反應、喘息、白血球低下、貧血、血小板低下、肝指數飆升以及甲狀腺功能失常。幸好一旦能成功達到持續病毒學反應，長期而論，患者可以永久消除體內的 C 型肝炎病毒，亦即在病毒學上被認為是達成治癒的狀態。同時，有許多的益處亦同時伴隨 SVR 而來，例如改善肝臟纖維化、減低肝細胞癌的發生、減少肝衰竭、降低肝因性死亡率，以及增進生活品質[9]。

有許多的研究運用各式的病毒(viral)及宿主(host)指標來預測治療的反應。病毒因子包含 C 型肝炎病毒的基因型、病毒的基礎量(治療前)、治療中的病毒動力學變化、以及是否同時合併其他親肝性病毒的感染，如 B 型肝炎病毒[10-12]。在運用宿主因素來預測治療是否能成功方面，則有下列的因素被發現，如：性別、感染病毒時的年紀、受感染的期間長短、種族、肝臟在治療前的纖維化/發炎反應/脂肪堆積的狀態、體重是否過重、胰島素阻抗(insulin resistance)、肝指數、患者的遵醫囑性、治療中是否產生副作用、以及宿主基因型差異，均能影響治療結果。其中，病毒基因型、宿主 IL28B 基因多形性以及肝臟纖維化狀態被認為是治療前最重要的預測因素[5-7,9,13-16]。

1.3 慢性 C 型肝炎感染的再次治療 (Re-treatment of chronic hepatitis C infection)

從上述的標準化治療方法下，可得知慢性 C 型肝炎患者在初次治療後仍有相當可觀的人無法達成持續的病毒學反應，亦即無法清除血液中的 HCV 而必須再一次治療 C 型肝炎病毒感染。目前並不清楚哪些才是再次治療的最佳當藥物組合，而藥物的治療效果也未完全明瞭。

依照初次治療過程中的病毒動力學變化的情況而分，所謂的復發者(relapser)，即在治療的過程中以及結束時，血液裡的病毒(HCV RNA)消失而測不到，但是病毒在治療結束後又再度出現；這群病患若使用長效型干擾素與雷巴威林進行再次治療，則約有 30~50%的成功率(即達成 SVR)。在初次治療過程中，第十二週

與治療前 HCV 病毒量相比較，若病毒變化量無法減少 2 log IU/mL 以上者稱為不反應者(non-responder)；這些不反應者僅有 10~15%的治療成功率[17-23]。學者們發現有數個因素可以預測再次治療時的持續病毒學反應，包含病毒基因型、治療前之病毒基礎量、治療第十二週時病毒被壓抑的程度、初次治療的藥物組合與治療時距，以及患者的年紀與體重，對於再次治療的反應均有重大的影響[19,21]。

1.4 全基因體相關研究與 IL28B 單一核苷酸多形性 (Genome-wide association study [GWAS] and IL28B single nucleotide polymorphism [SNP])

除了上述各種因子之外，是否另有重要與宿主基因有關的因素會影響到慢性 C 型肝炎的治療？由於科技的發展，對於人類體基因體的研究有長足的進步，從 2009 年起，有一系列獨立的全基因體相關研究(GWAS)，針對於不同地域、不同人種但採取相同的治療藥物與評斷治療成效的方法，發現在 IL28B 基因位點附近有一些單一核苷酸多形性(SNP)的差異，與得到第一基因型 C 肝病毒感染後是否會自發性的(spontaneous)痊癒或者是否能藉由藥物治療而清除病毒，皆與 IL28B SNP 有很大的關係[24-28]。

IL28B 基因的單一核苷酸多形性，例如 rs8099917 and rs12979860，位於第十九號染色體上，可以轉譯出 IFN λ-3 而具有對抗 HCV 病毒感染的作用，因此對於是否能達成持續病毒學反應上扮演一重要的角色[23,29-37]。受到第一基因型的 C 型肝炎病毒感染(HCV genotype 1) 的患者，在接受長效型干擾素與雷巴威林治療後，具有較佳的 IL28B SNP 的人(如 rs8099917 之 T allele，rs12979860 之 C allele)，能夠成功地清除病毒(即達成 SVR)的可能性較大。與治療前的 HCV 病毒量、肝臟纖維化程度、年紀與性別相互比較，IL28B 多形性對於是否能達成 SVR 有較佳的預測價值[29,31]。但是在 HCV genotype 2 或 3 感染的患者，IL28B 的角色在各個研究中並沒有一致的結論。

受到第一基因型的 C 肝病毒感染的患者，在以長效干擾素為基礎的治療之下，IL28B SNP 會影響到治療中的病毒動力學變化，而 IL28B SNP 是預測 SVR 的各

因素中最強而有力的。因此有人說，只要使用干擾素治療 C 型肝炎，IL28B SNP 還會持續影響治療的成功率；而未來若不再使用干擾素時，IL28B 的影響才會減少[9]。

1.5 比較東西方治療的不同(Comparison between eastern and western populations)

在許久之前，就有學者發現治療慢性 C 型肝炎感染時有人種的差異。特別是在同樣使用干擾素來治療較困難治癒的 HCV genotype 1 感染患者，東方人與西方人相較，具有較佳的持續病毒學反應[38-44]。全基因體相關研究(GWAS)發現 IL28B SNP 具有人種的差異。相較於黑人與白人，東方人具有更多對於治療反應較佳的 IL28B SNP 比例。因此，不同人種對於使用干擾素治療是否能成功的差異，有一部份或許可以具較佳的 IL28B SNP 比例的分歧來解釋。

1.6 直接抗病毒藥物 (Direct anti-viral agents, DAAs)

以干擾素與雷巴威林的標準治療後，仍有相當部份的病人無法清除體內病毒，尤其是那些受 HCV genotype 1 病毒感染、有著較差的 IL28B SNP(如 rs8099917 之 G allele，rs12979860 之 T allele)或者治療中的病毒動力學反應較差者(例如不反應者)。

所謂的直接抗病毒藥物(DAA)乃針對病毒生活史中的各個重要步驟，產生抑制作用進而達到抗病毒效果，是目前對抗 C 型肝炎病毒藥物中的重要研究發展項目。其中的蛋白酶抑制劑(serine protease inhibitor)，如 Boceprevir 或 Teleprevia，已於 2011 年在美國食品及藥物管理局(FDA)通過並且上市。因此，當前治療 C 型肝炎最重要的進展就是在原本的長效干擾素與雷巴威林的標準治療中，再加上這一類的直接抗病毒藥物，以增進病毒的治療反應與減少所需的治療期間。而這類藥物已展現明顯的抗病毒效果，尤其是在 HCV genotype 1 感染的患者中可明顯的增加 SVR 的機會。然而，即使在合併使用此類藥物的三合一療法中，初次治療[45,46]的患者有 25~35%仍無法達到 SVR；而需再次治療[47,48]的患者則有

34~41%的機會可能治療失敗。同時這種多重藥物的合併療法也會增加額外的醫療費用與藥物不良反應(如貧血、感覺失常、皮膚過敏反應與搔癢以及腹瀉) [45,46]。

1.7 對於初次治療失敗的慢性 C 型肝炎患者而需要再次治療時的目前指引 (Current Guidelines in retreatment of CHC patients who fail to achieve SVR)

1.7.1 2012 年亞太肝病研究學會的 HCV 感染處理共識 (APASL consensus statements and management for HCV infection)[9]

具有較佳條件的慢性 C 型肝炎復發者，目前或許可以同樣使用長效干擾素與雷巴威林來治療患者，而不用同時合併直接抗病毒藥物(DAA)。但是在不久的將來，對於這些曾經使用標準藥物而無法成功清除病毒者，合併上述三種藥物的三合一療法應當是未來的標準治療。

1.7.2 2011 年美國肝病研究學會針對 HCV genotype 1 感染者的更新指引 (AASLD, an update on treatment of CHC genotype 1 infection)[49]

在從未治療過的 HCV genotype 1 患者，最佳的治療處方是合併 boceprevir 或 teleprevir 與長效干擾素以及依體重計量的雷巴威林。若患者在治療過程中，有較好的病毒學反應，則可考慮縮短治療時間。

在曾經治療失敗的 genotype 1 患者，則依先前治療中的病毒動力學變化來分治。若是復發者(relapser)、部份反應者(partial responder，亦即在治療的第十二週的病毒量與初始量相比，有超過 2 log IU/mL 的下降量，但在 24 週時仍測得病毒稱之)，或是不反應者(null responder)，均可以再依上述的合併 boceprevir 或 teleprevir 與長效干擾素以及依體重計量的雷巴威林來治療患者。若為復發或是部份反應者，則可考慮依照再次治療中的病毒學變化來考慮縮短治療時間；而針對不反應者，則不建議縮短療程。

1.7.3 2011 年歐洲肝病研究學會的 C 型肝炎臨床處置指引 (EASL clinical practice

guideline: management of HCV infection)[16]

對於沒有禁忌症也從治療過的慢性 C 型肝炎患者，應該考慮合併長效干擾素與雷巴威林治療。在 HCV genotype 1 或 4/6 患者，雷巴威林劑量應以體重調整：而 genotype 2 或 3 患者，則採固定的雷巴威林劑量即可。

對於 genotype 1 感染的慢性 C 型肝炎患者，若是面臨初次治療失敗而需再次治療，則不應使用相同的藥物，因為能夠在此種處方下成功的清除病毒的機會很低。若是在該地區可以使用新型的藥物，即直接抗病毒藥，則應與之合併長效干擾素和雷巴威林來治療患者。然而，對於非 genotype 1 感染的患者，應為沒有充足證據的情況下，可考慮再次使用長效干擾素和雷巴威林來治療。

1.8 欲研究的問題及其重要性 (Issue and importance of the study)

在亞洲，吾人仍不清楚對於慢性 C 型肝炎的復發者，若是採用當今的標準治療(合併長效干擾素與雷巴威林)其成效為何。對於這些曾經治療而失敗者，在不使用 DAA 的情形下，吾人亦不明瞭 IL28B 的核苷酸多形性是否仍會影響治療的成敗。

1.9 研究的假說與特定目的 (Hypothesis and treatment endpoint)

吾人希望藉由一前瞻性的臨床研究來釐清 IL28B SNP 在慢性 C 型肝炎復發者的再次治療時的預測價值。此研究的主要目標(primary endpoint)為了解在使用長效干擾素與雷巴威林時的治療成功率，亦即達到持續病毒學反應(SVR)。次要目標(secondary endpoint)為評估治療中的病毒動力學變化，包含第 4、12 以及 24 週的病毒量變化。除此之外，其餘目標則是要收集更多宿主及病毒的資訊，對於這些先前治療失敗的病毒復發者在使用二種藥物的合併治療時，能提供最佳的治療模式，並能達成個人化治療(personalized therapy)決策的目的。

第二章　研究方法與材料

2.1 計畫目的

設計一前瞻性的觀察研究，驗證先前治療失敗的慢性 C 型肝炎患者再次接受長效干擾素及雷巴威林的標準治療時， IL28B 的單一核苷酸多形性是否可以預測患者再治療的成功率。主要目的在於觀察 IL28B 的單一核苷酸多形性與快速病毒學反應(rapid virologic response ;RVR)、早期病毒學反應(early virologic response; EVR)以及持續性病毒學反應(SVR)的關係及影響。次要目的在於比較其他宿主因素(如年齡、性別、身體質量比 BMI、肝纖維化程度)和病毒因素(如病毒基因型、治療前病毒量)與 SVR 的關係。藉由此觀察性的研究，期望對於慢性 C 型肝炎患者的治療預測因子以及個人化療法能更清楚地了解。

2.2 實施方法及進行步驟

2.2.1 收治病人源起(Enrollment of Patients)

在 2009 年十一月份，台灣的健康保險局發佈針對慢性 C 型肝炎患者在先前的24週合併干擾素與雷巴威林的治療後復發，而需要再次治療的保險納入計劃。所謂的復發者是指在初次治療時，治療結時(即第 24 週)的 HCV 病毒量無法測得而在後續的追踪過程中在血液中又出現了 C 型肝炎病毒，亦即無法達到持續病毒學反應。

2.2.2 納入條件 (Inclusion Criteria)

吾人收錄了上述定義的慢性 C 型肝炎的復發者進入此研究中。其餘的收入條件包括：

(1)年齡大於18歲

(2)C型肝炎血清抗體呈陽性，anti-HCV(+)，由Abbott HCV EIA 2.0 (Abbott Laboratories)偵測。

(3)血清中可測得C型肝炎病毒 (HCV-RNA)，由real-time RT-PCR analysis (CobasTaqMan HCV Test, version 2.0; Roche Diagnostics)偵測。

(4)C型肝的病毒基因型，由reverse hybridization assay (Inno-LiPA HCV II; Innogenetics)測得。

(5)血液中ALT異常。

2.2.3 排除條件(Exclusion Criteria)

若有下列情況者，不能參加本試驗

(1)貧血(男性<13 g/dl; 女性<12g/dL)

(2)中性球缺乏 (Neutrophil count < 1,500/mL)

(3)血小板缺乏 (platelet count < 90,000/mL)

(4)同時有B肝病毒或愛滋病毒感染者

(5)慢性酒癮者 (每日飲酒量>20g)

(6)失償性肝硬化患者 (Child classification, B或C)

(7)自體免疫性肝疾病

(8)器官移植者

(9)惡性腫瘤患者

(10) 患有其他嚴重心肺、自體免疫、腎臟、血液與腎臟疾病者

(11) 毒癮者

(12) 無法配合避孕者

2.3 研究設計(Study design)

這個是在台灣大學醫學院附設醫院所執行的前瞻性的觀察研究。實施其間是由 2009 年 11 月至 2012 年 6 月。此研究計劃在合於醫學倫理委員會的實施準則，並合乎 1975 年赫爾辛基宣言(Declaration of Helsinki)與國際醫藥法規協和會的優良臨床試驗規範(International Conference on Harmonization for Good Clinical Practice)。在納入研究之前，所有的病人均取得知情同意書(Written informed consent)。

所有合乎前述條件的慢性 C 型肝炎受試者，均予以為期 48 週的治療，包含施打每週一次皮下注射的長效干擾素(pegylated interferon alfa, PEG-IFN alfa)與每日口服依體重調整劑量的雷巴威林(Copegus® , F. Hoffman-LaRoche; or Rebetol® , Merck)。其中的長效干擾素，若為 PEG-IFN alfa-2a (Pegasys® , F. Hoffman-LaRoche)使用固定劑量 180 微克；若使用 PEG-IFN alfa-2b (PegIntron® , Merck)則劑量依體重調整，而劑量為每公斤體重 1.5 微克。對於 HCV genotype1 者，雷巴威林劑量為每日口服 800-1200 毫克；而 genotype 2 者，則劑量為每日口服 800 毫克。病人除了在門診接受 48 週的藥物治療外，另有額外 24 週不須投藥的門診追踪檢查。在藥物治療期間，患者在投藥後的第 1、2 及 4 週，然後每月一次回診，接受藥物療效及安全性的評估。實驗流程如圖 1 所示。

2.4 實驗診斷(Laboratory)

2.4.1 常規實驗檢查(Routine laboratory examination)

在治療前，患者皆須接受基本的理學檢查、過去疾病史與藥物史、精神評估、胸部 X 光、心電圖和眼底檢查。常規檢查包含 complete blood count and differential count (CBC/DC), prothrombin time (PT), albumin, bilirubin, aspartate transaminase (AST), alanine transaminase (ALT) , blood urea nitrogen (BUN), creatinine (Cre) , alfa-fetoprotein (AFP), free tetraiodothyronine (free T4), thyroid stimulating hormone (TSH), ferritin, fasting glucose (glucose AC), total cholesterol (T-CHO), triglyceride (TG) , urine pregnancy test (只限女性)。另按照健保局與台灣肝臟醫學會的治療準則，每月定期追蹤患者的 CBC/DC，AST，ALT，每三個月定期追蹤患者的 T4, TSH, fasting sugar。腹部超音波檢查(abdominal ultrasonography)則是在治療前與開始治療後每 6 個月實施，若有肝硬化患者，則為每 3-4 個月實施一次。

2.4.2 分子生物學分析(Molecular assays)

2.4.2.1 C 型肝炎病毒的基因分型(HCV genotyping)

C 型肝炎病毒的基因型是採用 reverse hybridization 的方法分析(Inno-LiPA HCV II; Innogenetics)。

2.4.2.2 C 型肝炎病毒 RNA 的定量分析與療效監測 (Quantitative HCV RNA testing and monitoring of treatment efficacy)

血清中的 HCV 病毒是由 RT-PCR analysis 執行定量分析 (CobasTaqMan HCV Test， version 2.0，Roche Diagnostics，檢測下限為 25 IU/mL)。檢查時機為治療前(基礎值)、治療中(第 4 週、12 週及 48 週)，以及治療後 24 週。

2.4.2.3 宿主基因分型(Host genotyping)

除此之外，宿主的 DNA 是由週邊血液之單核球萃取後，藉由 QIAamp kits (Qiagen, Inc., Valencia, CA, USA)分析而得。而宿主的基因分型是由 ABI TaqMan allelic discrimination kit and the ABI7900HT Sequence Detection System (Applied Biosystems)分析得之。因此，IL28B 基因的 rs8099917 之單一核苷酸多形性(SNP)的基因分型即可測得。

2.5 安全評估(Assessment of safety)

所有的臨床試驗參與者均會在每一次的門診訪視中評估是否有不良事件(adverse events, AEs)產生，並且會藉由實驗室檢測來執行安全性評估。其中包括類流感症狀、嚴重的疲倦、憂鬱、不安、睡眠障礙、睡眠障礙、皮膚過敏反應、喘息、白血球低下、貧血、血小板低下、肝指數飆升以及甲狀腺功能失常。無法完成治療計劃而退出的患者則會鼓勵持續接受門診訪視直至整個實驗的追踪期結束。依據不良事件與實驗室檢測結果的嚴重程度，以降階方式(stepwise)逐漸將長效型干擾素或雷巴威林減量。在不良事件與實驗室檢測異常的情況改善後，可恢復初始劑量。會告知患者雷巴威林的致畸胎性(teratogenicity)，且須在治療過程中與治療後 6 個月內採取避孕措施。

2.6 調整藥物劑量或中止治療(Treatment dose reductions and stopping rules):

(1)若 hemoglobin 小於 10.0 g/dL，則雷巴威林的劑量依照每次減少 200mg 的方式依次需減量。

(2)若 hemoglobin 小於 8.5 g/dL，則停止雷巴威林的使用 。

(3)若絕對白血球計數(absolute neutrophil count，ANC)小於 750/mL 或血小板計數小於 50,000/mL，則長效干擾素需減少劑量。若是使用 peginterferon alfa-2a (Pegasys)，劑量由每週 180 減至 135 再調至 90 μg。若是使用 peginterferon alfa-2b (PegIntron)，劑量由每週每公斤體重 1.5 減至 1.0 再減少為 0.5 μg。

(4)若白血球計數少於 500/mL 或血小板計數少於 30,000/dL，則停止長效型干擾素的使用。

(5)若產生嚴重的憂鬱症狀或是不良事件，亦應停止長效型干擾素。

(6)若在調整藥物劑量後，hemoglobin 回升而且超過 10.0 g/dL，雷巴威林可以重新使用，由每日 400~600 mg 的劑量開調整。

(7)待白血球計數大於 750/mL 或血小板計數大於 50,000/mL，則長效干擾素可以開始使用。長效干擾素由一較低的劑量開始使用，如 peginterferon alfa-2a (Pegasys)由每週 135μg 開始；而 peginterferon alfa-2b (PegIntron)則由每週每公斤體重 1.0μg 開始。

(8)若治療中第 12 週的 HCV RNA 量與治療前的量相比，若無法減少 2 log IU/mL，則終止治療。如此稱為不反應者(non-responder)，因為達成持續病毒學反應(SVR)的機會很低。

2.7 臨床上不良反應及處理方法：

(1)抽血檢驗時造成之疼痛：一般為暫時性疼痛，將傷口局部壓迫即可。

(2)抽血檢驗時造成之血腫：將傷口局部壓迫止血，原則上局部血腫於數日內會逐漸消失。

(3)試驗婦女在參加試驗期間不得懷孕。雖然長效型干擾素於動物試驗中沒有發現致畸胎性，並不能排除懷孕期間使用時可能對胎兒造成的傷害性；而雷巴威林於動物試驗中則有致畸胎性，因此在懷孕期間不宜使用。

(4)接受長效型干擾素合併雷巴威林的受試者中，約四分之一的人會有較明顯的下述不適或副作用。

(5)使用干擾素的不良反應：

I. 發燒、畏寒、頭痛、肌肉疼痛、關節疼痛、倦怠等類似感冒症狀：一般可以使用口服止痛退燒藥 (例如 acetaminophen 或 ibuprofen) 、適度的飲水、或調整干擾素的劑量加以治療。

II. 食慾不振、噁心: 原則上可以使用促進食慾的藥物或是調整干擾素的劑量加以治療。

III. 失眠: 原則上可以使用安眠藥加以治療。

IV. 掉髮: 治療其間若有美觀上的考量可以暫時使用假髮，當治療完畢後掉髮情形會消失。

V. 憂鬱症及易怒: 基本上若有不易控制之精神病患者則不列入合格受試者的範圍。若於受試期間發生憂鬱症及易怒則照會精神科醫師評估用藥或是終止試驗。

VI. 中性白血球或血小板下降: 根據抽血數值決定干擾素的劑量之調整。

VII. 其他: 其它罕見之合併症(少於 1%)，包括自體免疫疾病，心血管疾病，皮膚病，及眼科疾病等等... ， 原則上於受試者進入試驗前即先排除不易控制之自體免疫疾病，心血管疾病，皮膚病，及眼科疾病。若受試者於受試其間首次發病則會診專科醫師加以評估處理。

(6)使用雷巴威林的不良反應:

I. 噁心、嘔吐: 原則上可以使用促進食慾的藥物或是減低雷巴威林劑量加以治療。

II. 皮膚炎:以止癢藥膏局部塗抹加上口服抗組織胺藥物藥物或是減低雷巴威林劑量加以治療。

III. 鼻塞:以口服抗組織胺藥物藥物或是減低雷巴威林劑量加以治療。

IV. 貧血: 根據抽血數值決定雷巴威林的劑量之調整。

2.8 統計分析(Statistical analysis)

2.8.1 受試者樣本估計

依照非連續樣本大小計算公式 (Rosner, Foundamentals of Biostaticstics, 6th ed, 2006)

$$n = \frac{\left[\mu_\alpha\sqrt{2\bar{P}(1-\bar{P})} + \mu_\beta\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right]^2}{(P_1-P_2)}$$

P_1: 實驗組(genotype TT)，估計 SVR 的機率為 70%

P_2: 對照組(genotype GT/GG)，估計 SVR 的機率為 30%

$\bar{P}$: $(P_1+P_2)/2$

α= 0.05 時，μ_α=1.96

Power = 1-β = 0.8 時，μ_β=0.842

依據 type I error 為 0.05 而 type II error 為 0.20 的情況下，假設 rs8099917 TT(70%)與 GT/GG(40%)兩基型的持續病毒學反應的差距為 40%，採用 2-sided test 分析，可得最小樣本數為 58 人。

2.8.2 各變項的統計分析

連續變項由平均值(mean)與標準差(standard deviation, SD)來分析。類別變項則由百分率(percentage)來分析。治療組間的個別基礎特徵(baseline characteristic)之分析，乃採用合適之 chi-square test、Fisher's exact test 或 Student's t test 來進行統計分析。Primary efficacy end point 是由 Intention-to-treat analysis 法分析。治療反應的比較則使用 Fisher's exact test 分析法。若使用邏輯迴歸法(logistic

regression)分析的單變項(Univariate)或多變項(Multivariable)因子則會以勝算比(odds ration, OR)以及 95%信賴區間(95% confidence intervals, CIs)來表示。所有的顯著性檢定(test of significance)均採雙尾法(two-tailed)，若 P 值(P value)小於 0.05 則認為是具有統計顯著性。資料乃使用 Microsoft Excel database (Microsoft Excel 2001; Microsoft Corporation, Seattle, WA, USA) 收集，並以 Stata statistical software (version 9.2; Stata Corp, College Station, TX, USA)加以分析。

第三章　結果

3.1 研究對象之特徵(Characteristics of the Study Patients)

此研究共有 106 位患者進入篩選，其中有 3 位患者不願接受治療因而退出再次治療的研究計劃。其餘的 103 位患者即安排為期 48 週的長效型干擾素合併雷巴威林的療程(Figure 1)。其中，75 位(73%)是第一基因型 C 型肝炎病毒(HCV genotype 1)感染；28 位(27%)是第二基因型 C 型肝炎病毒(HCV genotype 2)感染(Figure 2)。在第一與第二基因型慢性 C 型肝炎患者中，分別有 65 位(87%)與 26 位(97%)患者完成 48 週的治療；其餘的 10 位 (13%, HCV genotype 1)及 2 位(7%, HCV genotype 2)患者因為在第四週的病毒量與初始值相比無法達成 2-log 下降量，因而提早終止治療。所有的患者均完成二十四週的治療後追踪觀察。

下文的內容僅納入第一基因型慢性 C 型肝炎患者做分析研究。此 HCV genotype 1 患者在初始治療與再次治療的基礎臨床特徵是有些許不同(Table 1)。平均來說，患者在再次治療時，年齡增長了 3 歲、身體質量指數增加(body mass index, BMI 上升 0.2 kg/m^2)、肝纖維化指數增加(AST to platelet ratio index [APRI] 上升 1.3)、而血液中的 ALT 與 albumin 則是下降的。

再次治療時，患者大部份超過 50 歲(77%)且以男性(56%)比例居多(Table 1)。47%的患者 BMI 超過 25 kg/m^2 而 60%患者的血液中 ALT 超過正常值上限 2 倍以上。大部份的患者接受 peginterferon alpha 2a 長效干擾素合併療法(Pegasys vs. PegIntron = 76% vs. 24%)。

在第一基因型的慢性 C 型肝炎患者中，IL28B 單一核苷酸多形性(IL28B SNP)(依 rs8099917 討論)以 TT 基因分型居多(TT vs. GT vs. GG = 72 % vs. 28% vs. 0 %)。因為無 GG 基因型，以下討論均忽略不論。與 rs8099917 GT 基因型相比較，TT 基因型患者較年輕(小 2.4 歲)、身體質量指數較低(BMI 少 0.7 kg/m^2)、肝指數較低(ALT 低 5 IU/L)。以 HCV RNA 病毒量而言，TT 基因型患者的病毒量高於 GT 基因型。上述 TT 與 GT 基因分型的指標雖有數值上的不同，但在統計分析上卻無明顯差異。

3.2 病毒動力學反應—治療進行中、治療結束後 24 週的持續病毒學反應與復發 (Viral Kinetics–On-Treatment, SVR and relapse)

以治療中與治療後的病毒動力學變化而言(Figure 4)，37%的第一基因型慢性 C 型肝炎患者在合併治療中的第四週就可以清除血液中的 HCV RNA (即快速病毒學反應，rapid virologic response, RVR)。第 12 週的治療時，13%患者無法讓血液中的 HCV RNA 至少下降 2 log IU/mL 以上(即無部份早期病毒學反應，without partial early virologic response, pEVR[-])而 13%可以減少 2 log IU/mL 以上但無法清除病毒(即 pEVR[+])，而 36%患者雖無法在第四週清除病毒但在第十二週時血液中已測不到病毒(即完全早期病毒學反應，complete early virologic response, cEVR)。此外，在治療 48 週時，73%患者可以維持血液中測不到病毒(即治療末病毒學反應，end-of-treatment virologic response, EOT-VR)。治療結束後 24 週，仍有 52%患者可以持續測不到血中的 HCV RNA 病毒(亦即持續病毒學反應，sustained virologic response, SVR)。其中有 55 位患者在治療結束時已測不到病毒，但是在追踪的過程中 16 位(29%)患者 HCV RNA 又出現在血液中(即復發, relapse)。

依 IL28B SNPs 而言，與 GT 基因型相較，具有 TT 基因型的患者有較高的快速病毒學反應(RVR, *P*=0.0002)、治療末病毒學反應(EOT-VR, *P*=0.0001)以及持續病毒學反應(SVR, *P* <0.0001)。而 GT 基因型患者，清除血液中的病毒速度較慢(因有較高比例的 pEVR 或 cEVR 患者)。而 GT 型患者亦有較高比例的病毒復發情況(*P* =0.006)。

3.3 依治療中的病毒動力學變化(第 4 及 12 週)以及 IL28B SNPs 分型來探討持續病毒學反應與復發(SVR and relapse rate according to on-treatment viral kinetics [week 4 and week 12], and IL28B SNPs) (Figure 5 and 6)

若可以達到快速病毒學反應(RVR)，即可以有較高比例的治療末病毒學反應 (EOT, RVR vs. non-RVR = 96% vs. 59%. *P*=0.0003)、較高的持續病毒學反應(SVR,

RVR vs. non-RVR = 86% vs. 32%. *P*<0.0001)以及較低的病毒復發(relapse, RVR vs. non-RVR = 11% vs. 46%. *P*=0.0034)。

IL28B TT 基因型患者有較高比例可達成持續病毒學反應(SVR, TT vs. GT = 67% vs. 14. *P*<0.0001)。若可以達成治療的重要基石--快速病毒學反應，則 IL28B 的基因型(TT 或 GT)均與持續病毒學反應(SVR)無關。相對的，若無法達成快速病毒學反應學，IL28B 基因型的差異對於病毒學反應則有顯著的不同；IL28B TT 基因型有較高的 SVR 比例(TT vs. GT = 48% vs. 10%. *P*=0.048)與較低的復發比例(TT vs. GT = 35% vs. 75%. *P*=0.0581)。

在治療過程中若患者無法達到快速病毒學反應，第 12 週的病毒下降量的差異則會顯著地影響到持續病毒學反應(SVR, pEVR[+] vs. cEVR[+] = 10% vs. 52%. *P*=0.015)。71%在治療末測不到血中病毒(即 EOT-VR)的患者可以達成持續病毒學反應；而 SNP TT 基因型有較高的比例達成 SVR (TT vs. GT = 78% vs. 33%. *P*=0.006)。

3.4 與快速病毒學反應及持續病毒學反應相關因素的探討(Factors associated with RVR and SVR)

3.4.1 快速病毒學反應(RVR)相關因素(Factors associated with RVR) (Table 3 and 4)

女性、較低的身體質量指數、較低的空腹血糖、較高的血清白蛋白以及較低的 HCV RNA 治療前基礎值均與快速病毒學反應(RVR)有關。而 IL28B 之 TT 基因型則是唯一與 RVR 有關的獨立預測因子(OR, 20; 95% CI, 2.5 – 159.8; *P*=0.005)。

3.4.2 持續病毒學反應(SVR)相關因素(Factors associated with SVR) (Table 3 and 4)

在單變項邏輯迴歸分析中，IL28B TT 基因型(OR, 12; 95% CI, 3.12–46.14; *P* < 0.001)與快速病毒學反應(OR, 12.8; 95% CI, 3.77 – 43.50; P < .001)對於持續病毒學反應均為強烈的預測因子。此外，女性(OR, 2.94; 95% CI, 1.14–7.61; *P* = 0.026)

以及高血中白蛋白濃度(OR, 3.67; 95% CI, 1.20 – 11.17; *P* = 0.022)亦為具有統計意義的 SVR 預測因子。

3.4.3 持續病毒學反應的多變項模式分析(Multivariable Models in predictors of SVR) (Table 5)

吾人使用迴歸模式而加以釐清有關持續病毒學反應的預測因子。在這 75 位受第一基因型慢性 C 型肝炎感染的患者中，有完整資料的變項(因子)全都納入這個模組中。吾人首先將所有的預測 SVR 因子轉成二分變項(dichotomous variable)，即將連續變項(continuous variable)與次序變項(ordinal variable)依適當的臨床閾值產生二項因子。因此吾人將下列因子納入預測持續病毒學反應的多變項邏輯式迴歸模組中，如 IL-28B 基因型、快速病毒學反應(RVR)、性別、年齡、白蛋白、空腹血糖、ALT 值、APRI、身體質量指數(BMI)、以及 HCV RNA 的基礎病毒量。IL28B 的基因型在此模組中最具預測 SVR 的勝算比(TT vs. GT: odds ratio, 22.81; 95% CI, 2.84 - 183.34; *P*=0.003)。其次為，性別(男 vs.女: odds ratio, 14.69; 95% CI, 1.98 – 108.88; *P*=0.009)、RVR (positive vs. negative: odds ratio, 6.58; 95% CI, 1.41 – 30.77; *P*=0.017), 與白蛋白 (大 vs. 小於 4.3 g/dL: odds ratio, 6.93; 95% CI, 1.24 – 38.54; *P*=0.027)亦為具有統計意義的預測 SVR 因子。

3.5 以 IL28B SNP 與治療中病毒動力學變化來預測持續病毒學反應(Prediction of SVR in combination with IL28B SNPs and/or on-treatment viral kinetics)

3.5.1 分別以 IL2B SNP 或病毒動力學變化來預測 SVR 的價值(Predictive value of SVR by IL28B SNP, or viral kinetics) (Table 6A)

吾人分別將 IL28B 基因型(TT vs. GT)、第 4 或 12 週病毒轉陰化(viral negativity，即血液中測不到病毒)當成預測持續病毒反應的二分變項。與 IL28B 基因型或第 12 週病毒轉陰化相較，第 4 週病毒轉陰化(即快速病毒學反應，RVR)之持續病毒反應的陽性預測值(positive predictive value , PPV)較高(PPV, 86 vs. 67 vs. 69% =

RVR vs. IL28B SNP vs. week 12 negativity)。然而，第 12 週病毒轉陰化與 IL28B 基因型之持續病毒反應的陰性預測值(negative predictive value , NPV)比第 4 週病毒轉陰化(RVR)高(NPV, 95 vs. 87 vs. 86% = week 12 negativity vs. IL28B SNP vs. RVR)。

3.5.2 合併 IL2B SNP 與病毒動力學變化來預測 SVR 的價值(Predictive value of SVR by IL28B SNP and viral kinetics) (Table 6B)

合併 IL28B 基因型與第 4 或第 12 週病毒轉陰化與否來預測 SVR 的比較中，將 IL28B 基因型結合第 4 週病毒轉陰化(即快速病毒學反應，RVR)的陽性預測值較高(PPV, 85 vs. 76% = TT/RVR(+) and TT/week 12 negativity(+))。而陰性預測值則在二組的比較是相當的(NPV, 90 vs. 100% = GT/RVR[-] and GT/week 12 negativity[-])。

第四章　討論

本研究是針對慢性 C 型肝炎的發復者進行再治療，使用的處方為亞太地區當今標準治療(即為合併長效型干擾素與雷巴威林的 48 週療程)的成功率約為 50%。在亞太地區，很少有慢性 C 型肝炎的再治療資料，此篇為首次的報導。根據歐美國家的研究資料，第一基因型的慢性 C 型肝炎患者(CHC genotype 1)再次治療的成功率與初次治療所使用藥物與病毒動力學變化不同而有所差別。若改以長效干擾素施予初次療程中使用短效干擾素的患者[19,50,51]，以復發者(relapser)而論持續病毒學反應(SVR)為 31-32 %，而不反應者(non-responder)的 SVR 則為 13-20 %。若與初次療程同樣予以長效干擾素治療[19,21]，若為復發者(relapser)，SVR 為 23 %，而不反應者(non-responder)之 SVR 則僅有 4-9 %。

就 IL28B 基因型加以探討，有二個位於此基因上游的單一核苷酸多形性(即 rs8099917 和 rs12979860)較為學者所討論；此二者之 favorable allele (如 rs12979860 C allele 或 rs8099917 T allele)與 unfavorable allele (如 rs12979860 T allele 或 rs8099917 G allele)之比例在黑人與西班牙語系略有不同，而在亞洲人中此二種 SNP 的 allele 分佈並無明顯不同[52]。所以，吾人在此研究中選擇了 rs8099917 當成 IL28B SNP 的指標。IL28B SNP 之 favorable allele 所占的比例會與疾病的狀態不同而有所差異。以 rs12979860 為例[28]，若受到 C 型肝炎病毒感染後而能自發性清除血液中病毒，其 favorable allele (TT)為 76%而 unfavorable allele (GT/GG)占 24%；若成為慢性 C 型肝炎帶原者而能經由治療清除病毒者，TT 型約 68 %而 GT/GG 型為 32 %;若是在治療失敗的患者，則 favorable allele (TT)降為 43 %，而 unfavorable allele (GT/GG)則上升為 47 %。亦即 favorable allele 所占的比率會隨著清除 C 型肝炎病毒難度的增加而下降。同樣的，依 rs8099917 而論[52]，在亞洲人的正常族群中 favorable allele (T allele)占 93%；若為慢性 C 型肝炎感染則 T allele 降為 90%；若無法治療成功(以本研究的復發者而言)，T allele 更降為 86% (54 位 TT，21 位 GT)。

在其他學者的研究中，IL28B SNP 俱有判斷治療成功予否的價值。初次治療時[53]，第一基因型的慢性 C 型肝炎患者，TT 型 rs8099917 (30 %)而 GT/GT 型(6-7 %)可達成 RVR；而 TT 型(79 %)而 GT/GT 型(41-44 %)可達成 SVR。若需再次治療時，並無正式的報告可以提供 IL28B SNP 是否會影響慢性 C 型肝炎再次治療時的治療中病毒動力學變化、持續病毒學反應或者復發；而本研究正可提供 IL28B SNP 再次治療時的病毒反應與預測價值的相關訊息。本研究中僅有 TT (72%)與 GT (28%)二種分型，而無 GG (0%)型。本研究中，TT 與 GT 基因型分別為 50 %與 5 %可達成快速病毒學反應(RVR) (*P*=0.0002)；TT (85 %)與 GT (43 %)達成治療結束病毒學反應(EOT-VR) (*P*=0.0001)；TT (67 %)與 GT (14 %)達成持續病毒學反應(SVR) (*P*=0.0001)，而 TT (22 %)與 GT (67 %)會復發(relapse) (*P*=0.0006)。此外，在合併 DAA 的多重藥物治療下的非正式報告中，IL28B 基因型的差別對於 SVR 的影響就不明顯了。

治療過程中第四週的病毒動力學變化，即快速病毒學反應(RVR)對於是否能達成持續病毒學反應(SVR)具有指標上的意義。有學者對於第一基因型的慢性 C 型肝炎的初次治療的研究中指出[29]，若能達成 RVR 則 SVR 為 84 %；若無法達成 RVR 則 SVR 成為 41 %。若有 RVR，則 CC (85%)與 CT/TT (76 – 100%) IL28B (rs12979860)基因型可達到 SVR；若無 RVR，則 SVR 的機會下降(CC vs. CT/TT = 66% vs. 24- 31%)。本研究則能提供 RVR 於再次治療時對 SVR 所產生的影響，若能達成 RVR 則 SVR 為 86 %；若無法達成 RVR 則 SVR 降為 32 %，RVR 對於能否達成 SVR 具有統計上的意義(*P*<0.0001)。若能達成 RVR，則 TT (85%)與 GT (100%)對 SVR 無明顯差別；若無法達到 RVR，則 TT (48%)與 GT (10%)就有顯著的統計差異(*P*=0.0048)。

是否能在治療初期即可預估患者的治療反應，一直是學者們研究的目標。若預期能清除病毒的機率較大，則應鼓勵患者持續治療；若成功的機率甚小，則應考慮終止治療或更換治療處方。吾人利用合併 IL28B SNP 與第 4 週的血液病毒轉陰化(即快速病毒學反應，RVR)做為參考指標，在本研究中，若有 favorable allele

(TT IL28B 基因型)且能達成 RVR，則 SVR 為 85 % (陽性預測值，PPV=85 %); 相較於 GT IL28B 基因型與無 RVR，SVR 則減為 10 % (陰性預測值，NPV= 90%)。與待至第 12 週時的病毒轉陰化合併 IL28B SNP 相比並不遜色(SVR, TT with viral negativity vs. GT without viral negativity = 76 vs. 0 %)。因此，合併 IL28B 與第四週時的病毒動力學變化，似乎可以做為早期終止治療或者是更換藥物的參考(rapid terminative marker)。若無法取得新藥(直接抗病毒藥，DAA)使用，則考慮停止治療，如此可以減少患者在治療中所受的身體不適及心理壓力及減少醫療費用。若有新藥可用，則可以建議儘早合併多重藥物進行治療，方可增進患者清除病毒的機會。

第五章　展望(Perspectives)

5.1 本研究對於臨床應用、學術研究及國家發展預期之貢獻

本研究可以讓吾人藉由慢性 C 型肝炎患者再次接受長效型干擾素與雷巴威林的標準治療時，觀察 IL28B 單一核苷酸多形性對於治療的反應。此外吾人也可以分析及了解慢性 C 型肝炎患者於再次治療時病毒動力學指標之變化、其他宿主因子以及治療不良反應等相關指標之差異性及影響。將可以用來改善現今慢性 C 型肝炎患者的治療與個人化處置。

5.2 本研究面臨的限制與未來研究方向

由於第二基因型的慢性 C 型肝炎(CHC genotype 2, n=28)患者人數不足，無法更進一步的分析，將來須要更大的樣本(可能需要 1000 人)才可以，因此需要多中心或更久的時間來收集。

本研究病人族群於初次治療時所使用的藥物不甚一致(有使用長效干擾素，亦有短效干擾素)；此外，臨床資料不甚完整，尤其是病毒動力學變化的資料。未來在從事進一步的研究，應讓研究族群更同質化，收集在初次治療時有完整的治療藥物與病毒動力學反應資料的病人，加以分組而納入研究分析。此外，再次治療患者缺乏肝臟切片檢查的資料，因此無法就肝纖維化程度分析，應可列入將來研究方向。另外、肝功能正常化程度與持續病毒學反應亦有學者在研究，於再次治療時的價值也無相關研究，可以列為接下來研究的目標。在基礎研究方面，未來可以將 HCV viral core gene polymorphism 分析初次治療與再次治療時的變化，同時分析與再次治療是否能成功的相關性。

若患者是 GT IL28B 基因型同時無法達成快速病毒學反應(RVR)，如果仍採用 48 週的標準治療，達成持續病毒反應的機會很低，未來可以將此難治族群加入臨床研究。若無新藥可用時，或可延長治療時間(72 週或更久)，或可增加藥物劑量；一方面可以加增這些急需再治療患者的成功機會，一方面可以檢測這一早期終止指標(GT IL28B 合併無 RVR)是否適用。若有新藥可用時，則採用合併療法，

觀察治療中與治療後的病毒動力學反應對於 SVR 的影響，這當然須要更多病人數的前瞻性研究才可以解釋。

第七章　英文論文簡述

Chapter 1. Introduction

1.1 Background

Up to 60–80% of patients fail to eradicate the virus spontaneously after being infected with hepatitis C virus (HCV)[1], especially in asymptomatic individuals. Chronic hepatitis C infection (CHC) is one of the major causes of chronic liver disease and becomes a disease of substantial global burden. An estimated number of 170 million people in the world are chronically infected with HCV[2,3]. In Asian-Pacific regions, the crude prevalence of HCV infection estimates from 0.3% to 12%, with markedly geographical difference[4].

CHC is associated with variable degrees of hepatic injury, which has become a leading cause of decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation. Therefore, to treat CHC earlier and reduce transmission is needed to decrease the liver-related morbidity and mortality.

1.2 Current standard of care (SOC) for treatment-naïve CHC infection

Clinical care for CHC patients has advanced considerably and has been revised in the past two decades. The major goal of CHC treatment is to eradicate circulating HCV and achieve sustained virologic response (SVR, defined as undetectable HCV RNA six months posttreatment, which is regarded as virologic cure).With the approval of pegylated interferon (PEG-IFN) in 2001 by the Food and Drug Administration (FDA) in the United States, weekly PEG-IFN in combination with weight-based ribavirin (RBV) is well accepted and has been the current SOC for CHC patients. Viral genotype- and on-treatment-response-guided personalized therapy under such SOC regimen can only achieve an overall SVR of 40-50% in patients with

genotype 1 for 48 weeks and 80% or more in those with genotypes 2 or 3 infection for 24 weeks[5-8].

Treatment with PEG-IFN plus RBV is also associated with many adverse effects, i.e. flu-like symptoms, severe fatigue, depression, irritability, sleeping disorders, skin reactions, dyspnea, neutropenia, anemia, thrombocytopenia, ALT flares and thyroid dysfunction. Fortunately once accomplishing SVR, long-term clearance of HCV infection is achieved and is regarded as cure virologically. Many beneficial effects accompany SVR, including fibrotic regression, reducing rate of HCC, decreasing rate of liver failure/liver-related death, and improving quality of life[9].

There are various pretreatment viral and host factors to predict treatment response. Viral factors include HCV genotype, baseline viral load, viral kinetics during treatment and co-infection with another hepatotropic virus or with HIV[10-12]. Host factors include gender, duration and age of infection, race or ethnicity, baseline hepatic fibrosis /necroinflammation /steatosis status, overweight, insulin resistance, serum ALT level, noncompliance, adverse events during treatment and genetic factors[5-7,9,13-15]. The strongest baseline predictors of SVR are HCV genotype, IL28B polymorphisms and status of liver fibrosis[16].

1.3 Re-treatment of chronic hepatitis C infection

A substantial proportion of treatment-naïve HCV patients fail to achieve SVR with standard combination therapy. In re-treating HCV patient, the optimal regimen is not well established yet and the efficacy remains unclear.

Retreatment with PEG-IFN and RBV could achieve SVR in 30–50% of relapsers (undetectable HCV RNA during therapy but reappeared after the end of treatment) and only 10–15% of non-responders (less than 2 log IU/mL drop of HCV RNA from baseline at week 12) [17-23]. SVR in retreating patients can be predicted by several

factors, including viral genotype, baseline HCV RNA level, viral suppression at week 12, previous treatment regimen/duration, age and body weight[19,21].

1.4 Genome-wide association study (GWAS) and IL28B single nucleotide polymorphism (SNP)

Is there another critical host genomic factor influencing the HCV therapy? It is reported that the single nucleotide polymorphism (SNP) near the interleukin-28B (IL28B) in several independent genome-wide association studies (GWAS) is associated with spontaneous or treatment-induced viral clearance in previously untreated patients[24-28].

The IL28B SNP such as rs8099917 and rs12979860, which is located upstream of chromosome 19, can encode IFN λ-3 with anti-viral effects against HCV and plays a key determinant for SVR[23,29-37]. The favorable IL28B SNPs are strongly associated with SVR in HCV genotype 1 patients who receive PEG-IFN and RBV, but are controversial in HCV genotypes 2 or 3. The value of IL28B variant to predict SVR is better than pretreatment HCV RNA level, fibrosis status, age, and gender[29,31].

In IFN-based therapy, IL28B SNPs variations are also associated with on-treatment viral kinetic and are the strongest pretreatment predictor of SVR in HCV-genotype-1-infected patients. It is said that the impact of IL28B SNPs will keep influencing SVR in IFN-based regimen against HCV but might be decreased in interferon-free era[9].

1.5 Comparison between eastern and western populations

Asians have better treatment response than white patients who received PEG-IFN plus weight-based RBV therapy in CHC genotype 1[38-44]. Heterogenous viralogical responses to PEG-IFN-based treatment among various ethnicities might be partially explained by the difference of favorable allele distribution of IL28B.

1.6 Direct anti-viral agents, DAAs

A considerable portion of CHC patients fail to respond to current SOC with PEG-IFN and RBV treatment, especially for HCV genotype 1 and unfavorable IL28B SNP and poor on-treatment viral response.

DAAs, targeting several steps in the HCV lifecycle, are drug classes which are current developing for CHC treatment. Serine protease inhibitors (Boceprevir and Teleprevir) are approved by FDA in 2011. The current significant advance is the addition of DAAs in combination with PEG-IFN and RBV to improve virological response and abbreviate the duration of treatment. DAAs have shown significant viral suppression and improvement of SVR rate, especially in HCV genotype 1 infection. However, 25-37% (treatment-naïve[45,46]) and 34-41% (treatment-experienced[47,48]) CHC patients fails to achieve SVR in triple therapy with combination of protease inhibitors, PEG-IFN and RBV in addition to excessive unpleasant adverse events (eq., anemia, dysgeusia, rash, pruritus and diarrhea[45,46]) and medical costs.

1.7 Current Guidelines in retreatment of CHC patients who fail to achieve SVR

1.7.1 APASL consensus statements and management for HCV infection[9]

Relapsers who have favorable factors may be retreated with PEG-IFN plus RBV without the addition of DAAs. In the future, triple therapy with combination of PEG-IFN, RBV and DAAs should be the standard care for retreating CHC patients who fail in the initial SOC[45-48].

1.7.2 2011 AASLD, an update on treatment of CHC genotype 1 infection[49]

In treatment-naïve patients, the optimal regimen for CHC genotype 1 infection is the use of boceprevir or telaprevir in combination with PEG-IFN and weight-based RBV. Shortened duration of therapy could also be considered in favorable virologic

response.

In treatment-experienced CHC genotype 1 patients, re-treatment with boceprevir or telaprevir in combination with PEG-IFN plus weight-based RBV in relapser, partial responder (more than 2 log IU/mL drop of HCV RNA from baseline at week 12 but still detectable at week 24) and null responder. Response-guided therapy could be considered in for relapser and partial responder but not in null responder.

1.7.3 2011 EASL clinical practice guideline: management of HCV infection[16]

Treatment-naïve CHC patients without contra-indication to PEG-IFN and RBV should be considered for therapy and weekly PEG-IFN in combination of weight-based RBV for HCV genotype 1 and 4-6 and flat-dose RBV should be used for genotype 2 and 3.

In re-treating CHC genotype 1 patient who failed in response to prior PEG-IFN based therapy, they should not be retreated with the same regimen, because the SVR rates are relatively low. These patients should be retreated with PEG-IFN, RBV and DAAs if available. However, patients with HCV non-1 genotype infection can be re-treated with PEG-IFN and RBV because there is no option available soon.

1.8 Issue and importance of the study

It remains unclear for the result of Asian CHC relapsers undergoing current SOC. It is still unknown whether IL28B SNP will influence the treatment outcome in HCV treatment-experienced patients who receive combination therapy of PEG-IFN plus RBV without adding DAAs.

1.9 Hypothesis and treatment endpoint

We conduct a prospective study to clarify the predictive value of IL28B SNP in

HCV relapsers. The primary endpoint of this study is to evaluate sustained virologic response under the SOC of PEG-IFN and RBV. The secondary endpoint of therapy is to assess the likelihood of an SVR by evaluate he on-treatment virologic responses at 4, 12, and 24 weeks of therapy. In addition, another goal of this research is to yield sufficient information that offers optimal management and clinical personalized decision-making process for CHC retreated patients in response to treatment of PEG-IFN and RBV.

Chapter 2. Materials and Methods

2.1Enrollment of Patients

In Taiwan, since November 2009, the Bureau of National Health Insurance launched a reimbursement program for the re-treatment of chronic hepatitis C patients who had relapse after a 24-week peginterferon plus ribavirin combination therapy. We defined virologic relapse in patients who had undetectable serum HCV RNA at the end of 24-week treatment and had recurrent hepatitis C viremia during the post-treatment follow-up period, i.e. not obtaining a sustained virologic response (SVR).

2.2 Inclusion Criteria

We consecutively enrolled patients with CHC relapse into this study. Further inclusion criteria for this clinical study included: age >18 years old, presence of anti-HCV antibody (determined using Abbott HCV EIA 2.0; Abbott Laboratories), a detectable serum HCV RNA level by real-time RT-PCR analysis (CobasTaqMan HCV Test, version 2.0; Roche Diagnostics), HCV genotyping by a reverse hybridization assay (Inno-LiPA HCV II; Innogenetics) and serum alanine aminotransferase (ALT) level greater than the upper limit of normal.

2.2.3 Exclusion Criteria

Patients were excluded if they had anemia (hemoglobin level, <13 g/dL for men and <12 g/dL for women), neutropenia (neutrophil count, <1500 cells/mm3), thrombocytopenia (platelet count, <90,000 cells/mm3), coinfection with hepatitis B virus or HIV, chronic alcohol abuse (daily alcohol consumption, >20 g/day), decompensated cirrhosis (Child-Pugh class B or C),autoimmune liver disease, liver transplantation, neoplastic disease, evidence of drug abuse, pregnancy, poorly controlled autoimmune/heart/lung/hematology/renal disease or unwillingness to

receive contraception during the study period.

2.4 Study design

This prospective observational clinical study was conducted from November 2009 through June 2012 at National Taiwan University Hospital, Taipei, Taiwan. Written informed consent before enrollment was obtained from all patients in accordance with ethical committee approved protocols, the principles of the Declaration of Helsinki of 1975 and the International Conference on Harmonization for Good Clinical Practice.

Eligible patients were prescribed 48 weeks of weekly, subcutaneous injections of peginterferon alfa (Pegasys, 180 mcg, F. Hoffman-LaRoche; or PegIntron 1.5 mcg per kilogram of body weight, Merck) and a divided daily weight-based oral ribavirin (Copegus, F. Hoffman-LaRoche; or Rebetol, Merck; 800-1200 mg per day). Patients received 48-week therapy on an outpatient basis and then an additional 24-week follow-up period without treatment. Visits occurred at week 1, 2, 4 and then monthly (every 4 weeks) following initiation of therapy to assess the efficacy and safety.

2.5 Laboratory

2.5.1 Routine laboratory examination

Routine laboratory test findings, including complete blood cell count and serum ALT level, were assessed at enrollment and at each following outpatient visit; prothrombin time, serum albumin level, bilirubin level, and creatinine level were assessed at enrollment and every 12 weeks until the end of the follow-up period.

2.5.2 Molecular assays

2.5.2.1 HCV genotyping

HCV genotyping was performed at baseline by a reverse hybridization technique

(Inno-LiPA HCV II; Innogenetics).

2.5.2.2 Quantitative HCV RNA testing and monitoring of treatment efficacy

Serum HCV viral load was evaluated quantitatively by RT-PCR analysis (Cobas TaqMan HCV Test, version 2.0; Roche Diagnostics; limit of detection, 25 IU/mL) at baseline, on-treatment (week 4, week 12, the end of treatment), and 24 weeks after the end of treatment.

2.5.2.3 Host genotyping

In addition, genomic DNA was extracted from peripheral blood mononuclear cells by using the QIAamp kits (Qiagen, Inc., Valencia, CA, USA). Genotyping was performed using ABI TaqMan allelic discrimination kit and the ABI7900HT Sequence Detection System (Applied Biosystems). An SNP located around IL28B loci (rs8099917) was genotyped.

2.6 Assessment of safety

Participants were evaluated for adverse events (AEs) and laboratory tests to assess safety at each outpatient visit, including flu-like symptoms, severe fatigue, depression, irritability, sleeping, disorders, skin reactions, dyspnea, neutropenia, anemia, thrombocytopenia, ALT flares and thyroid dysfunction. Patients who withdrew from the study were encouraged to receive outpatient visits without treatment until the end of the follow-up period. Stepwise reduction in PEG-IFN or RBV therapy was determined according to the severity of AEs and the laboratory abnormalities. The initial dose resumed after improvement in the laboratory abnormalities and the severity of AEs. Patients are advised of the risk of teratogenicity with RBV and the need for birth control for 6 months after treatment.

2.7 Treatment dose reductions and stopping rules

(1) If hemoglobin is <10.0 gram per deciliter, the dose of ribavirin is reduced and adjusted by 200 mg at a time.

(2) If hemoglobin is <8.5 gram per deciliter, ribavirin administration is stopped.

(3) If the absolute neutrophil count is < 750 per cubic milliliter, or the platelet count < 50,000 per cubic milliliter, the PEG-IFN dose is reduced. If peginterferon alfa-2a is used, the dose can be reduced from 180 to 135 and then 90 μg per week; if using peginterferon alfa-2b, the dose can be reduced from 1.5 to 1.0 and then 0.5 μg/kg per week.

(4) If the neutrophil count is <500 per cubic milliliter or the platelet count is＜30,000 per cubic milliliter, PEG-IFN is stopped.

(5) PegIFN is also stopped if there is severe depression or severe adverse effects.

(6) If hemoglobin goes up (>10.0 gram per deciliter), ribavirin can be re-started from the dose of 400-600 mg per day.

(7) If neutrophil (>750 per cubic milliliter) or platelet(> 50,000 per cubic milliliter) counts go up, PEG-IFN is re-stared from a reduced dose, i.e. peginterferon alfa-2a (135μg per week) or peginterferon alfa-2b (1.0 μg per week).

(8) PegIFN is stopped if there is severe depression or severe adverse effects.

(9) If the decrease of serum HCV RNA is less than 2 log IU/ml at week 12 from base line, treatment is stopped due to a minimal change of SVR.

2.8 Statistical analysis

2.8.1 Estimation of sample size

The sample size was estimated to be 58 patients in each group on the basis of a type I error rate of 0.05 and a type II error rate of 0.20 for a primary 2-sided test with the assumption of a 40% difference in SVR rates (70% and 30% for different

rs8099917 TT or GT/GG, respectively).

2.8.2 Statistical analysis of variables

Mean and standard deviation (SD) were calculated for continuous variables. Percentage was used for categorical variables. The baseline characteristics of treatment groups were compared using the chi-square test, Fisher's exact test, or Student's t test, when appropriate. Intention-to-treat analysis for the primary efficacy end point was performed. Treatment responses were compared with use of Fisher's exact test. Univariate and Multivariable-adjusted odds ratio (OR) and 95% confidence intervals (CIs) were derived for each factor using logistic regression. All of the tests of significance were two-tailed, and a P value of less than 0.05 was considered statistically significant. Data were collected in a Microsoft Excel database (Microsoft Excel 2001; Microsoft Corporation, Seattle, WA, USA) and analyzed with Stata statistical software (version 9.2; Stata Corp, College Station, TX, USA).

Chapter 3. Results

3.1 Characteristics of the Study Patients

Of the 106 patients screened, 3 did not meet the inclusion criteria (unwillingness for treatment) and were excluded from the study. The remaining 103 eligible patients were scheduled to receive a 48-week treatment of PEG-IFN plus ribavirin (Figure 1). Seventy-five patients (73%) were HCV genotype 1 infection and twenty-eight patients(27%) were HCV genotype 2 (Figure 2). Eight-seven percent (HCV genotype 1, n=65) and 97% (HCV genotype 2, n=26) of patients had accomplished the 48-week treatment, 13% (HCV genotype 1, n=10) and 7 % (HCV genotype 2, n=2) of the patients prematurely discontinued because of less than 2-log reduction in serum HCV RNA level from baseline in week 12 of therapy. Twenty-four- week follow-up after therapy was completed in all patients.

Only HCV genotype1 infected patients were included for the following analysis. The baseline characteristics of retreatment were somewhat different from those comparing with initial treatment in HCV genotype 1 infected patients (Table 1). Patient were around 3 years older in average, increasing body weight (BMI, 0.2 kg/m^2 increase), increasing liver fibrosis score (AST to platelet ratio index, APRI, 1.3 increase) and decreased ALT and albumin level in retreatment status.

In retreatment, a majority of the patients were older than 50 years of age (77%) and male predominant (56%) (Table 1). Forty-seven percent of the patients have a BMI of 25 kg/m2 or greater, and 60% have a serum ALT level greater than 2-fold the upper limit of normal (ULN) . Most patients received peginterferon alpha 2a for combination therapy (Pegasys vs. PegIntron = 76% vs. 24%).

As for the IL-28B SNP genotype (rs8099917) in HCV genotype 1 infection in retreatment (Table 2), the TT genotype was predominant (TT vs. GT vs. GG = 72 % vs. 28% vs. 0%). In comparison with rs8099917 GT genotype, patients with TT

genotype was younger (2.4 years old younger), lighter (BMI, 0.7 kg/m^2 less), and less impaired liver function tests (ALT, 5 IU/L less). Baseline HCV RNA viral load was higher in TT genotype than GT. However, the above-mentioned parameters between TT and GT were not statistically significant.

3.2 Viral Kinetics–On-Treatment, SVR and relapse

As for on- and post-treatment viral kinetics (Figure 4), 37% of CHC genotype 1 patients could eradicate the serum HCV RNA in week 4 of combination therapy (i.e. rapid virologic response, RVR). At week 12 of treatment, 13% patients could not reduce 2 log IU/mL of serum HCV RNA (i.e. pEVR[-]); 13% achieved pEVR (i.e. pEVR[+]) and 36% attained undetectable virus (i.e. complete early virologic response, cEVR). Seventy-three percent of patients remained undetectable virus at the end of 48 weeks treatment (i.e. EOT-VR). Twenty-four weeks after treatment, 52% patient had accomplished undetectable HCV RNA, i.e. sustained virologic response (SVR). Of the 55 patients whose virus were undetectable at the end of treatment, serum HCV RNA virus appeared again in 16 of them (29%), i.e. relapse.

According to IL28B SNPs, patient with TT genotype had higher rate of RVR (P=0.0002), EOT-VR (P=0.0001) and SVR (P <0.0001) in comparison with GT genotype. Those with GT genotype could clear serum virus slower (i.e. higher ratio in pEVR or cEVR) than TT genotype. GT genotype had a higher relapse rate than TT genotype (P=0.006).

3.3 SVR and relapse rate according to on-treatment viral kinetics (week 4 and week 12), and IL28B SNPs (Figure 5 and 6)

Achieving a RVR ensured a higher EOT rate (96% vs. 59% for RVR and non-RVR, respectively. P=0.0003), higher SVR rate (86% vs. 32% for RVR and non-RVR,

respectively. *P*<0.0001) and lower relapse rate (11% vs. 46% for RVR and non-RVR, respectively. *P*=0.0034).

The TT IL28B genotype increased the proportion of patients who attained SVR (67% vs. 14 for TT and GT, respectively. *P*<0.0001). In those who achieved the key therapeutic milestone of RVR, SVR rates were independent of IL-28B SNP genotype. In contrast, in patients who did not achieve RVR, the effect of IL-28B SNP genotype was strikingly different; SVR rates were significantly higher in patients with the TT IL-28B genotype (48% for TT vs. 10% for GT; *P*=0.048); the rate of relapse was lower (35% for TT vs. 75% for GT; *P*=0.0581).

Viral reduction ability in week 12 during treatment had significant difference SVR rate in patient who did not achieve a RVR (10% for pEVR[+] vs. 52% for cEVR[+]; *P*=0.015). Seventy-one percent of patients whose HCV RNA was undetectable at the end-of-treatment (i.e. EOT-VR) attained SVR; significantly higher in TT genotype (78% for TT vs. 33% for GT; *P*=0.006).

3.4 Factors associated with RVR and SVR

3.4.1 Factors associated with RVR (Table 3 and 4)

Female sex, less body mass index, lower fasting glucose level, higher serum albumin and lower baseline HCV RNA level were associated with RVR. TT IL28B SNP was the only independent predictive factor of RVR (OR, 20; 95% CI, 2.5 – 159.8; *P*=0.005).

3.4.2 Factors associated with SVR (Table 3 and 4)

Furthermore, TT IL28B SNP (OR, 12; 95% CI, 3.12–46.14; *P* < 0.001) and RVR (OR, 12.8; 95% CI, 3.77 – 43.50; P < .001) were the strongest predictive factors of sustained virologic response in univariable logistic regression analysis. In addition,

female gender (OR, 2.94; 95% CI, 1.14–7.61; *P* = 0.026) and higher serum albumin level (OR, 3.67; 95% CI, 1.20 – 11.17; *P* = 0.022) were independent factors predictive of SVR.

3.4.3 Multivariable Models in predictors of SVR (Table 5)

Regression modeling was used to identify treatment factors that were associated independently with SVR. Data from 75 patients of CHC genotype 1 infection with a complete dataset of the covariates of interest were included in the model. We first modeled SVR considering all predictors as dichotomous variables (continuous and ordinal variables were dichotomized according to clinically relevant thresholds). Multivariable logistic regression using backward selection identified IL-28B genotype, rapid viral response (RVR), gender, age, albumin, fasting glucose and serum ALT level, APRI, BMI and baseline HCV RNA viral load as being associated with SVR. IL-28B SNP genotype had the greatest odds ratio favoring SVR in this model (TT vs. GT: odds ratio, 22.81; 95% CI, 2.84 – 183.34; *P*=0.003). Gender (female vs. male: odds ratio, 14.69; 95% CI, 1.98 – 108.88; *P*=0.009), RVR (positive vs. negative: odds ratio, 6.58; 95% CI, 1.41 – 30.77; *P*=0.017), and albumin (greater vs. less than 4.3 g/dL: odds ratio, 6.93; 95% CI, 1.24 – 38.54; *P*=0.027) were also statistically insignificant in predicting SVR.

3.5 Prediction of SVR in combination with IL28B SNPs and/or on-treatment viral kinetics

3.5.1 Predictive value of SVR by IL28B SNP, or viral kinetics (Table 6A)

The performance of the IL28B SNP genotype (TT vs. GT), week 4 viral negativity (with-RVR vs. without-RVR) or week 12 viral negativity (with vs. without) were regarded as binary predictor for SVR. The RVR had a highest positive predictive

value (PPV) for SVR than TT IL-28B genotype or week 12 viral negativity (PPV, 86 vs. 67 vs. 69% for RVR, IL28B SNP and week 12 negativity, respectively); however, IL28B genotype and week 12 viral negativity had superior negative predictive value (NPV) for SVR than RVR (NPV, 95 vs. 87 vs. 68% for week 12 negativity, IL28B SNP and RVR, respectively).

3.5.2 Predictive value of SVR by IL28B SNP and viral kinetics (Table 6B)

In combination of week 4 (i.e. RVR) or week 12 viral negativity with IL28B genotype, a higher positive predictive value of SVR achieved in SNP plus RVR (PPV, 85 vs. 76% for TT/RVR[+] and TT/week 12 negativity[+]). The negative predictive value was equally good (NPV, 90 vs. 100% for GT/RVR[-] and GT/week 12 negativity[-]).

Chapter 4. Discussions

Around half of the CHC genotype 1 relapsers attained SVR under the current SOC of combination with 48-week pegylated interferon and weight-based ribavirin in this study. In Asia-Pacific region, there was few data about the CHC retreatment. According to the western country reports, whether the CHC genotype 1 infected patients could achieve SVR in retreatment depends on the different interferon and viral kinetics. If shifted to PEG-IFN for retreating patients who were previously treated with conventional interferon (IFN) [19,50,51], SVR could be achieved in 31-32% and 13-20% for relapse and non-responder respectively. If retreating patient with PEG-IFN as in initial treatment[19,21], SVR would decrease to 23 % and 4-9 % for relapse and non-responder respectively.

Two SNPs (rs8099917 和 rs12979860), upstream of IL28B gene, were associated with SVR in CHC treatment. The distribution difference between favorable allele (rs12979860 C allele or rs8099917 T allele) and unfavorable allele (rs12979860 T allele or rs8099917 G allele) are different in black and Hispanic populations[52]. There is no difference between allele distributions in these two IL28B SNPs in Asian population. Therefore, we chose rs8099917 IL28B SNP as the indicator in this study. Proportion of favorable allele in IL28B SNP would be different according to the disease status of CHC patient. Taking rs12979860 as an example[28], favorable allele (TT, 76%) was high in proportion in comparison with unfavorable allele (GT/GG, 24%) in patients who could eradicate the circulating HCV RNA spontaneously. In CHC patients who could achieve SVR after treatment, the distribution of favorable allele would be less in comparison with spontaneous clearance (68% for TT vs. 32% for GT/GG). In treatment failure, favorable allele (TT) would be even lower(TT vs. GT/GT = 43% vs. 47%). The more difficult to clear the HCV, the lower frequency of

the favorable allele. The distribution of favorable allele (T allele) of rs8099917 IL28B SNP[52] in Asian normal population is 93%. If being chronically infected with HCV, patient would have lower T allele frequency (90%). If treatment failure (taking our study for example), T allele would be even lower (86% , n=54 for TT, n=21 for GT).

IL28B SNP is reported to have the predictive value of SVR. In treatment-naïve CHC genotype 1 patient[53], RVR could be achieved in 30 % and 6-7 % for TT and GT/GT rs8099917 respectively. SVR could be attained in 79 % and 41-44% for TT and GT/GT genotype respectively. There is no official data to clarify whether IL28B SNP would influence the on-treatment viral kinetics, SVR or relapse rate during retreatment. Our study could provide the information of IL28B SNP during retreatment. IL28B SNP distribution for rs8099917 is 72%, 28% and 0% for TT, GT and GG genotype. As for on-treatment viral kinetics, RVR could be achieved in 50 % and 5 % for TT and GT respectively (*P*=0.0002). EOT-VR could be achieved in 85 % and 43 % for TT and GT respectively (*P*=0.0001). SVR could be attained in 67 % and 14% for TT and GT respectively (*P*=0.0001). In addition, relapse rate is 22% and 67% for TT and GT respectively (*P*=0.0006). In combination with DAA and PEG-IFN plus RVB, the impact of IL28B SNP to SVR is not so significant in some unpublished studies.

Week 4 viral kinetics during treatment, i.e. RVR, is the milestone for SVR. In treatment-naïve CHC genotype 1 patient [29], RVR ensures SVR (84% vs. 41% for with vs. without RVR). If achieving RVR, CC rs12979860 IL28B genotype can attain higher SVR (CC vs. CT/TT = 85% vs. 76 – 100% respectively). If failure of achieving RVR, SVR rate would decrease (CC vs. CT/TT = 66% vs. 24- 31% respectively). Our study could provide the information about the impact of RVR to SVR. RVR is statistically significant in influence SVR (86% vs. 32% for with vs. without RVR respectively. *P*<0.0001)。Once achieving RVR, there is no difference between these

two IL28B SNPs (SVR, 85% vs. 100% for TT and GT respectively). If no RVR, unfavorable allele would influence SVR (48% vs. 10% for TT and GT respectively. *P*=0.0048).

It is the goal of many researchers earlier to predict the response during treatment. If patient is prone to eradicate the serum virus, we should encourage them to complete the whole course of therapy despite the discomfort accompanied with PEG-IFN or RBV. If they have minimal possibility for clearance, we might consider stopping or changing the medical regimen. Therefore we use the combination of IL28B SNP and week 4 viral negativity (i.e. RVR) for determinant of SVR. In our study, the SVR rate 85% (positive predictive value, PPV=85%) if there are favorable allele (TT IL28B genotype) with RVR. SVR will be only 10% if there is GT IL28B genotype without achievement of RVR (negative predictive value，NPV= 90%)。If we consider later until week 12, the preceding markers are not inferior to combination of week 12 viral negativity and IL28B SNP (SVR, TT with week 12 viral negativity vs. GT without achievement of week 12 viral negativity = 76 vs. 0 %)。Combination of IL28B SNP with week 4 virologic response (RVR) seems to the rapid terminative marker for stopping or changing the therapy. If direct antiviral agent (DAA) is not feasible, we can consider terminating the therapy. Not only can we decrease the physical and psychological discomfort induced by the treatment, but also decrease the budget burden. If DAA is available, we can combine multiple drugs to increase the opportunity to eradicate HCV.

Chapter 5. Perspectives

The number of genotype 2 patients is insufficient for statistically analysis. We could not conclude whether there was any predictive value of IL28B SNP or on-treatment virologic kinetics. We need multi-center study or a longer time to collect adequate cases for analysis.

In addition, it is not homogenous in our study group, that is the use of different PEG-IFN or conventional INF; besides, clinical data in the initial treatment is not complete, especially the viral kinetics. In the future, we can make comparison between the effect of initial virologic response (RVR or EVR) and retreatment response (RVR, EVR and SVR). There is lacking data of the liver biopsy in the retreatment group and it is impossible for analysis between liver fibrosis and SVR. The predictive value of on-treatment liver function normalization for SVR is ongoing. Besides, we can analyze the core gene polymorphism of HCV RNA of initial and retreated status to see if there was any difference between virologic responses.

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第八章　圖表

圖 1.本試驗流程圖

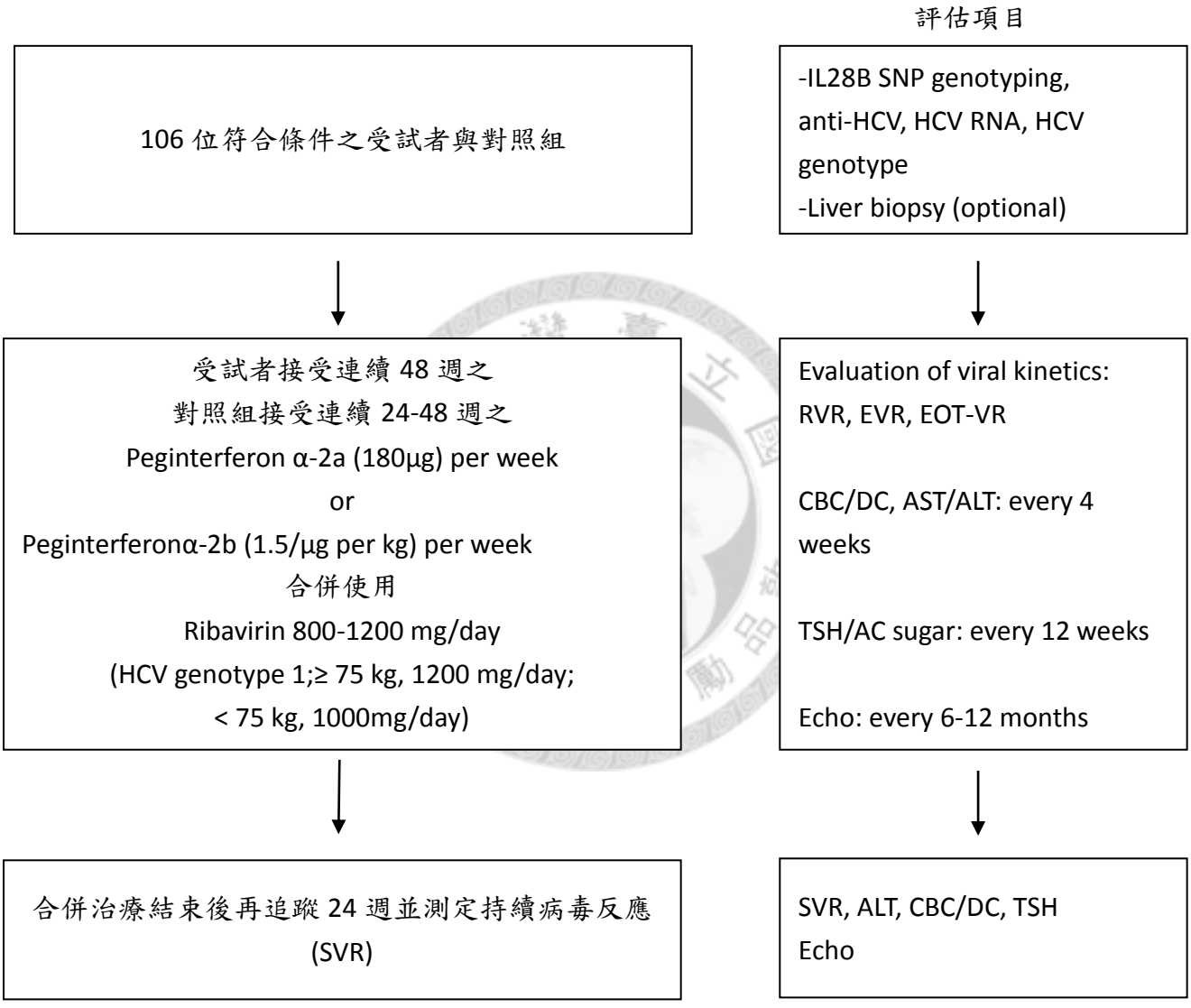
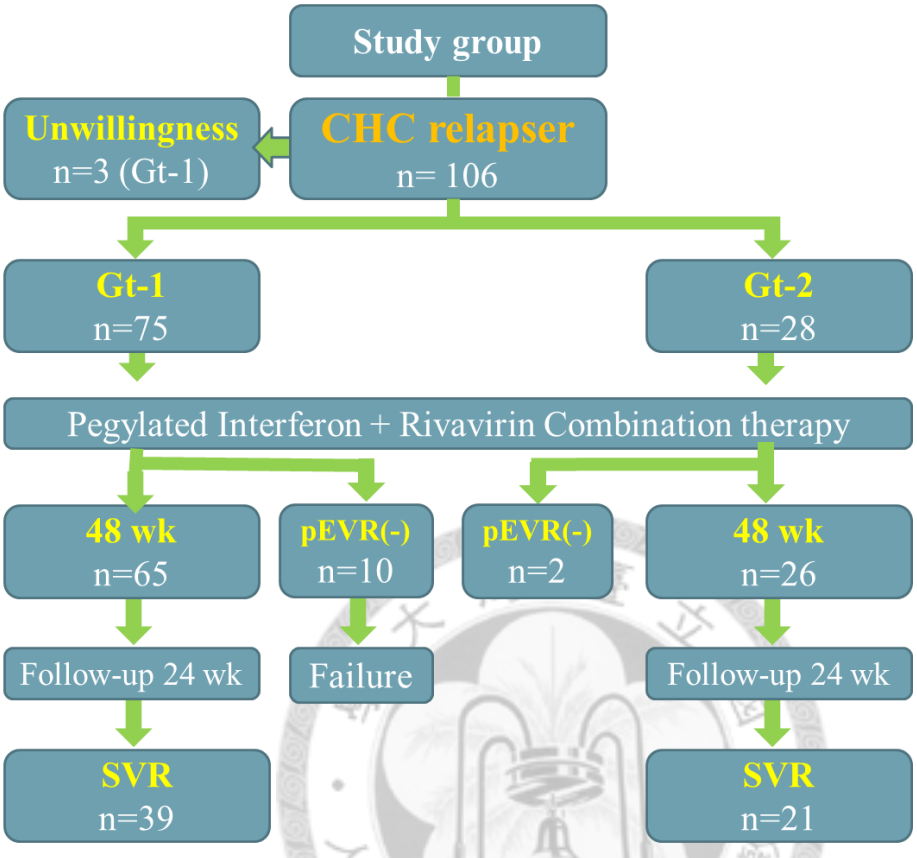


圖 2. 實驗設計 (Study design)



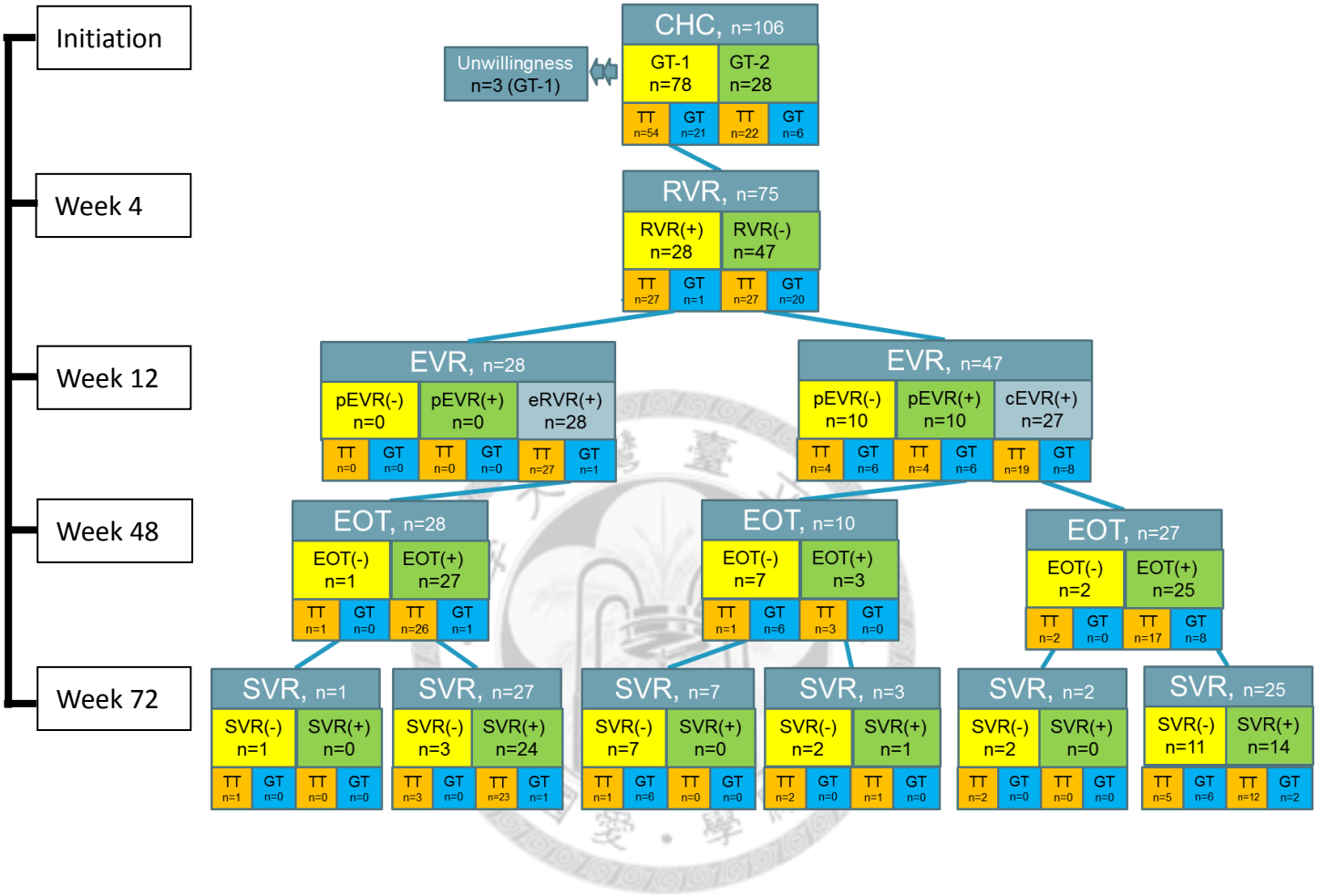
說明:

共收錄 106 位患者，其中 3 人不願治療。共有 75 位 HCV genotype 1 與 28 位 HCV genotype 2 患者進行治療，最後僅納入 HCV Gt-1 患者進行統計分析。

英文縮寫:

CHC, chronic hepatitis C viral infection; Gt-1, HCV genotype 1; Gt-2, HCV genotype 2; pEVR(-), without partial early virologic response, and is regarded as treatment failure; SVR, sustained virologic response.

圖 3. 第一基因型慢性 C 型肝炎患者之治療中及治療後的病毒動力學變化與 IL28B SNP 分佈之流程圖 (Flow chart of on-treatment and post-treatment viral kinetics and distribution of IL28B SNP of CHC genotype 1 patients)



說明:

1. 共收錄 106 位患者，其中 3 人不願治療。共有 75 位 HCV genotype 1 與 28 位 HCV genotype 2 患者進行治療，最後僅納入 HCV Gt-1 患者進行統計分析。

2. IL28B SNPs: IL28B single nucleotide polymorphisms (以 rs8099917 為例)，T 為 favorable allele，G 為 unfavorable allele。本案僅有 TT 與 GT 二種分型，而無 GG 型，故省略不以列出。

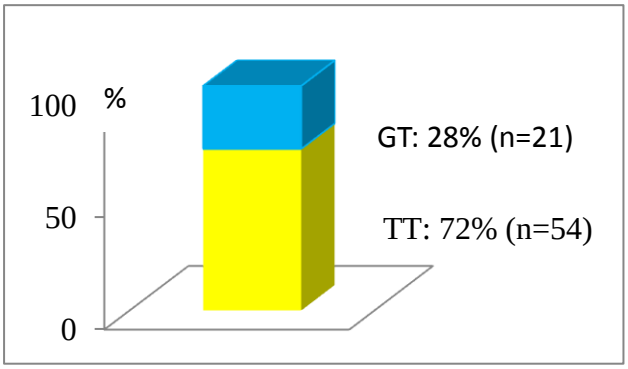
英文縮寫:

CHC, chronic hepatitis C viral infection; Gt-1, HCV genotype 1; Gt-2, HCV genotype 2; RVR, rapid virologic response; EVR, early virologic response; pEVR(+), with

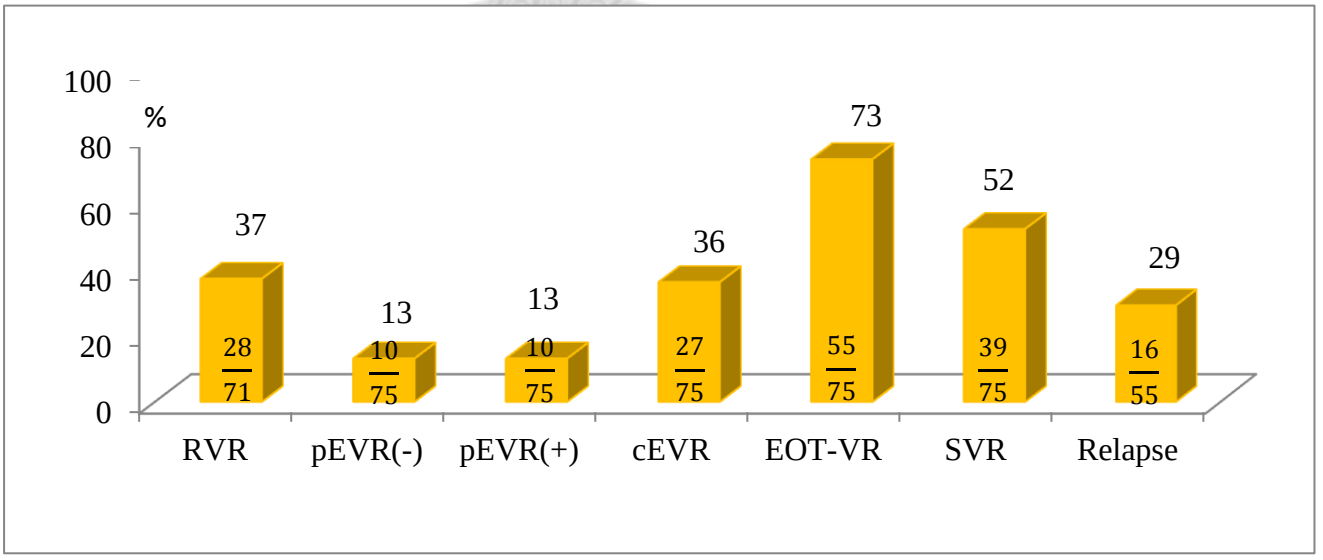
partial early virologic response; pEVR(-), without partial early virologic response, and is regarded as treatment failure; cEVR, complete virologic response; EOT, end-of-treatment virologic response; SVR, sustained viral response.

圖 4. 第一基因型之慢性 C 型肝炎患者的治療中病毒動力學變化，依 IL28B SNP 而論 (On-treatment viral kinetics of CHC Gt-1 according to different IL28B SNPs)

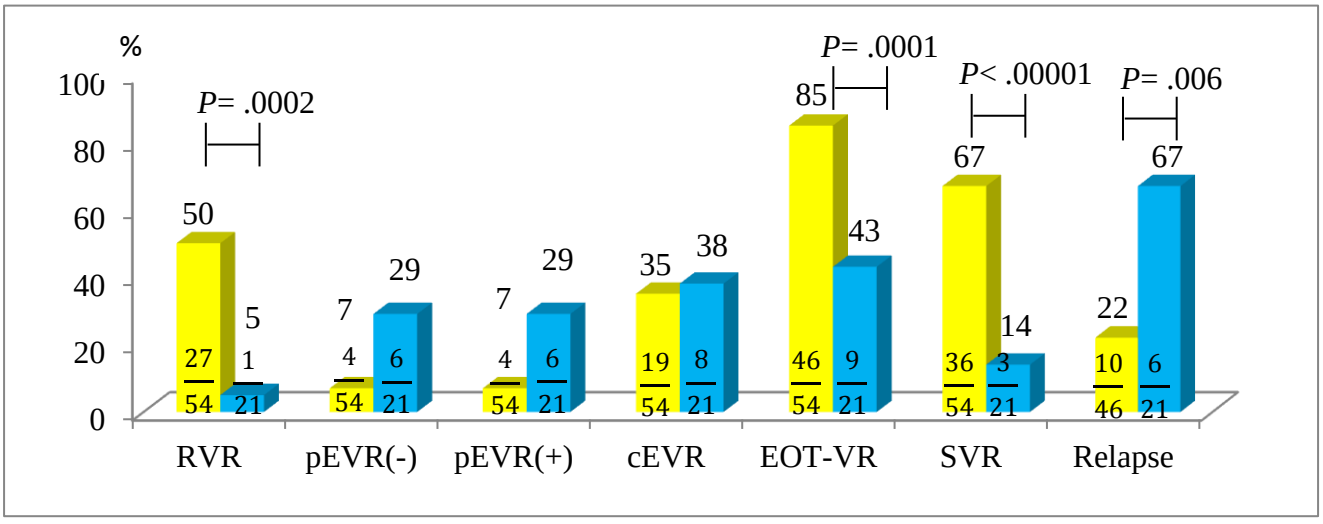
(A)



(B)



(C)



說明:

(A)基因第一型的慢性 C 型肝炎患者的 IL28B SNPs 比例。

(B)治療中與治療 24 週後以及(C)依 IL28B SNPs 的病毒動力學變化(黃色柱為 TT，藍色柱為 GT)。

+ IL28B SNPs: IL28B single nucleotide polymorphisms (以 rs8099917 為例)，T 為 favorable allele，G 為 unfavorable allele。本案僅有 TT 與 GT 二種分型，而無 GG 型，故省略不以列出。

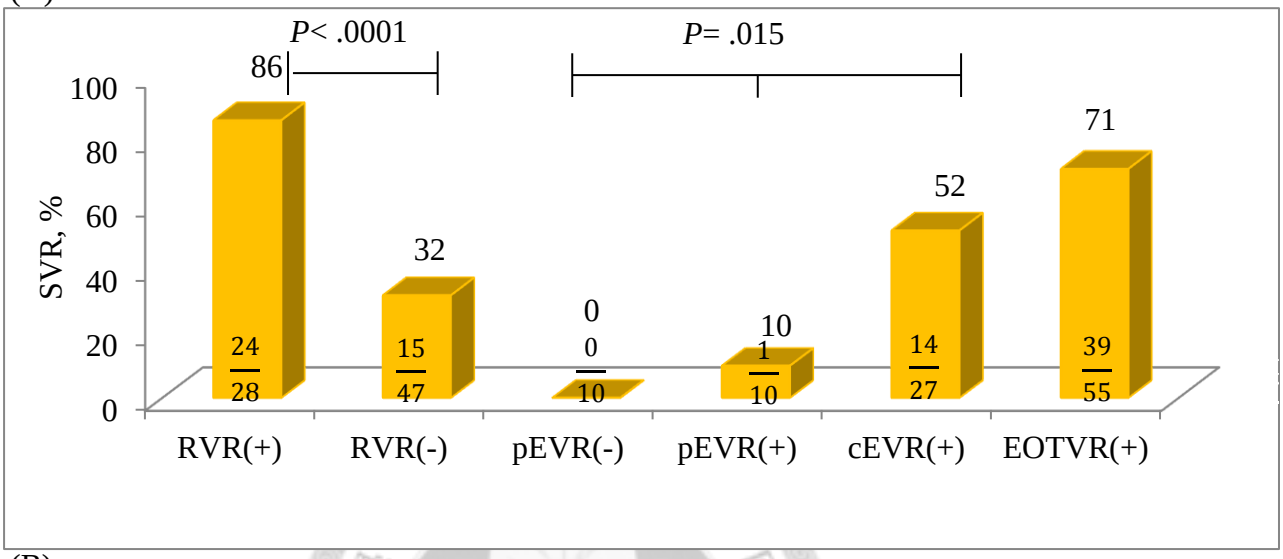
**P* value 是由 student *t* test 統計分析法而得。

英文縮寫:

RVR, rapid virologic response; pEVR(-), without partial early virologic response; pEVR(+), with partial early virologic response; cEVR, complete early virologic response; EOT-VR, end-of-treatment virologic response; SVR, sustained virologic response。

圖 5. 第一基因型之慢性 C 型肝炎患者的持續病毒反應，依治療中病毒動力學變化及 IL28B SNP 而論(Sustained virologic response according to on-treatment viral kinetics and IL28B SNPs of CHC Gt-1)

(A)



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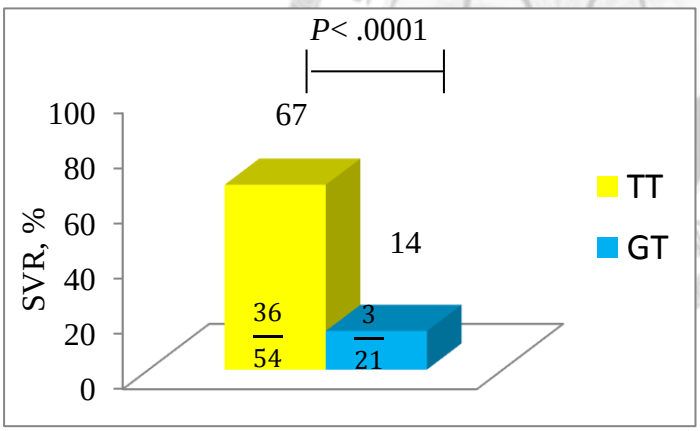
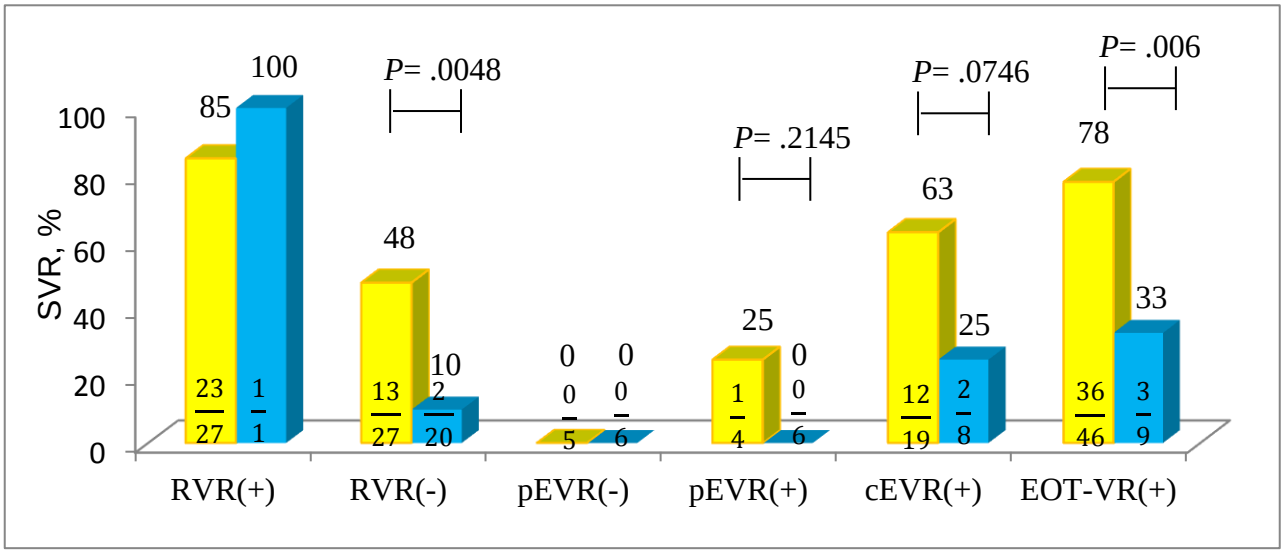


(C)



說明:

(A)Sustained virologic response according to viral kinetics。

(B) Sustained virologic response according to IL28B SNPs。

(C) Sustained virologic response according to viral kinetics and IL28B SNPs。

+ IL28B SNPs: IL28B single nucleotide polymorphisms (以 rs8099917 為例)，T 為 favorable allele，G 為 unfavorable allele。本案僅有 TT 與 GT 二種分型，而無 GG 型，故省略不以列出。黃色柱為 TT，藍色柱為 GT。

**P* value 是由適當之 student *t* test 或 logistic regression 統計分析法而得。

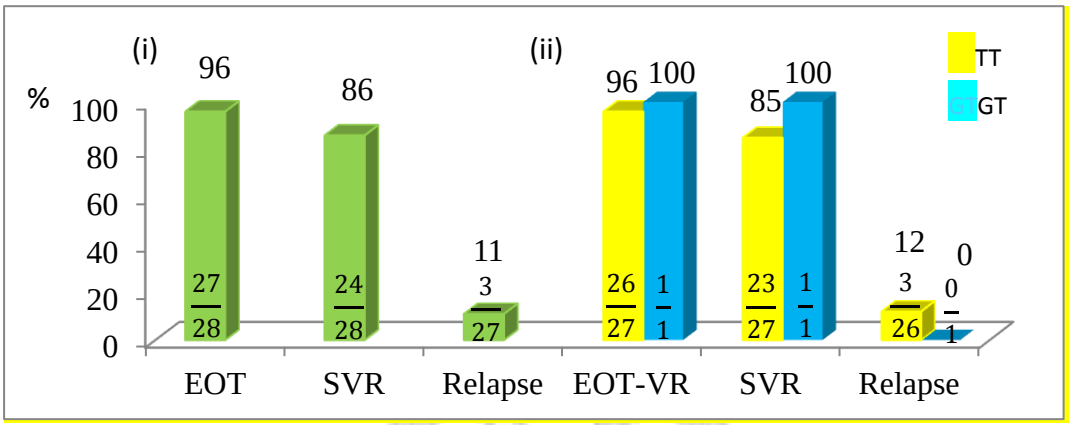
英文縮寫:

RVR(+), with rapid virologic response; RVR(-), without virologic response; pEVR(-), without partial early virologic response; pEVR(+), with partial early virologic response; cEVR, complete early virologic response; EOT-VR(+), with end-of-treatment virologic response; SVR, sustained virologic response。

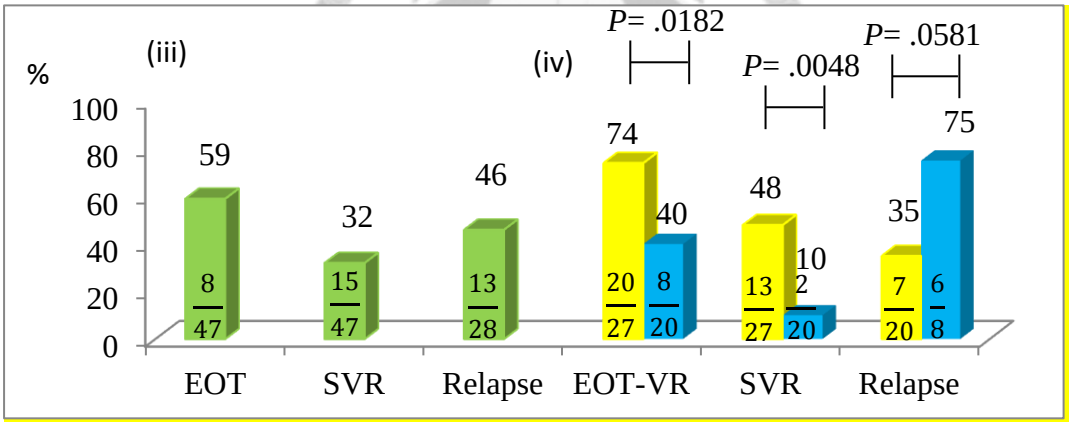
圖 6. 快速病毒學反應以及 IL28B SNP 與治療中及治療後動力學變化之關係

(The relationship of RVR and IL28B SNP with on-treatment and post-treatment viral kinetics)

(A) with rapid virologic response



(B) without rapid virologic response



說明:

(A)有達成 RVR 的患者，治療與追踪過程中的病毒動力學變化(i)及依 IL28B SNPs(ii)之比較。

(B)未達成 RVR 的患者，治療與追踪過程中的病毒動力學變化(iii)及依 IL28B SNPs(iv)之比較。

+ IL28B SNPs: IL28B single nucleotide polymorphisms (以 rs8099917 為例)，T 為 favorable allele，G 為 unfavorable allele。本案僅有 TT 與 GT 二種分型，而無 GG 型，故省略不以列出。TT 為黃色柱，GT 為藍色柱。

*P value 是由 student t test 統計分析法而得。

英文縮寫:

RVR, rapid virologic response; EOT-VR, end-of-treatment virologic response; SVR, sustained virologic response。

表 1. 75 位第一基因型慢性 C 型肝炎患者之初次/再次治療的特徵(Features of 75 HCV genotype 1 infected patients at initial treatment and at retreatment)

臨床特徵, n=75	**初次治療**	**再次治療**
Male gender*, n (%)	42 (56)	42 (56)
Age, year	55.3 (±10.5)	58 (±9.9)
BMI, kg/m^2	24.7 (±2.8)	24.9 (±3.1)
ALT, IU/L	135 (±82)	117 (±80)
WBC, /uL	5512 (±1673)	5330 (±1703)
Albumin, g/dL	4.5 (±0.3)	4.3 (±0.3)
APRI score	1.54 (±1.19)	2.29 (±2.07)
Ishak activity score	7.4 (±3.2), n=40	NA
Ishack fibrosis score	3.4 (±1.3), n=40	NA
Baseline viral load, log_{10} IU/mL	6.09 (±1.14), n=17	6.02 (±1.02)
RVR*, n(%)	1 (14), n=7	28 (37)
cEVR*, n(%)	8 (100), n=8	27 (57)

說明:

1.初次治療: 24-week pegylated interferon plus ribavirin

2.所有數值(除標*之外)均以算數平均值(mean)±標準差(standard deviation)表示。

3.APRI: AST (ULN) / platelet ($x10^3$) x 100

英文縮寫:

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood count; APRI, AST to platelet ratio index; NA, not available; RVR, rapid viral response; cEVR, complete early virologic response

表 2. 75 位第一基因型慢性 C 型肝炎患者的臨床特徵，依 IL28B SNP 而論(Features of 75 CHC genotype 1 patients according to different IL28B SNPs)

臨床特徵	**Gt-1**, n=75		
	rs8099917, TT n=54 (72%)	**rs8099917, GT** n=21 (28%)	***P* value**
Male*, n (%)	31 (57)	11 (52)	0.694
Age, year	57.8 (±9.5)	60.2 (±11.1)	0.3642
If age >60*, n(%)	20 (37)	10 (48)	0.1025
BMI, kg/m^2	24.8 (±2.9)	25.5 (±3.5)	0.4020
Baseline viral load, log_{10} IU/mL	6.10 (±1.01)	5.81 (±1.03)	0.2591
ALT, IU/L	116 (±88)	121 (±57)	0.8053
Albumin, g/dL	4.4 (±0.3)	4.3 (±0.3)	0.8989
WBC, /uL	5216 (±1477)	5630 (±2207)	0.3703
Hemoglobin, g/dL	14.3 (±1.2)	14.7 (±1.1)	0.1928
Platelet, 10^3/uL	152 (±58)	159 (±54)	0.6014
Fasting blood glucose, mg/dL	104 (±30)	105 (±24)	0.8925
APRI score	2.29 (±2.22)	2.26 (±1.63)	0.9640

說明:

1. 所有數值(除標示*之外)以算數平均值(mean)±標準差(standard deviation)來表示。

2. IL28B SNPs: IL28B single nucleotide polymorphisms (以 rs8099917 為例)，T 為 favorable allele，G 為 unfavorable allele。本案僅有 TT 與 GT 二種分型，而無 GG 型，故省略不以列出。

3. APRI: AST (ULN) / platelet ($x10^3$) x 100

4. *P* value 是由 student *t* test 統計分析法而得。

英文縮寫:

BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood count; APRI, AST to platelet ratio index

表 3. 影響 RVR 與 SVR 的因素(Factors associated with RVR and SVR in HCV Gt-1)

臨床特徵	RVR			SVR		
	RVR(+) n=28	**RVR(-)** n=43	***P* value**	**SVR(+)** n=36	**SVR(-)** n=39	***P* value**
Male*, n (%)	13 (46)	29 (62)	0.200	17 (44)	25 (69)	0.026
Age, year	58.3 (±9.9)	58.6 (±10.1)	0.889	57.9 (±8.7)	59.1 (±11.3)	0.614
BMI, kg/m^2	24.2 (±2.8)	25.5 (±3.2)	0.082	24.6 (±3.2)	25.4 (±3.0)	0.287
Baseline viral load, log_{10} IU/mL	5.77 (±1.08)	6.17 (±0.96)	0.099	5.95 (±1.12)	6.10 (±0.90)	0.517
ALT, IU/L	119 (±102)	115 (±66)	0.823	123 (±92)	111 (±67)	0.522
WBC, /uL	5239 (±1532)	5389 (±1819)	0.724	5193 (±1508)	5480 (±1905)	0.488
Fasting blood glucose, mg/dL	97 (±15)	109 (±33)	0.150	99 (±19)	109 (±35)	0.195
Albumin, g/dL	4.4 (±0.3)	4.3 (±0.3)	0.077	4.4 (±0.26)	4.3 (±0.39)	0.129
APRI score	2.30 (±2.72)	2.27 (±1.59)	0.957	2.45 (±2.47)	2.10 (±1.52)	0.460

說明:

1. 所有數值(除標示*外)以算數平均值(mean)±標準差(standard deviation)來表示。

2. APRI: AST (ULN) / platelet ($x10^3$) x 100

英文縮寫:

RVR, rapid virologic response; SVR, sustained virologic response; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood count; APRI, AST to platelet ratio index

表 4. 邏輯迴歸法分析影響 RVR 及 SVR 的因素 (Logistic regression analysis of factors associated with RVR and an SVR)

臨床特徵	RVR			SVR		
	Odds Ratio	**95% CI**	***P* value**	**Odds Ratio**	**95% CI**	***P* value**
Gender						
Female	1	0.21-1.39	0.200	1	0.13 - 0.88	0.026
Male	0.54			0.34		
Age , year						
< 60	1	0.37-2.48	0.922	1	0.34 - 2.21	0.777
≥ 60	0.95			0.88		
BMI (kg/m2)						
< 25	1	0.28 -1.84	0.088	1	0.43 - 2.63	0.897
≥ 25	0.72			1.06		
ALT, IU/L						
< 2ULN	1	0.34 - 2.37	0.836	1	0.48 - 3.11	0.671
≥ 2ULN	0.90			1.22		
Albumin, g/dL						
<4.3	1	0.79 - 7.44	0.121	1	1.20 - 11.17	0.022
≥4.3	2.43			3.67		
Glucose, mg/dL						
<126	1	0.17 - 1.47	0.207	1	0.59 -1.91	0.221
≥126	0.50			0.34		
APRI score						
<1	1	0.13-1.27	0.124	1	0.29 – 2.40	0.729
≥1	0.41			0.83		
Viral load, IU/mL						
< 800,000	1	0.28 - 2.06	0.595	1	0.33 - 2.33	0.797
≥ 800,000	0.76			0.88		
RVR						
negative	-	-	-	1	3.12 - 46.14	<0.001
positive				12.8		
IL28B SNP						
GT	1	2.5- 159.8	0.005	1	3.12 - 46.14	<0.001
TT	20			12		

說明:

1. 以單變項線性迴歸方式分析，以 RVR 或 SVR 為依變項。

2. IL28B SNPs: IL28B single nucleotide polymorphisms (以 rs8099917 為例)，T 為 favorable allele，G 為 unfavorable allele。本案僅有 TT 與 GT 二種分型，而無 GG 型，故省略不以列出。

3. APRI: AST (ULN) / platelet ($x10^3$) x 100

英文縮寫:

RVR, rapid virologic response; SVR, sustained virologic response; 95% CI, 95% confidence interval; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Glucose, fasting blood glucose; APRI, AST to platelet ratio index; viral load, baseline viral load; SNP, single nucleotide polymorphism

表 5. 多變項邏輯迴歸法分析影響 SVR 的因素 (MultiVariable Logistic regression analysis of factors associated with SVR in CHC Gt-1 patients)

臨床特徵	Odds Ratio	95% CI	*P* value
RVR			
Positive vs. negative	6.58	1.41 – 30.77	0.017
IL28B SNP			
TT vs. GT	22.81	2.84 – 183.34	0.003
Baseline viral load			
≥ vs. < $8x10^5$ IU/mL	1.05	0.91 – 5.94	0.956
Gender			
Female vs. Male	14.69	1.98 – 108.88	0.009
Age			
< vs. ≥ 60 years old	1.76	0.35 – 8.87	0.492
ALT			
≥ vs. < 2xULN	6.08	0.57 – 64.71	0.135
Albumin			
≥ vs. < 2 g/dL	6.93	1.24 -38.54	0.027
Fasting blood Glucose			
≥ vs. < 126 g/dL	3.93	0.66 – 23.49	0.133
APRI			
≥ vs. < 2	1.09	0.69 – 1.69	0.711
BMI			
≥ vs. < 25 kg/m^2	1.82	0.42 – 7.84	0.422

說明:

1. 以多變項線性迴歸方式分析，以 SVR 為依變項(dependent variable)，以 RVR, IL28B SNP, baseline viral load, gender, age, ALT, Albumin, fasting blood glucose,

APRI 及 BMI 為獨立變項(independent variables)。

2. IL28B SNPs: IL28B single nucleotide polymorphisms (以 rs8099917 為例)，T 為 favorable allele，G 為 unfavorable allele。本案僅有 TT 與 GT 二種分型，而無 GG 型，故省略不以列出。

3. APRI: AST (ULN) / platelet ($x10^3$) x 100。

英文縮寫:

RVR, rapid virologic response; SVR, sustained virologic response; 95% CI, 95% confidence interval; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Glucose, fasting blood glucose; APRI, AST to platelet ratio index; viral load, baseline viral load; SNP, single nucleotide polymorphism

表 6. 依 IL28B SNP 及病毒動力學變化以預測 SVR (Prediction of SVR by IL28B SNP and/or viral kinetics)

(A)

Parameter, n		**SVR n (%)**	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**
SNP	TT, n=54	36 (67)	92	50	67	86
	GT, n=21	3 (14)				
Viral negativity at week 4 (RVR)	RVR(+), n=28	24 (86)	62	89	86	68
	RVR(-), n=47	15 (32)				
Viral negativity at week 12	Yes, n=55	38 (69)	97	53	69	95
	No, n=20	1 (5)				

(B)

Parameter, n		**SVR n (%)**	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**
SNP + Viral negativity at week 4 (RVR)	TT + RVR(+) n=27	23 (85)	92	82	85	90
	GT + RVR(-), n=20	2 (10)				
SNP + Viral negativity at week 12	TT + no virus at week 12, n=46	35 (76)	100	52	76	100
	GT + detectable virus at week12, n=12	0 (0)				

說明:

(A)依 IL28B、或 HCV RNA viral negativity 的時間(第 4 週或第 12 週)，評估持續病毒學反應之可能性。

(B)合併 IL28B 與 HCV RNA viral negativity 的時間以評估持續病毒學反應之可能性。

+ IL28B SNPs: IL28B single nucleotide polymorphisms (以 rs8099917 為例)，T 為 favorable allele，G 為 unfavorable allele。本案僅有 TT 與 GT 二種分型，而無 GG 型，故省略不以列出。

英文縮寫:

RVR, rapid virologic response; cEVR, complete early virologic response; EOT, end-of-treatment response; SVR, sustained virologic response; PPV, positive predictive value; NPV, negative predictive value。