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Treating Chronic Hepatitis C with Pegylated Interferon and Ribavirin Between the Incarcerated and the Community Patients

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Abstract

To investigate the use of pegylated interferon 2a plus ribavirin (Peg-Riba) for treating the incarcerated HCV patients compared to HCV patients from community. A retrospective study was conducted to compare the Peg-Riba therapy between the community and the incarcerated HCV patients. Cirrhosis, hepatoma, experienced therapy, HIV/HBV and complicated comobidity were excluded. The SVR rate was the primary outcome measure and the demographic parameters, biochemistry, HCV genotype, adverse effects, withdrawal rate and lost-to-follow-up rate were measured as the secondary outcomes. A total of 215 male HCV patients were enrolled, of which 103 were incarcerated patients and 112 were from the community. The incarcerated patients were younger (39.3 ± 5.9 vs 49.3 ±12.3 years), had less genotype 1b (17% vs 54%), higher viral load (5.98 ± 0.73 vs 5.35 ± 1.17 Log_{10} IU/mL), and higher Alanine aminotransferase (ALT) (97 ± 50 vs 127±79 IU/L). While on treatment, the incarcerated HCV patients experienced more skin side effects and lower RVR rate (70.9% vs 75.9%, p=0.001), however no difference in the withdrawal rate due to side effects was observed. After treatment, higher SVR was observered in the incarcerated patients regardless of per-protocol (95.2% vs 73.7%, p=0.000) and intention-to-treat analysis (82.5% vs 62.5%, p=0.001). The lost-to-follow-up rate due to prison transfer and early release in the incarcerated patients was not rare. Peg-Riba therapy in the incarcerated HCV patients achieved excellent SVR about 95.2%. It should be a golden time to eradicate HCV during the inmates staying in the facility. (J Intern Med Taiwan 2017; 28: 33-40)

Key Words: Chronic hepatitis C, Correctional facility, Incarcerated, Pegylated interferon

Introduction

Hepatitis C virus (HCV) infection is a world-wide problem which can lead to development of severe end stage liver disease[1]. The prevalence of HCV infection is around 4.4% in Taiwan general population, and up to 58% in some hyper endemic areas in south Taiwan[2,3]. Although interferon-free direct anti-viral agents (DAA) are currently the mainline treatment option for HCV infection in the west, pegylated interferon plus ribavirin (Peg-Riba) is still considered the standard of care for treating chronic hepatitis C in the Asia-Pacific region because of it's favorable clinical response in the Asians and the economic aspect. Notably, in Taiwan, the risk of cirrhosis and hepatocellular carcinoma

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(HCC) was declined when sustained viral eradication was achieved[4,5]. The sustained viral response (SVR) of Peg-Rib therapy reached 76-94% among community adults in Taiwan[6,7,8,9], therefore, majority of known chronic HCV infected adults in community could be cured since the standard-of-care Peg-Riba regimen was reimbursed by the Bureau of National Health Insurance (BNHI) from 2006 onward.

The seroprevalence of hepatitis C infection among correctional departments in USA is reported between 9.6 to 41% and HCV-related mortality has been increasing by a rate of 21% per year[10,11]. Recent series case studies on treating incarcerated chronic hepatitis C patients with Peg-Riba in the west contries reported the overall SVR around 28-52% (18-43% for genotype 1, 50-68% for genotype 2/3), discontinuation due to adverse effect 13-36%, and non-response rate 7-30%[12-15]. Rice et al. published an ambulatory clinic care experience of treating incarcerated patients with Peg-Riba and reported a comparable SVR in incarcerated and community patients[16]. In Taiwan, the anti-HCV seroprevalence in the jailed injection drug user (IDU) was reported to be around 89%[17,18,19]. But these patients did not receive the standard of care treatment due to lack of healthcare system inside the correctional facility, lack of insurance reimbursement and the shortage of the government budget. Therefore, there is no any data on the treatment of the jailed chronic hepatitis C patients in Taiwan. As the 2nd generation NHI policy started covering the healthcare expenses of the correctional systems from Jan 2013 onward, the hospital backed-up care could enter the correctional facilities to provide the treatment to the incarcerated patients with chronic hepatitis C. Therefore, the objective of this study was to investigate the clinical outcome of Peg-Riba in treating the incarcerated HCV patients by a hospital backed-up clinic in a correctional institution, compared with the community HCV patients in south Taiwan.

Materials and methods

A total of 535 Peg-Riba dual therapies (pegylated interferon 2a or 2b plus Ribavirain 15 mg/kg/day) for the treatment of chronic hepatitis C were registered under the NHI reimbursement scheme in Pingtung Christian hospital from 2006 to 2015. The Peg-Riba therapy was guided by the Taiwan NHI guideline---24 weeks if rapid viral response (RVR) achieved and 48 weeks if failed RVR but early viral response (EVR---Negative RNA or decrease of > 2 Log10 at weeks 12) achieved regardless of genotype. This was a retrospective case control study to compare the chronic hepatitis C patients treated with Peg-Riba between the community and the incarcerated patients. The exclusion criteria included cirrhosis, HCC, complicated comorbidity, prior interferon therapy, Neutrophil < 1500 cells/μ, Hemoglobin < 11 g/dL, Platelets counts < 90000 cells/μ, creatinine >1.5 mg/dL, known immune disorder, known psychiatric disorder, positive HBs Ag, positive anti-HIV, current alcoholism history and length of penalty < 18 months for the inmates.

The SVR rate was the primary outcome and the demographic data, biochemistry, HCV genotype distribution, adverse effects, lost-to-follow-up and withdrawal rate were measured as the secondary outcomes. RVR was defined as negative HCV RNA at week 4 of therapy. EVR was defined as negative HCV RNA or at least 2 $-\log_{10}$ decrease in the serum HCV RNA level from baseline at week 12 of treatment. The end-of-treatment virologic response (ETVR) was defined as negative HCV RNA at the end of treatment. SVR was defined as negative HCV RNA 6 months after the end of treatment.

Statistics. All statistical analyses were carried out using SPSS (version 18). The results were expressed as the mean (standard deviation) for quantitative variables and frequency for categorical variables. Normally distributed quantitative variables were analyzed by Student's t-test. The

categorial variables were analyzed using the chi-squared test. The primary results were analyzed on an intention-to-treat and per-protocol basis. Multivariate analysis was performed using binary logistic regression $p < 0.05$ was considered to indicate statistical significance.

Results

A hospital backed-up clinic in the correctional facility was set up to manage the HCV infected prisoners after the NHI reimbursed the health care for the inmates since 2013. All the medications were adminstered under observation. It is easy to deliver interferon injection and oral medication to the prisoners, but erythropoitein or blood transfusion was not available inside the facility. One-hundred and three incarcerated HCV patients were enrolled for the analysis. They were all male, 39.3 ± 5.9 years old, all IDU, and the genotype (G) distribution was as follow: G1a (31%), G1b (17%), G2 (12%), G3 (3%) and G6 (31.3%). On the other hand, 112 HCV male patients from the community were enrolled for the analysis because all of them received same pegylated interferon 2a (Pegasys). The patients in the incarcerated group were younger (39.3 ± 5.9 vs 49.3 ±12.3 years), had lesser genotype 1b (17% vs 54%) , higher HCV viral load (5.98 ± 0.73 vs 5.35 ± 1.17 Log_{10} IU/ML), and higher ALT (97 ± 50 vs 127±79 IU/L) elevation compared to HCV patients in the community group (Table 1).

Table 1. Characteristics of the incarcerated and community HCV patients

	Incarcerated (N=103)	Community (N=112)	P value
Male (%)	100	100	-------
Age (years)	39.3 ± 5.9	49.3 ± 12.3	0.000
BW (Kg)	69.8 ± 10.1	70.3 ± 9.8	0.65
IDU (%)	100 %	---	0.000
Genotype 1b (%)	17%	54%	0.000
6 (%)	31.3 %	---	---
Log HCV RNA IU/mL	5.98 ± 0.73	5.35 ± 1.17	0.000
WBC (1000/u)	7.05 ± 1.97	7.03 ± 2.13	0.96
Hb (g/dL)	16.0 ± 6.11	15.2 ± 1.5	0.18
Platelet (1000/u)	215 ± 58	191 ± 63	0.007
ALT (IU/L)	97 ± 50	127 ± 79	0.001
Creatinine (mg/dL)	0.92± 0.13	0.97± 0.16	0.019
On-treatment			
Skin rash/itching	56/103	5/112	0.000
Ribavirin dose (tab)	5.1 ± 0.9	5.1 ± 0.8	0.68
RVR	73 (70.9%)	85 (75.9%)	0.000
Withdrawal			
-Side effect	7 (6.8%)	7 (6.5%)	0.87
-transfer/release	3	-	
Post-Treatment			
Missing follow-up	8 (7.8%)	10 (8.9%)	0.75
SVR			
Intention-to-treat	82.5% (85/103)	62.5% (70/112)	0.001
Per-protocol	95.2% (80/84)	73.7% (70/95)	0.000

Out of the 112 community HCV patients, the RVR rate was 75.9%, 7 patients stopped the treatment due to intolerable side effects of insomnia and flu-like symptomes, with remaining 105 patients completing the treatment. But only 95 patients finished the follow up as 10 patients were lost to follow-up before viral load check at 6 months after treatment (Figure 1). SVR was achieved in 70 patients, so the per-protocol SVR and intention-to-treat SVR were 73.7% and 62.5% respectively. Amongst the 103 incarcerated HCV patients, the most commonly experienced side effects of Peg-Riba therapy was skin rash associated with skin itching which required anti-histamine medication but did not cause withdrawal. The RVR rate was 70.9%, eleven patients stopped treatment including 4 flu-like side effects, 1 insomnia, 1 hyperthyroidism, 1 flared psoriasis, 2 early releases and 2 prison transfer. In the remaining 92 cases of completed treatment, 8 patients lost to follow up (5 due to prison transfer and 3 due to early release) (Figure 2). SVR was achieved in 80 patients and non-SVR was achieved in 4 patients although among whom 3 patients gained RVR. The per-protocol and intention-to-treat SVR was 95.2% and 77.7% respectively (Figure 3). Among the 7 withdrawals due to side effects, 5 patients also achieved SVR although only less than 80% dose was given.

In the total 215 Peg-Riba therapies, multivariate analysis using binary logistic regression was performed on correlated demographic factors, laboratory parameters, including age, ALT level, creatinine, viral load, RVR, genotype 1b/non-1b, and incarceration. Of these factors, only incarceration was significantly associated with SVR (p=0.001)

Discussion

The prevalence of HCV infection in the correctional facility is higher than the general population but it is difficult to treat the HCV infection because of limited budget and health care service in

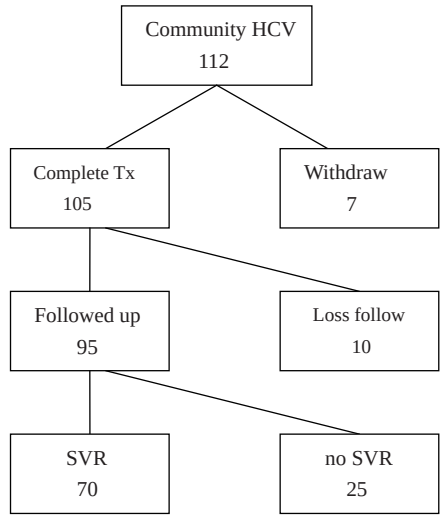


Figure 1. The outcome of the community HCV patients treated with Peg-Riba therapy.

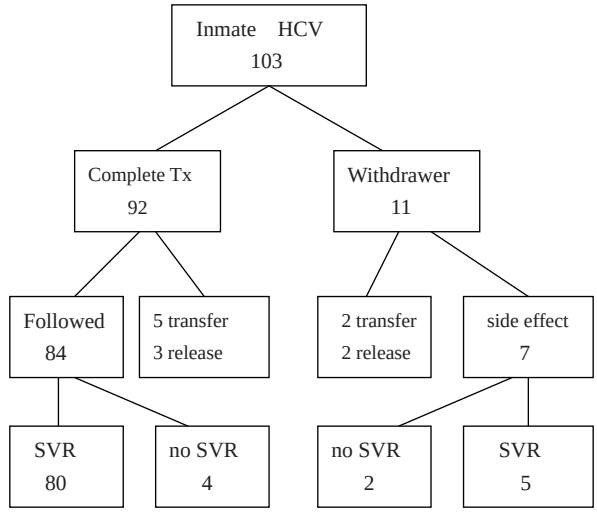
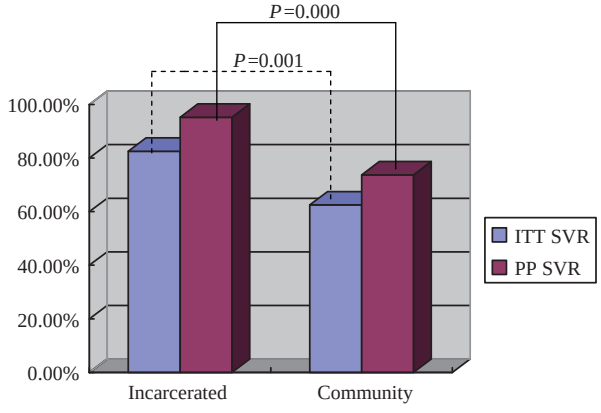


Figure 2. The outcome of the incarcerated HCV patients treated with Peg-Riba therapy.



ITT: Intention-to-treat, PP: Per-protocol

Figure 3. The SVR of Peg-Riba therapy between the incarcerated and community HCV patients.

the eastern countries even though interferon based dual therapy has been reported as a feasible and safe option to treat the incarcerated hepatitis C patients in the western countries. This study is the first case control study in Taiwan to compare the clinical outcome of dual therapy for chronic hepatitis C between incarcerated and community patients.

The results of this study indicate that higher SVR is achieved in the incarcerated patients (95.2% vs 73.7%, p=0.000), the reasonable explanation for this observation is that because of the younger age and source of infection from IDU, the inmates had shorter infection period than the community non-IDU patients whose infectious source was not definite. Secondly, during the implementation of Peg-Riba therapy, the correctional environment provides better access to health service, directly observed treatment, and control of risk behavior such as alcoholism, drug addition, etc. Lastly, the younger inmates can better tolerate the treatment-associated side effect because of less physical activity in the prison as community patients have more physical burden of working and household work. So, it can be concluded that imprisonment represents a golden opportunity to implement control and treatment of chronic hepatitis C[20,21].

Initially, we estimated that discontinuing therapy due to side effects may be higher than general population because of the possible personality disorder in these IDU inmates. However, data from out study reveals no such difference (6.8% vs 6.5%). During the initial period of treating HCV, our incarcerated patients were all voluntary for therapy and hence, no benefit was obtained from the correctional institution. They had strong motivation to receive treatment after our explanation of the treatment course and possible side effects of dual therapy. Once the treatment had started, the experience of HCV treatment was shared among the inmates, so the following inmates who came for the treatment were aware of the treatment side effects, cost, and benefits. Those who were wary of side effects never came to receive the treatment. That explains why the discontinuation rate was not higher in the incarcerated patients. In another Spanish study described, the personality disorder did not affect discontinuation and SVR for chronic HCV infection in prisoners[22].

In the routine practice of treating HCV in community, loss of contact and lack of adherence is a problem for patient's free willing. Given that the correctional facility provides a close environment, surveillance of treatment adherence and follow-up of treatment outcome should be better among the incarcerated inmates. However, our experience indicates that the discontinuation and missed follow-up due to non-medical cause was not uncommon in the incarcerated patients. Although we ensured the remaining sentence periods before treatment was started should be longer than 18 months for the inmates, the discontinuation of therapy due to early release or prison transfer was about 2.9% (3/103) and the lost to follow-up due to early release or prison transfer was 7.8% (8/103). The proportion of treatment discontinuation due to side effects, treatment-related adverse events, and personal reasons has been reported in some prisoners of Canada (21%), USA (31%), and Italian (60%)[23,14,24].

Recently, a prospective multicenter study in Spain reported the treatment discontinuation rate of 22.5% with most common cause of discontinuation being early release or prison transfer (7.9%) in imprisoned chronic hepatitis C patients whose length of penalty was at least 2 years[25]. Compared to the Spanish report, the overall treatment discontinuation in this study was less frequent 10.6% (11/103) with lower discontinuation due to early release or prison transfer (2.9% vs 7.9%) but the missing follow-up after completing treatment due to early release/ prison transfer was 7.8% in our study which was not reported in the Spanish study. In our study, the missing follow-up rate of the inmates was comparable to the community missing follow-up

rate (7.8% vs 8.9 % p=0.75). It suggests that further efforts should be made to improve the coordination between the prison settings and external center to ensure treatment or follow-up after the inmates were early released to community or transferred to others prisons.

However, limitations of this retrospective study need to be mentioned. First, all incarcerated patients received treatment in the past two years since 2013 while the community patients were treated from 2006–2015. The physicians might became more experienced in treating chronic hepatitis C and may have given more aggressive therapy to the incarcerated patients to reach the better outcome. Second, only 1b and non-1b was genotyped in the community patients due to laboratory limitation before 2011, and hence, inadequate information about subtyping was available to compare them because genotype 1b is lesser responsive to Peg-Riba therapy and it is the dominant genotype in north Taiwan, 58–73% and in south Taiwan, 48–64.3%[26-28], but genotype 6 is rare in the general population. The Peg-Riba therapy response of type 6 HCV is reported to be superior to genotype 1, even comparable to genotype 2[29,30]. But in our incarcerated patients, the genotype 1b was less frequent 17% and genotype 6 was not rare around 32%. This is one of the possible reasons why the incracerated patients had better treatment response than the community patients. The last limitation is that the body weight and the severity of liver fibrosis could not be discussed due to lack of record.

In conclusion, treating incarcerated chronic hepatitis C patients by a hospital backed-up clinic is as safe as treating community patients and it achieved excellent SVR rate. The good results may be due to the younger age and good adherence in the incarcerated patients. The side effects from therapy could be managed by clinics inside the correctional facility. However, interruption in the treatment or follow-up due to early release or prison transfer is a more important issue when implementing HCV treatment in the correctional facilities. Therefore, this model of hospital backed-up clinic care could be extended to all the correctional institutions to eradicate HCV as early as possible but the coordinated cares between the correctional facilities, or between facilities and the external community centers is very important to eliminate the treatment discontinuation and missing follow-up. At last and the most importantly, strategies to prevent reinfection of HCV in this special population should be emphasized in additional to active eradication of hepatitis C virus.

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長效干擾素併雷巴威靈治療受刑人慢性C型肝炎與社區病人之比較

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摘 要

自從 2013 實施二代健保以來，罹患慢性 C 型肝炎之受刑人得以接受治療。本研究是國內首次比較長效干擾素併雷巴威靈治療受刑人與社區病人之臨床結果。自 2005-2015 本院登錄慢性C肝治療計畫有 530 例 --- 包含肝炎特診進駐矯正機關治療受刑人。採回溯分析同性別，使用相同廠牌干擾素，排除肝硬化，肝癌，治療過，合併 HIV 或 HBV，複雜合併症者。比較兩組人口學特徵，檢驗值，病毒量，治療中斷，追蹤中斷，RVR，與治療後 SVR 為比較結果。共有 103 位接受治療之男性受刑人與 112 位社區接受治療之中壯年男性病患收入分析比較。受刑人組皆有毒癮史，年紀較輕 (39.3 ± 5.9 vs 49.3 ±12.3 歲)，治療前較少 1b 基因型 (17% vs 54%)，較高 C 肝病毒量 (5.98 ± 0.73 vs 5.35 ± 1.17 Log_{10}) 與較高 GPT (97 ± 50 vs 127±79 IU/L)。治療中超過半數患者有皮膚癢 / 皮膚疹之副作用，較低快速病毒反應率 (RVR) (70.9% vs 75.9%, p =0.001)，因副作用而中斷治療無差異，治療成功率明顯優於社區組 (Per-protocol SVR 95.2% vs 73.7%, p =0.000. Intention-to-treat SVR 82.5% vs 62.5%, p =0.001)。然而因提早出獄或轉獄而無法完成追蹤者也不少。進駐矯正機關治療 C 肝受刑人是可行與安全的模式，治癒率可達 95%。對於因毒癮感染 C 肝之患者，在矯正機關服刑期間不失為一治療良機，因為治療服從性高，效果好。但是監獄與監獄，或監獄與社區醫院必須合作提供整合性的追蹤照顧。