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Original Article

Evaluation of cost-effectiveness of peginterferon plus ribavirin for chronic hepatitis C treatment and direct-acting antiviral agents among HIV-infected patients in the prison and community settings

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Abstract *Background:* In Taiwan, the majority of chronic hepatitis C carriers with HIV co-infection are intravenous drug users and inmates in correctional facilities. Peginterferon and ribavirin (PegIFN/RBV) have been the standard-of-care for chronic hepatitis C virus (HCV) infection more than decades. We evaluated the estimated cost-effectiveness of PegIFN/RBV from the National Health Insurance Research Database, covering the population of Taiwan from 1998 to 2013.

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Direct-acting antiviral agents (DAAs);
Cost-effectiveness

Materials and methods: This is an observational study, and study during was 2010—2016 and a total of 239 patients were treated with PegIFN/RBV. Of them, 156 patients were treated in the correctional facilities of Taipei, Taoyuan, Taichung and Taitung prisons, and 83 patients were treated in communities. The cost-effectiveness was analyzed in regimens of PegIFN/RBV and direct-acting antiviral agents.
Results: By multivariate analysis, the patients completed PegIFN/RBV in prison (adjusted odds ratio [aOR]: 4.56, 95% confidence interval [CI]: 1.58—13.12, $p = 0.005$), HCV RNA level <800,000 IU/mL (aOR: 4.0, 95% CI: 1.27—12.66, $p = 0.02$) at baseline, and the presence of early virologic response (EVR) (aOR: 7.67, 95% CI: 1.89—31.06, $p = 0.004$) were independent predictors for sustained virologic response (SVR). For the subgroups of prisoners, HIV-infected prisoners and HIV-infected patients in communities, the SVR rate was 73.8%, 72.0% and 36.8%, and the average medical-care cost was US$7,701, $7,893, and $15,443 per SVR achieved, respectively. Also, the estimated medical-care cost for genotype 6 was US$9211.
Conclusions: Chronic HCV/HIV co-infected patients with genotype 1 and 6 in the community setting could benefit from DAAs in Taiwan.

Abbreviations

PegIFN/RBV	Peginterferon and ribavirin
HCV	hepatitis C virus
IVDU	intravenous drug users
PLHIV	people living with human immunodeficiency virus
SVR	sustained virologic response
DAA	direct-acting antiviral agent
RNA	ribonucleic acid
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HIV/HCV	human immunodeficiency virus with hepatitis C virus
PCR	polymerase chain reaction
NHIRD	national health insurance research database
SD	standard deviation
aOR	adjusted odds ratio
CI	confidence
MSM	men who have sex with men
IQR	interquartile range
RVR	rapid virological response
EVR	early virological response
G1	genotype 1
G2	genotype 2
G3	genotype 3
G6	genotype 6

Introduction

Chronic hepatitis C is an important cause of liver-related morbidity and mortality worldwide.[1] intravenous drug users (IVDU) are at an increased risk of hepatitis C (HCV) and are also over-represented within the correctional facilities. The global prevalence of HCV antibody among the prison population estimated to be 26%, and 64% of them reported a history of IVDU.[2,3] The seroprevalence of chronic HCV infection in correctional facilities ranged from 16% to 49%.[4,5] Injection drug users are criminalized in Taiwan, and 28,320 people (88% male, 12% female) were found guilty of drug crime. Of them, 78.6% were aged between 30 and 50 years old in 2017.[6] There were 1899 people living with human immunodeficiency virus (PLHIV) in detention centers (out of a total of 56,560 detained persons) taken care by different HIV designated hospitals, and IVDU population accounted for 19.5% (n = 7023) of all diagnosed HIV-infected subjects in Taiwan.[7] The overall prevalence of HCV infection among HIV-infected IDUs was 96.6%.[8] Unfortunately, HIV-infected prisoners with chronic HCV infection have fewer opportunities to receive treatment than the same patients in community setting. Thus, a health burden of liver-related morbidities is significant in patients within correctional systems. Few studies have been conducted on the treatment of pegylated interferon (Peg-IFN) plus ribavirin (RBV) in chronic hepatitis C-infected prisoners,[9,10] and some convincing results were observed. Canadian penitentiaries using standard interferon plus ribavirin were with an overall sustained virologic response (SVR) of 55.9% (31.6% for genotype 1, 100% for genotype 2 and 71.4% for genotype 3).[11] Maru et al. also showed an overall SVR to Peg-IFN plus ribavirin of 47.1% (43.1% for HCV-genotype 1 and 58.8% for HCV-genotypes 2 and 3).[12] In Taiwan, Cheng CH et al. showed that treatment response among incarcerated patients with HCV infection demonstrated conclusive evidence (overall SVR of 84.5%, 70.8% for genotype 1, 94.1% for genotype non-1).[13]

Even so, the therapeutic response and cost-effectiveness of peg-IFN remains unclear among HIV-infected and incarcerated patients with chronic HCV infection. Moreover, although most new direct-acting antiviral agents (DAAs) are now reimbursed by the national health insurance administration in Taiwan since January 2017 with outstanding efficacy over 90%—100% and few adverse effects,[14—17] the accessibility of DAAs is still limited due to its high price. The purpose of this study was to evaluate the cost-effectiveness between peginterferon plus ribavirin and direct-acting

antiviral agents among HIV-infected patients and to compare their outcomes in prison and community settings.

Materials and methods

Study population

This is an observational study. Between January 2010 and December 2016, patients with chronic HCV infection were enrolled to receive antiviral therapy at Taoyuan General Hospital, Taitung Mackay Memorial Hospital and China Medical University Hospital in Taiwan. The inclusion criteria were patients aged above 20 years with chronic HCV infection (defined as detectable anti-HCV antibody and serum HCV ribonucleic acid (RNA) more than 6 months), who were treated with peg-IFN combined with RBV according to the National Health Insurance clinical practice guidelines. Most of them were drug dependent, and incarcerated in the correctional facilities of Taipei, Taoyuan, Taichung and Taitung, and completed their antiviral courses while incarcerated. Patients with hepatocellular carcinoma before antiviral treatment, or with overt clinical manifestations or medical history related to autoimmune diseases were excluded.

This was an observational and retrospective study. All included patients received similar medical care as other patients with HCV infection. The study was approved by the Research Ethics Committee and the Institutional Review Board in the participating hospitals, and oral or written informed consent was waived because of the retrospective study design. Confidentiality of the included patients was protected by adhering to the guidelines of Good Clinical Practice.

Clinical data

The following baseline information was collected, including age, gender, concurrent infections with chronic hepatitis B virus (HBV) and human immunodeficiency virus (HIV), HCV genotype, HCV RNA level, platelet level, and risk factor of HCV infection.

HCV genotyping was performed using primer-specific polymerase chain reaction (PCR) and direct PCR population sequencing with an ABI 3730 sequencer. Serum HCV RNA viral loads were quantified using a Roche Amplicor PCR assay, for which the lowest level of detection was 15 IU/mL. Patients whose HCV RNA levels were not measured at the time point of SVR and patients who did not complete the scheduled course of treatment because of side effects or lost to follow-up were coded as treatment failures.

Cost measurement from the national health insurance research database (NHIRD)

Tsai et al. conducted a large cohort, real-world cost-effectiveness analysis by linking a clinical cohort to the NHIRD of the entire population from 1998 to 2013 to investigate the cost-effectiveness of PegIFN/RBV among treatment-naïve chronic hepatitis C patients in Taiwan.[18] Of 829 treatment-naïve Genotype 1 patients with SVR rates of 68.6%, the average medical-care cost was US$5683 per treatment. Of 980 treatment-naïve Genotype 2 patients with SVR rates of 87.8%, the average medical-care cost was US$4094 per treatment. Zeuzem S et al. conducted a retrospective analysis on participants with chronic HCV Genotype 1b infection enrolled in 11 phase II/III clinical trials.[17] Of 1070 participants who received elbasvir 50 mg plus grazoprevir 100 mg once daily for 12 weeks, the SVR12 was 97.2%. This regimen was reimbursed by the national health insurance in Taiwan starting from August 2017, and the average medical-care cost was US$8064 per treatment. The average cost per treatment and per genotype subgroup from these two studies was cited in our study. The exchange rate of all medical costs was converted by 30 New Taiwan dollars per US dollar.

Statistical analyses

Variables were summarized as proportions for categorical variables, and the mean and standard deviation (SD) for continuous variables. Chi-square test or Fisher's exact test was used for categorical variable analyses and the Mann–Whitney U test or Student's t test was used for continuous variable analyses. Variables associated with AHA ($p < 0.1$) in univariate analyses were considered candidates in a conditional logistic regression model. A two-sided $p < 0.05$ was considered statistically significant. Multivariate analyses of categorical variables were conducted using binary logistic regression. Unadjusted and adjusted odds ratio (aOR) and 95% confidence (CI) were estimated. Data were analyzed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

During 2010–2016, a total of 239 patients were treated with PegIFN/RBV. Of them, 156 patients were treated in the correctional facilities in Taipei, Taoyuan, Taichung and Taitung, and 83 patients were treated in community settings. Fifty-one discontinued PegIFN/RBV because of grade 3 or 4 of adverse effects, and 15 patients lost to follow-up during the treatment (Fig. 1). The baseline characteristics of the incarcerated and non-incarcerated patients with HCV infection in our study are shown in Table 1. All 173

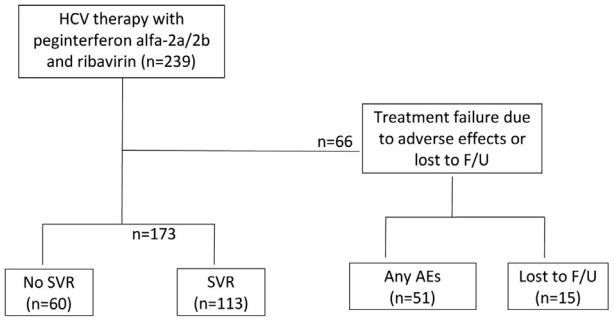

Figure 1. Descriptions of patient enrollment. RVR: Rapid virological response; EVR: early virological response; SVR: sustainable virological response; AE: adverse effect; F/U: follow-up.

Table 1 Baseline characteristics of incarcerated and community patients with chronic HCV infection.

	Total patients (n = 173)
Age (years, mean (SD))	41 (7)
Male, n (%)	160 (92.5)
HIV co-infection, n (%)	130 (75.1)
HBV co-infection, n (%)	13 (7.5)
Risk factor	
IVDU, n (%)	157 (90.8)
MSM, n (%)	16 (9.2)
Platelet count ($10^3/\mu L$, mean ± SD)	189 ± 63
Liver cirrhosis, n (%)	10 (5.8)
Genotype	
1, n (%)	80 (46.2)
2, n (%)	17 (9.8)
3, n (%)	26 (15.0)
6, n (%)	47 (27.2)
HCV-RNA $\log_{10}$ IU/mL, median (IQR)	6.31 (1.26)
HCV-RNA > 800,000 IU/mL, n (%)	113 (65.3)
Patients completed PegIFN/RBV in prison, n (%)	91 (52.6)

SD: standard deviation; IVDU: intravenous drug users; MSM: men who have sex with men; IQR: interquartile range; PegIFN/RBV: Peginterferon and ribavirin.

patients had the mean age of 41 ± 7 years, 160 (92.5%) patients were male and 130 patients (75.1%) were co-infected with HIV while 13 (7.5%) were with HBV. The major risk factor of HCV infection was drug injection (n = 157, 90.8%) and men who have sex with men (MSM, n = 16, 9.2%). At the baseline, 65.3% (n = 113) of these patients had HCV viral loads larger than 800,000 IU/mL. The most prevalent genotype was genotype 1 (46.2%), followed by genotypes 6 (27.2%) and 3 (15.0%). Ninety-one patients (52.6%) completed PegIFN/RBV in prison, and 82 patients in community as shown in Table 1.

Specified factors to predict SVR

By univariate analysis, without HIV co-infection ($p = 0.001$), complete treatment of PegIFN/RBV in prison ($p < 0.001$), HCV genotype 2 or 3 ($p = 0.001$), HCV RNA level <800,000 IU/mL ($p = 0.003$), RVR ($p < 0.001$) and EVR ($p < 0.001$) were associated with SVR in patients with chronic HCV infection. Multivariate analysis showed that complete treatment of PegIFN/RBV in prison (adjusted odds ratio [aOR]: 4.56, 95% confidence interval [CI]: 1.58–13.12, $p = 0.005$), HCV RNA level <800,000 IU/mL (aOR: 4.0, 95% CI: 1.27–12.66, $p = 0.02$), and the presence of EVR (aOR: 7.67, 95% CI: 1.89–31.06, $p = 0.004$) were independent predictors for SVR (Table 2).

Analysis of cost-effectiveness, stratified by the HCV genotypes

We retrieved the data from Tsai et al.[18] and Zeuzem et al.,[17] and analyzed the cost-effectiveness of therapy stratified by the viral genotype (Table 3). The subgroups of patients with favorable SVR, including non HIV-infected prisoners (SVR of 82.4%), HIV-infected prisoner (SVR of 72.0%) with genotype 1, and genotype 2 (SVR of 82.4%) and genotype 3 (SVR of 88.5%) (US$7893 and $6901 in non HIV-infected prisoners and HIV-infected prisoner with HCV genotype 1; US$4968 and $4626 in HCV genotype 2 & 3) had significantly lower average costs per SVR achieved when compared with HIV-infected non-prisoners with genotype 1 (SVR of 36.8%) due to much lower SVR rates. HIV-infected non-prisoners with genotype 1 had the highest cost per SVR achieved, followed by those with genotype 6 (SVR of 61.7%) (US$15,443 and $9211 in HIV-infected non-prisoners with HCV genotype 1 and 6). The average medical-care cost of elbasvir 50 mg plus grazoprevir 100 mg was higher (US$8064 per treatment), but the regimen has similar costs per SVR achieved (US$8296) due to high SVR rate of 97.2%.

Discussion

The study was the first to survey the SVR and cost-effectiveness of HCV treatment using PegIFN/RBV in prisons, including HIV-infected and non HIV-infected patients with different genotypes. The patients who completed treatment of PegIFN/RBV in prison, lower HCV RNA level at baseline (<800,000 IU/mL) and the presence of EVR were associated factors to SVR in the study. Also, we found that higher SVR of 72.0% and lower average cost per SVR achieved was US$7893 in HIV-infected prisoners (genotype 1), and SVR of 82.4% with average cost per SVR achieved was US$6901 in non HIV-infected prisoners (genotype 1). HIV-infected patients who received treatment in community was unfavorable factor of SVR incurred much higher costs per SVR achieved. The cost per SVR was US$15,443, which was 2.24 times by the cost of US$6901 in non HIV-infected prisoners. Treatment for naïve genotype 2 and 3 patients had significantly lower costs per SVR achieved compared to genotype 1 patients, which remained around US$4968 and $4626 per SVR, respectively. In comparison, for treatment-naive genotype 6 patients, the cost per SVR achieved was 1.99 times by the average cost of genotype 3 patients (US$9211).

HIV and HCV co-infected patients were seldom to be diagnosed acute retroviral syndrome or acute hepatitis,[19] because hepatitis C virus is prone to establish chronicity in a nature course of infection; hence, this phenomenon could easily cause outbreaks among IVDUs.[20] In the general population, genotype 1b and 2 are predominant in Taiwan, and genotype 3a and 6a is more predominant in Thailand, Vietnam, India, and Australia.[21] Genotype 6a is almost restricted to South China, Southeast Asia, and migrant patients from endemic countries.[21–23] However, the molecular epidemiology studies revealed that HIV CRF07_BC, which has circulated among IDUs in Southwest China, caused the epidemic of HIV infection among IDUs in Taiwan since 2014.[24,25] The study also demonstrated a high prevalence of HCV infection with a predominance of genotypes 1a, 6a, and 3a, as a result of the impact of IVDUs' heroin trafficking route from China or Southeast Asia.[8,26] In general, several small-scale studies have examined treatment outcomes in patients with HCV genotype 6, and SVR was

Table 2 The possible contributing factors of sustained virological response to hepatitis C treatment in the correctional facility and community settings.

	SVR	No SVR	Univariate analysis		Multivariate analysis	
	n = 113	n = 60	Odds ratio (95%CI)	*p*	Adjusted odds ratio (95%CI)	*p*
Male, n (%)	105 (92.9)	55 (91.7)	0.84 (0.26–2.68)	0.766		
Age (years, mean (SD))	41 (8)	42 (7)	1.02 (0.98–1.06)	0.419		
HIV co-infection, n (%)	78 (69)	55 (91.7)	0.2 (0.07–0.55)	0.001	0.36 (0.07–1.95)	0.24
HBV co-infection, n (%)	11 (9.7)	2 (3.3)	0.32 (0.07–1.49)	0.128		
Treatment in prison, n (%)	75 (66.4)	16 (26.7)	5.43 (2.72–10.85)	<0.001	4.56 (1.58–13.12)	0.005
IVDU, n (%)	101 (89.4)	56 (93.3)	1.66 (0.51–5.40)	0.393		
Liver cirrhosis, n (%)	4 (3.5)	6 (10)	0.29 (0.08–1.10)	0.056	0.85 (0.13–5.54)	0.87
Platelet ($10^3/\mu L$, mean ± SD)	189 (69)	178 (65)	0.998 (0.993–1.003)	0.345		
HCV genotype 1, n (%)	45 (39.8)	35 (58.3)	0.47 (0.25–0.89)	0.02	0.85 (0.28–2.53)	0.77
HCV genotype 2 or 3, n (%)	37 (32.7)	6 (10.0)	3.27 (1.47–7.32)	0.001	4.28 (0.997–18.38)	0.05
HCV genotype 6, n (%)	29 (25.7)	18 (30)	1.24 (0.62–2.49)	0.542		
HCV RNA, $\log_{10}$ IU/mL	5.95 (0.94)	6.29 (0.79)	0.62 (0.41–0.92)	0.016		
RNA < 800,000 IU/mL, n (%)	48 (42.5)	12 (20)	2.95 (1.42–6.16)	0.003	4.0 (1.27–12.66)	0.02
RVR, n (%)	78 (69)	16 (26.7)	6.13 (3.05–12.31)	<0.001	1.86 (0.68–5.10)	0.23
EVR, n (%)	105 (92.9)	36 (60)	8.75 (3.61–21.20)	<0.001	7.67 (1.89–31.06)	0.004

Abbreviations: VDU: intravenous drug users; RVR: rapid virological response; EVR: early virological response; SVR: sustainable virological response.

60–90% in patients treated for 48 weeks with standard doses of PegIFN/RBV.[27] However, no study has examined HIV and HCV co-infected patients with HCV genotype 6. Our study showed that the SVR rate was 56.3% for HCV genotype 1, 82.4% for HCV genotype 2, 88.5% for HCV genotype 3 and 61.7% for HCV genotype 6, indicating substantially lower rates than those reported in previous real-world clinical studies.[2,13,18,27] This difference might be due to the relatively high proportion of HIV-infected patients who completed treatment in community settings.

In general, several small studies have examined treatment outcomes in this patient population. If only incarcerated patients were enrolled, the SVR rate was 76.2% in HCV genotype 1 patients. Also, the inferior SVR rate was led by more than 65% of patients with high baseline viral loads (>800,000 IU/mL) or who did not achieve an EVR. For HCV genotype 1 patients with or without HIV co-infection and who did not complete PegIFN/RBV treatment in prison, the cost per SVR increased from US$6901 to $15,443, indicating that the newly introduced DAA may need to be considered for these patients. For HCV genotype 2 and 3 patients, the cost per SVR achieved was significantly lower than other genotypes because most of the patients (86%) completed PegIFN/RBV treatment in prison. Therefore, the factors such as HIV co-infection, baseline high viral loads and the lack of RVR did not have impacts on SVR rates. The finding was different from Tasi's study[18] because there was no incarcerated patient in their population. There were few studies regarding HCV genotype 6 patients, especially incarcerated patients. Of 55 incarcerated patients in

Table 3 The comparisons of cost-effectiveness between peginterferon plus ribavirin and direct-acting antiviral agents among HIV-infected patients (n = 173).

Genotype	Agents of treatment	Population	Number	SVR (%)	Cost per treatment	Cost per SVR
G1	PegIFN/RBV	Tsai et al.[18]	829	68.6	5683	8285
G1	PegIFN/RBV	our study	80	56.3	5683	10,103
G1	PegIFN/RBV	HIV-negative prisoners	17	82.4	5683	6901
G1	PegIFN/RBV	HIV-positive prisoners	25	72.0	5683	7893
G1	PegIFN/RBV	HIV-positive patients in community	38	36.8	5683	15,443
G1	Elbasvir/grazoprevir	Zeuzem et al.[17]	1070	97.2	8064	8296
G2	PegIFN/RBV	our study	17	82.4	4094	4968
G3	PegIFN/RBV	our study	26	88.5	4094	4626
G6	PegIFN/RBV	our study	47	61.7	5683	9211
G6	PegIFN/RBV	Prisoners	23	87.0	5683	6532
G6	PegIFN/RBV	Non-prisoners	24	37.5	5683	15,155

Abbreviations: G1: genotype 1; G2: genotype 2; G3: genotype 3; G6: genotype 6; PegIFN/RBV: pegylated interferon plus ribavirin; SVR: sustainable virological response.

Cheng's study, 24.1% of them were genotype 6 while the SVR rate of 92.9%.[13] However, the SVR rate was 61.7% in our study since only 23 incarcerated patients (48.9%) completed PegIFN/RBV treatment in prison. For HCV genotype 6 patients, the SVR rate of patients in prison and community settings was 87% and 37.5%. The cost per SVR was US$15,155, which was 2.32 times by the cost of US$6532 in non-prisoners. Elbasvir 50 mg plus grazoprevir 100 mg was newly introduced DAA in Taiwan, and the medical-care cost was the highest (US$8064), but the cost per SVR achieved ($8296) was similar to those with genotype 1 and 6 who completed PegIFN/RBV treatment in prison. Hence, DAA may be more suitable for HCV genotype 1 and 6 patients in community in terms of cost-effectiveness.

One of the limitations of our study was the small number of patients, which affected our ability to detect significant publication bias and perform additional subgroup analyses. Then, the treatment duration of PegIFN/RBV was not standardized, and it was dependent on the physician's decision, instead of the genotype or the status of EVR. Therefore, SVR rate could be variable between hospitals. This retrospective study enrolled patients from 3 different hospitals, and there was no standardized protocol to record baseline characteristics, such as fibrosis stage, IL-28B variant, reinfection rate, dose adjustment of PegIFN/RBV and data collection. This study cited Tsai's data as reference of cost-effectiveness analysis, including costs of prescribed medications, laboratory tests and consultations.[18] However, the current study underestimated direct medical and nonmedical costs since high proportion of HIV/HCV co-infected patients were enrolled and longer treatment course was conducted, and more adverse effects were found during the period of observation. Moreover, no real-world cost-effectiveness analysis of DAAs was currently available in Taiwan, only Zeuzem's data were available to imitate potential medical costs. Further studies are warranted to include medical and miscellaneous costs, including expenses related to psychological stress and loss of work as well as the assessment of quality of life in order to have a comprehensive analysis between PegIFN/RBV and DAAs regimens.

In conclusion, this study reveals a higher SVR rate in prisons, including HCV and HIV/HCV co-infected patients, and those with HCV RNA <800,000 IU/mL at baseline and the presence of EVR. Our results also show that DAAs regimens could be more cost-effective in HIV/HCV co-infected patients with genotype 1 and 6 in community settings.

Conflicts of interest

The authors declare no conflict of interests regarding the publication of this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2018.10.002.