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Original Article

A real world cost effectiveness analysis of interferon-based therapy for HCV naïve super-responders

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Abstract

Background: A direct-acting antiviral (DAA) era in hepatitis C virus (HCV) treatment is fast approaching; unfortunately, the availability and affordability of DAAs in Asia–Pacific areas vary, making it difficult to develop universal HCV practice guidelines appropriate for the all Asian populations. This study aimed to evaluate the real-world cost-effectiveness of IFN-based therapy according to the current strategies with PegIFN/RBV for "easy-to-treat" to provide a reference for application of future DAA development for IFN-eligible, treatment naïve HCV patients.
Methods: A total of 1032 chronic hepatitis C treatment-naïve patients who corresponded to response-guided therapy (RGT) guidelines of PegIFN/RBV regimens were linked to the entire population of expenditures and order in the National Health Insurance Research Database of Taiwan. The average total cost per SVR achieved was calculated as the summation of the total cost for all treated patients/number of SVR cases.
Results: Current RGT suggested 24 weeks of PegIFN/RBV for G1 naïve patients with baseline LVL and RVR at treatment week 4 achieved an average treatment cost per SVR of \$5090 ± 2400. This was of superior cost-effectiveness compared with those other subgroups of G1 patients. In terms of G2 patients, according to current RGT of 16 weeks of treatment duration, PegIFN/RBV treatment with RVR achieved was of a very competitive cost per SVR (\$3237 ± 488).
Conclusion: For a naïve patient in the new DAA era, the PegIFN/RBV treatment might be conserved for those with all favorable risk parameters, considering the treatment duration and cost per SVR, in the resource-constrained countries.

Keywords: Chronic hepatitis C; Cost-effectiveness analysis; Naïve; Pegylated interferon; Response-guided therapy

1. Introduction

The prevalence and number of people with antibodies to hepatitis C virus (anti-HCV) globally are estimated to be 2.8% and 185 million respectively, with two-thirds (124 million) of these population in Asia.[1] HCV genotype distribution varies greatly in the Asian regions, with estimated populations of 54, 12, 48, 7.5, and 9.7 million, respectively, for HCV genotypes 1 (HCV-1), HCV-2, HCV-3, HCV-4, and HCV-6, respectively.[2] More than 80% of Asian persons infected with HCV have a more favorable host genotype (either interleukin-28B (IL28B) rs12979860 CC[3] or IL28B rs8099917 TT[4]). These innate immune genotypes are associated with a higher rate of sustained virological response (SVR) to treatment with pegylated interferon and ribavirin (PegIFN/RBV).

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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For Asian patients infected with HCV genotype 1 or 4, the SVR rates to PegIFN/RBV for 48 weeks and 24 weeks ranged from 60% to 75%, whereas the SVR rate for patients with HCV genotype 2 or 3 infections to 24 weeks regimen were 80%–90%.[5] With a strategy of response-guided therapy (RGT) based on HCV genotype and on-treatment virological responses,[6–10] treatment duration could be abbreviated to 24 weeks for HCV-1/4 patients with a low viral load and a rapid virological response (RVR) (undetectable HCV RNA at treatment week 4)[11] and to a shorter 16 weeks for HCV-2 patients with RVR. Treatment should be stopped for those not achieving an early virological response (EVR) (week 12 HCV RNA decline <2 logs from baseline).[12] Alternatively, with baseline predictors Asian HCV gentotype-1 patients with lower viral loads (LVL) and the IL28B rs12979860 CC genotype were highly expected to achieve an SVR after a 24-week course of PegIFN/RBV.[13]

The progress of direct-acting antiviral (DAA) agent in HCV treatment is moving from interferon-containing regimens in 2011 to interferon-free regimens, which are the current standard of care in most Western countries. Unfortunately, the availability and affordability of DAAs in Asia–Pacific areas vary, making it difficult to develop a universal HCV practice guideline appropriate for the all Asian populations. The current recommendations should be based on the availability, indication, and cost-effectiveness of antiviral agents in Asia. Therefore, this study aimed to evaluate the real-world cost-effectiveness of IFN-based therapy according to the current strategies with PegIFN/RBV for "easy-to-treat" to provide a reference for application of future DAA develop for IFN-eligible, treatment naïve HCV patients.

2. Methods

2.1. Study population

A total of 1032 chronic hepatitis C (CHC) treatment-naïve patients who corresponded to RGT guidelines of PegIFN/RBV regimens were linked to the entire population of outpatient/inpatient expenditures and order in the National Health Insurance Research Database (NHIRD) in Taiwan. In this hospital-based cohort study, all on-treatment clinical data were collected from a medical center and two core regional hospitals from 1998 to 2003. All patients provided written informed consent. The Institutional Review Boards at the participating hospitals approved the protocols, which conformed to the guidelines of the International Conference on Harmonization for Good Clinical Practice costs.

2.2. Laboratory test

We used a qualitative real-time polymerase chain reaction (COBAS AMPLICOR Hepatitis C Virus Test, ver. 2.0; Roche, Branchburg, NJ, USA)[14] and a quantification-branched DNA assay (Versant HCV RNA 3.0, Bayer, Tarrytown, New Jersey, USA) or RealTime HCV (Abbott Molecular, Des Plaines IL, USA)[15] to detect serum HCV RNA. The HCV genotypes were determined using the Okamoto method[16] or a real-time PCR assay (Abbott Molecular, Des Plaines IL, USA). Liver histology findings obtained within one year prior to the initiation of antiviral therapy were graded and staged according to the scoring system described by Knodell and Scheuer.[17] The IL28B single nucleotide polymorphism rs8099917 was determined using the method described previously.[18] The treatment efficacy, including RVR at week 4, EVR at week 12 treatment and SVR at 24-week post-treatment follow-up was assessed.

2.3. Cost measurement

The outpatient costs associated with the studied conditions were calculated using the 1998–2013 database for the whole population. All of the costs were based on the records of prescribed medications, laboratory tests, and consultations retrieved from the linked NHIRD. The assessed period for the medical care costs was retrieved from three months before starting antiviral treatment to six months after stopping antiviral treatment. All medical costs were expressed in US dollars with a currency rate at 32 New Taiwan dollars to one US dollar.

2.4. Statistical analyses

The mean and standard deviation are presented in the calculations of the medical-care costs. The average total cost per SVR achieved was calculated as the summation of the total cost for all treated patients/number of SVR cases. The subgroup analysis of the average cost per SVR was stratified by HCV genotype. The host, viral and genetic subgroups were based on age (<60 and ≥ 60), gender, baseline viral load (low viral loads, LVL: $\leq$400 KIU/mL or high viral loads, HVL: >400 KIU/mL), fibrosis stage (F0-2 and F3-4), IL28B (rs8099917 TT and non-TT), RVR at week 4 and EVR at week 12. All analyses were conducted using SAS software (SAS Institute Inc., Cary, NC, USA). All statistical analyses were based on two-sided hypothesis tests with a significance level of $p < 0.05$.

3. Results

3.1. Strategies of corresponding to RGT between G1 patients and G2 patients

Of the 1032 CHC treatment-naive patients treated based on RGT. The mean treatment duration was 32.7 weeks (standard deviation [SD], 7.6) with an overall SVR rate of 81.0%. Among them, 551 patients were infected with difficult-to-treat HCV genotype 1 (G1). Real-world data showed that the mean treatment duration was 23.9 weeks for 202 (36.7%) patients with LVL at baseline and RVR achieved at week 4; 46.3 weeks for 345 (62.6%) patients with HVL at baseline or no RVR achieved at week 4, but EVR achieved at week 12; and 10.7 weeks for the other 4 (0.7%) patients with HVL at baseline, without RVR achieved at week 4, and without EVR achieved at week 12. The SVR rates were 94.1%, 65.8% and 0.0%, respectively, for LVL/RVR, HVL or no RVR/EVR, and HVL or no RVR/no EVR (Table 1). The average treatment costs and

Table 1
Clinic demographic profiles of 551 naïve HCV genotype 1 (G1) patients and 481 naïve HCV genotype 2 (G2) patients.

	G1			G2		
Subgroups[a]	A	B	C	D	E	F
Case no.	202	345	4	2	70	409
Age, ≥60 years, no. (%)	53 (26.1)	99 (28.9)	1 (25.0)	1 (50.0)	19 (26.4)	139 (34.1)
Sex, female, no. (%)	68 (33.9)	166 (48.2)	2 (50.0)	2 (100.0)	47 (67.1)	195 (47.7)
IL28B rs8099917, non TT, no. (%)[b]	6 (4.0)	36 (14.1)	0 (0.0)	0 (0.0)	12 (21.4)	40 (12.3)
Cirrhosis (F3-4), no. (%)[b]	12 (15.4)	46 (34.8)	1 (25.0)	1 (50.0)	13 (36.8)	41 (21.0)
Treatment Duration, weeks	23.9 ± 2.4	46.3 ± 4.5	10.7 ± 5.5	8.0 ± 5.7	22.3 ± 3.7	15.9 ± 1.0
SVR rate, no. (%)	190 (94.1)	227 (65.8)	0 (0.0)	0 (0.0)	41 (58.6)	378 (92.4)

G1 = HCV genotype 1; G2 = HCV genotype 2; IL28B = interleukin-28B rs8099917; RVR = rapid virologic response; EVR = early virologic response; SVR = sustained virologic response.

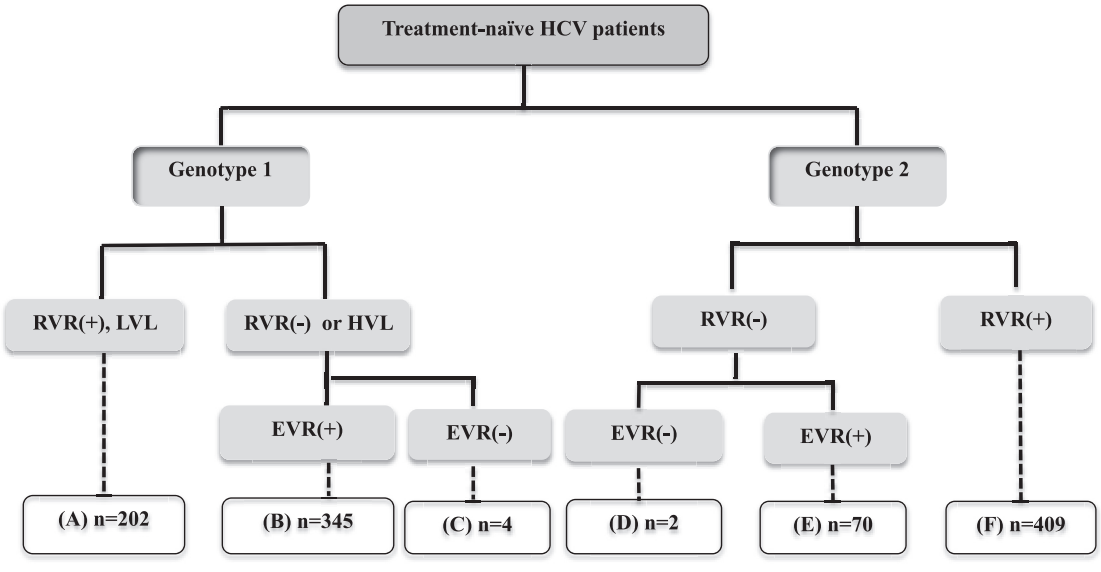
[a] Subgroups were classified based on HCV genotype, baseline viral load and on-treatment viral response at week 4 and week 12. A: HCV G1 patients with LVL and RVR achieved; B: HCV G1 patients with HVL and no RVR achieved, but EVR achieved; C: HCV G1 patients with HVL and no RVR achieved, also no EVR achieved; D: HCV G2 patients without RVR achieved, also without EVR achieved; E: HCV G2 patients without RVR achieved, but EVR achieved and F: HCV G2 patients with RVR achieved.

[b] Data was available in 210 for histopathology and 404 for IL28B rs8099917 of G1 group; 477 for treatment duration, 230 for histopathology, 382 for IL28B rs8099917 of G2 group.

SD per an SVR achieved on G1-naïve patients were $5090 ± 2400 for LVL/RVR and $10,457 ± 5112 for HVL or no RVR/EVR, respectively (p value < 0.0001) (Fig. 1A and B). However, the patients with low viral load and RVR achieved at week 4 were the best cost-effectiveness subgroup of HCV G1-naive patients for PegIFN/RBV therapy.

Of 345 patients with EVR, 289 achieved complete EVR (cEVR, HCV RNA undetectable at treatment week 12). There was higher SVR rate on cEVR patients than those on partial EVR (pEVR, HCV RNA decline > 2 logs but detectable at treatment week 12), while the cost per treatment was similar between the two groups (SVR: 78.2% for cEVR and 16.5% for pEVR; cost per treatment: 6837 ± 2393 for cEVR and 7116 ± 8560 for pEVR). Therefore, significantly higher cost per SVR achieved was observed among patients with pEVR than those with cEVR (9104 ± 3186 vs. 44,401 ± 53,411, p value < 0.0001).

In regards to HCV G2-naïve patients of easy-to-treat, the mean treatment duration was 15.9 weeks for 409 (85.0%) patients with RVR achieved at week 4; 22.3 weeks for 70 (14.6%) patients without RVR achieved at week 4, but EVR achieved at week 12; and 8.0 weeks for the other 2 (0.4%)



	A	B	C	D	E	F
Tx duration	23.9±2.4	46.3±4.5	10.7±5.5	8.0±5.7	22.3±3.7	15.9±1.0
SVR	94.1%	65.8%	0%	0%	58.6%	92.4%
$ Cost/Tx	4,790±2,258	6,881±3,364	3,463±2,213	1,419±945	4,431±999	2,991±451
$ Cost/SVR	5,090±2,400	10,457±5,112	∞	∞	7,561±1,705	3,237±488

Fig. 1. A real-world cost-effectiveness analysis on 551 naïve G1 patients and 481 naïve G2 patients with following RGT of PegIFN/RBV. *57 patients with unavailable data of EVR or RVR were excluded.

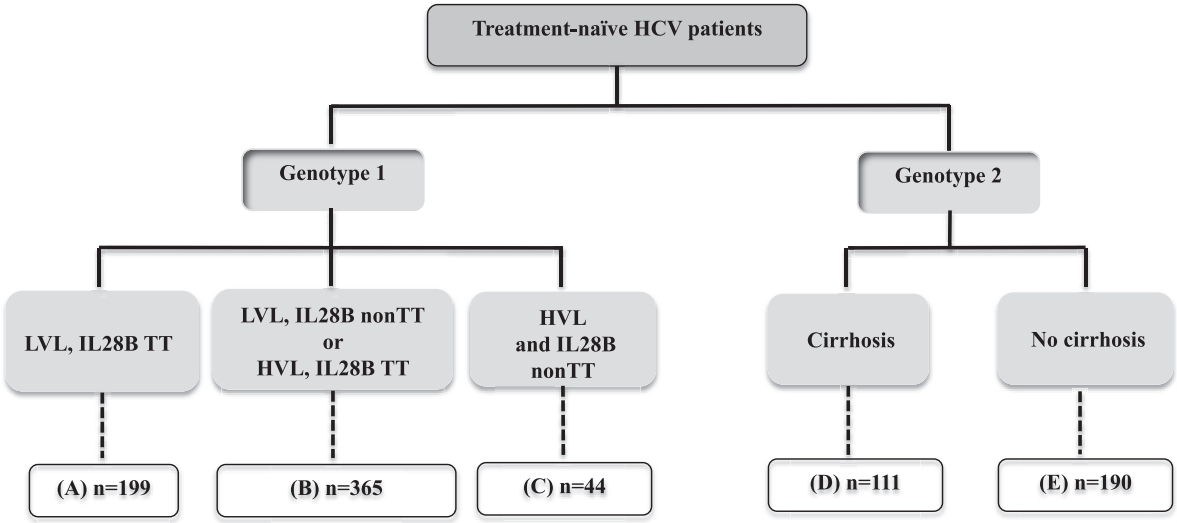
patients without RVR achieved at week 4 and also without EVR achieved at week 12. The SVR rates were 92.4%, 58.6% and 0.0% for RVR, no RVR/EVR, and no RVR/no EVR, respectively (Table 1). The average treatment costs and standard deviation per an SVR achieved on G2 naïve patients were \$3237 ± 488 for RVR and \$7561 ± 1705 for no RVR/EVR, respectively (p value < 0.0001) (Fig. 1F and E). However, those patients with RVR achieved at week 4 were the best cost-effectiveness subgroup of HCV G2-naïve patients for PegIFN/RBV therapy.

Of 70 EVR patients, 59 achieved cEVR. The SVR rate of patients with cEVR was 69.5% while none of the pEVR patients responded to the treatment. The cost per treatment was similar between the two groups (cost per treatment: 4495 ± 795 for cEVR and 4088 ± 2093 for pEVR). However, PegIFN/RBV was discontinued for the HCV-naïve patients without EVR achieved after 16 weeks of therapy according to the health insurance policy of Taiwan. The real-world results also showed that less cost-effectiveness on these groups due to poor SVR rate (Fig. 1C and D).

3.2. Strategies of IL28B SNP on G1 patients and cirrhosis on G2 patients

Since 2015, we have provided a therapy strategy according to the IL28B rs8099917 genotype in G1 patients and cirrhosis in G2 patients, not considering the on-treatment viral response. The cost-effectiveness was better on G1 patients with baseline low viral load and IL28B favorable type than those with the at least one risk of viral load and IL28B genotype. The average costs and SD per an SVR achieved were \$5944 ± 2577 for LVL/IL28B TT, \$8794 ± 2918 for LVL/IL28B nonTT or HVL/IL28B TT and \$23,268 ± 24,276, respectively (Fig. 2A–C). Approximately 1.5-fold and 4-fold cost per SVR was incurred for patients with one risk and two risks than those without any risk of viral load and IL28B genotype (both of p values < 0.0001 for no risk vs. one risk or for no risk vs. two risks, respectively). However, the cost-effectiveness on cirrhotic G2 patients was significantly worse than that of on non-cirrhotic G2 patients (\$4634 ± 1082 for cirrhosis and \$4117 ± 589 for non-cirrhosis, respectively, p value < 0.0001) (Fig. 2D and E).

Taken together, the real world cost-effectiveness of IFN-based therapy according to the current two strategies and combined strategy with PegIFN/RBV for "easy-to-treat" is shown on Table 2. HCV G1 super-responders to 24 weeks of PegIFN/RBV therapy were patients with LVL/IL28B-TT or LVL/RVR or LVL/RVR/IL28B-TT. The average costs per SVR for three strategies were 5090 ± 2,400, 5944 ± 2,577, and 4937 ± 1,884, respectively (compared with strategy 1, p value = 0.0004 for strategy 2 and p value = 0.53 for strategy 3). HCV G2 super-responders to 16 weeks of PegIFN/RBV therapy were patients with RVR, non-cirrhosis or RVR/non-cirrhosis. The average costs per SVR were 3237 ± 488, 4117 ± 589 and 3207 ± 260, respectively (compared with strategy 1, p value < 0.0001 for strategy 2 and p value = 0.49 for strategy 3).



	A	B	C	D	E
Tx Duration	28.9±4.5	38.6±13.4	41.8±16.5	23.0±9.1	19.4±3.5
SVR	85.4%	66.0%	29.6%	83.8%	86.3%
$ Cost/Tx	5,076±2,201	5,804±1,926	6,887±7,186	3,884±907	3,553±508
$ Cost/SVR	5,944±2,577	8,794±2,918	23,268±24,276	4,634±1,082	4,117±589

Fig. 2. A real-world cost-effectiveness analysis on treatment-naïve patientswith following RGT of PegIFN/RBV considering to IL28B rs8099917 in G1 and cirrhosis in G2 *608 G1 patients with IL28B genotype were available and 301 G2 patients with liver biopsy data were available being included in the analysis.

Table 2
Medical-care costs per treatment and per SVR on easy-to-treat HCV G1 patients to 24 weeks of PegIFN/RBV and G2 patients to 16 weeks of PegIFN/RBV.

	G1 (24 weeks)			G2 (16 weeks)		
	Strategy 1	Strategy 2	Combined strategies	Strategy 1	Strategy 2	Combined strategies
Subgroups of easy-to-treat	LVL/RVR	LVL/IL28B-TT	LVL/RVR/IL28B-TT	RVR	Non-cirrhosis	RVR/non-cirrhosis
Case no.	202	199	143	409	190	141
Treatment Duration, weeks	23.9 ± 2.4	28.9 ± 4.5	24.0 ± 2.3	15.9 ± 1.0	19.4 ± 3.5	15.9 ± 0.5
SVR rate, no. (%)	190 (94.1)	170 (85.4)	137 (95.8)	378 (92.4)	164 (86.3)	135 (95.7)
Total cost per treatment (U.S. $)	4790 ± 2258	5076 ± 2201	4730 ± 1805	2991 ± 451	3553 ± 508	3070 ± 248
Total cost per SVR (U.S. $)	5090 ± 2400	5944 ± 2577	4937 ± 1884	3237 ± 488	4117 ± 589	3207 ± 260
	reference	$p = 0.0004$	$p = 0.53$	reference	$p < 0.0001$	$p = 0.49$

4. Discussion

Current RGT suggested that for 24 weeks of PegIFN/RBV for G1 naïve patients with baseline LVL and RVR at treatment week 4 achieved,[19] the average treatment cost per SVR was $5090 ± 2400. This was of superior cost-effectiveness compared with the other subgroups of G1 patients. In terms of G2 patients, according to current RGT of 16 weeks of treatment duration, PegIFN/RBV treatment with RVR achieved was of a very competitive cost per SVR ($3237 ± 488). For a naïve patient in the new DAA era, the PegIFN/RBV will might be conserved for those with all favorable risk parameters, considering the treatment duration and cost per SVR, in the resource-constrained countries.

In the previous cost-utility study of IFN-based therapy, PegIFN/RBV 24 weeks for all HCV genotype is the most cost-effectiveness strategy for SVR at USD $9361 by the prediction of Markov model 10 years ago.[20] Although the cost per SVR achieved was similar to our recent reports for HCV G1 patients at $7627–$8,285, it was much higher for HCV G2 patients at $4663–$4799.[21,22] The results indicated the importance of personalized HCV therapy not only in treatment efficacy but also in cost-effectiveness. In the current study, we further highlighted that the cost per SVR achieved with PegIFN/RBV for naïve HCV patients could be significantly lowered among the "easy-to-cure" population, down to $4937–$5944 by 24-week regimen for G1 super-responders and $3207–$4117 by 16-week regimen for G2 super-responders.

The emerging DAA regimens are becoming the standard-of-care for HCV patients. Nowadays, there are five IFN-free DAA regimens approved in Taiwan, including daclatasvir plus asunaprevir for G1b, paritaprevir/ritonavir/ombitasvir plus dasabuvir with/without ribavirin for G1, grazoprevir/elbasvir for G1, sofosbuvir plus ribavirin for G2 and sofosbuvir/ledipasvir for G1 patients. The overall SVR rates are around 95% or more if G1b patients with baseline resistance-associated substitutions are excluded from regimen with daclatasvir plus asunaprevir.[23] Nevertheless, the costs remain high in Taiwan ranging from USD $8750 to $27,500 per treatment course. As a result, the cost per SVR achieved would range from USD $9200 to $29,000 with IFN-free DAA regimens in Taiwan. It would be worthy and cost-effective to treat the patients of "difficult-to-treat" or treatment-experienced patients, because that the cost per SVR by PegIFN/RBV therapy has been as high as $15,520 and $10,324 for treatment experienced G1 and G2 patients,[24] respectively. Nevertheless, we identified a group of PegIFN/RBV super-responders with high SVR rates to abbreviated PegIFN/RBV therapy: G1 patients with favorable host and/or virologic factors with a 24-week regimen and G2 patients with RVR or non-cirrhotic with a 16-week regimen.

Currently, only daclatasvir plus asunaprevir and paritaprevir/ritonavir/ombitasvir plus dasabuvir for patients with advanced hepatic fibrosis (F3 or F4) are reimbursed by National Health Insurance Administration due to foreseeable huge budget impact in the short term. Since delayed treatment could increase the risk of HCC overtime,[25] it is justifiable to identify patients eligible for IFN-based therapy with benefit cost-effectiveness and treat them as early as possible. Herein, we demonstrated that the treatment strategies toward the interferon-sensitive population produced much more cost-savings. If we treat patients based on RGT, the cost per SVR would be much lower at $5090 and $3237 for G1 and G2, respectively. Similarly, if we treat CHC patient based on their baseline virologic and host genetics, the cost per SVR would be at $5944 and $4117 for G1 and G2. With the concept of "Resource-Guided Therapy",[23] we are expected to treat the patients in a timely manner based on the cost-effectiveness to decrease the risk of end-stage liver diseases and the source of infection as well.

Successful antiviral therapy has been associated with improved long-term outcome, in terms of reduced risk of cirrhosis, HCC and mortality.[26–29] Nevertheless, the risk of HCC remains even after HCV eradication, especially among those of old age, with advanced fibrosis or abnormal glucose metabolism, carrying a risk genetic allele and unable to reverse the risk gene signatures.[25,30–32] Therefore, real world long-term cost-effectiveness of antiviral therapy based on overall post-treatment morbidity and mortality needs further elucidation.

Given the low cost, high SVR and relatively shorter treatment duration, we suggest that for IFN-eligible and IFN-super-responders, immediate treatment with 16–24 weeks of PegIFN/RBV could be recommended in the resource-constrained area where IFN-free DAA are unavailable and/or unaffordable.

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