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Cost-Effectiveness Analysis of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with or without Ribavirin Regimen for Patients Infected with Chronic Hepatitis C Virus Genotype 1 in Malaysia

Asrul Akmal Shafie, PhD,[1,*] Muhammad Radzi Abu Hassan, FRCP,[2] Siew Chin Ong, PhD,[1] Suchin Virabhak, PhD,[3] Yuri Sanchez Gonzalez, PhD[4]

[1]School of Pharmaceutical Sciences, Universiti Sains Malaysia, Gelugor, Penang, Malaysia; [2]Medical Department, Hospital Sultanah Bahiyah, Alor Setar, Kedah Malaysia; [3]Medicus Economics LLC, Milton, MA, USA; [4]AbbVie Inc., Health Economics and Outcomes Research, North Chicago, IL, USA.

ABSTRACT

Objectives: The combination of pegylated-interferon and ribavirin (PegIFN+RBV) is currently the gold standard in treating chronic hepatitis C virus (HCV) patients in Malaysia and is reimbursed by the Malaysian authorities. This analysis evaluated the cost-effectiveness (CE) of the ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin (OBT/PTV/r+DSB±RBV) regimen as compared with the PegIFN+RBV or no treatment in chronic HCV Genotype 1 (GT1) treatment-naïve and treatment-experienced cirrhotic and noncirrhotic patients in Malaysia.

Methods: A Markov model based on previously published CE models of HCV was adapted for the Malaysian public healthcare payer perspective, based on good modeling practices. Treatment attributes included efficacy, regimen duration, and EQ-5D treatment-related health utility. Transitional probabilities and health state health utilities were derived from previous studies. Costs were derived from Malaysian data sources. Costs and outcomes were discounted at 3.0% per year. Deterministic and probabilistic sensitivity analyses were performed to evaluate the impact of uncertainties around key variables.

Results: Based on the analysis, patients treated with the OBT/PTV/r+DSB±RBV showed less frequent progression to compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and liver-related deaths when compared with standard care (ie, PegIFN+RBV or no treatment). At a price of MYR 1846/day, the OBT/PTV/r+DSB±RBV regimen is cost-effective over PegIFN+RBV and yields better outcomes in terms of life-years (LYs) gained and quality-adjusted life-years (QALYs) at a higher cost, which is still well below the implied willingness to pay threshold of MYR 384 503/QALY.

Conclusion: The OBT/PTV/r+DSB±RBV regimen is cost-effective for treatment naïve, treatment experienced, cirrhotic, and noncirrhotic GT1 chronic HCV patients in Malaysia.

Keywords: cost-effectiveness analysis, genotype 1, hepatitis C virus, quality-adjusted life-year, sensitivity analysis.

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Introduction

Approximately 160 million individuals worldwide (2.35% of the world's population) are chronically infected with the hepatitis C virus (HCV).[1] To date, 7 HCV genotypes (GTs), numbered 1 to 7, and a large number of subtypes have been identified, with GT1 being the most prevalent genotype worldwide.[2] The World Health Organization (WHO) estimates that there are 400 000 hepatitis C patients in Malaysia[3] and the incidence rate of HCV infection saw an increase from 3.71 per 100 000 in the population in the year 2009 to 9.54 per 100 000 in the year 2017.[4] The most prominent modes of HCV transmission identified are intravenous drug use (77.8%), followed by blood/blood product transfusion (4.9%), sexual contact with an infected person (3.9%), hemodialysis (3.5%), and others (9.5%).[5]

In the initial stages of the disease, patients may be asymptomatic or may present with mild and nonspecific symptoms (eg, fatigue, flu-like symptoms, depression, cognitive impairment),

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* Address correspondence to: Asrul Akmal Shafie, PhD, School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800 Gelugor, Penang, Malaysia. Email: aakmal@usm.my

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which in turn adversely affect health-related quality of life (HRQoL). Approximately 70% to 80% of the HCV infected patients progress to become chronic HCV carriers, with most having relatively mild disease and slow progression.[6] Chronic HCV patients progress to develop either long-term stable cirrhosis (compensated cirrhosis [CC]) or decompensated cirrhosis (DCC) and/or hepatocellular carcinoma (HCC), which may result in liver failure, the need for liver transplantation, and ultimately death.[2]

The combination of pegylated interferon (PegIFN) and ribavirin (RBV), (PegIFN+RBV), when available, has been the standard of care for treating individuals with chronic HCV infection for many years.[2] In Malaysia, newer direct-acting antiviral agents (DAAs) were recently approved for licensed indications. These DAAs, however, are not reimbursed by government public payer programs. Therefore, PegIFN+RBV remains the standard of care as it is reimbursed by the government to treat treatment-naïve patients with HCV with and without cirrhosis, as well as treatment-experienced patients with HCV without cirrhosis.

Although the favorable cost-effectiveness (CE) profile of the ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavarin (OBT/PTV/r+DSB±RBV) regimen compared with multiple standards of care has been documented worldwide,[7,8] evidence from Malaysia is limited. The objective of this study was to assess the CE of the OBT/PTV/r+DSB±RBV regimen compared with PegIFN+RBV or no treatment in Malaysia for treatment-naïve patients with HCV GT1 infection without cirrhosis, treatment-naïve patients with HCV GT1 infection with cirrhosis, treatment-experienced patients with HCV GT1 infection without cirrhosis, and treatment-experienced patients with HCV GT1 infection with cirrhosis.

Methods

In this CE study, previously published CE models of the HCV Markov model[7-11] were adapted for a Malaysian public healthcare payer perspective based on good modeling practices.[12-14]

HCV Natural History Model

The Markov model is comprised of 9 health states, including 6 disease progression states (Metavir fibrosis F0-F1 [mild fibrosis]; Metavir fibrosis F2-F3 [moderate fibrosis]; Metavir fibrosis F4 [CC]; DCC; and HCC), 3 recovered states (sustained virologic response [SVR]; ie, recovered, history of mild fibrosis; recovered, history of moderate fibrosis; and recovered, history of CC), and an absorbing mortality state (ie, liver death and non-liver death). In contrast with previously published models of HCV,[9] liver transplantation is excluded from the model as it is not often performed in Malaysia.

Patients enter the model and initiate treatment in 1 of the 3 initial fibrosis states: mild fibrosis, moderate fibrosis, or CC.[9] From these initial states of fibrosis, progression to more severe states depends on whether or not SVR is achieved. Patients who do not achieve SVR are at risk of progressive liver disease and assumed to face the same risks of disease progression as untreated patients. With successful treatment, patients achieve SVR; the model assumes that SVR is a permanent condition characterized by transition to recovered states. The exception is SVR from the CC state, where there remains an excess risk of HCC. Lastly, the states represented by more advanced liver disease, namely DCC and HCC, are commonly accepted as distinct stages of progressive liver disease, and as such, carry excess liver-related mortality risks.[9,10]

Model Characteristics

The model was developed and analyzed with MS Excel (with VBA). The model validity involved checking the software program and analyzing it for potential programming errors. An experienced, independent modeling team at an academic institution in Austria also reviewed the model structure and parameters. Internal validation involved comparing the model's predictions with the data that were used. Costs and outcomes were discounted at 3.0% per year aligned with Malaysian pharmacoeconomic guidelines.[15]

Model Inputs

The clinical parameters for the model were based on pooled data from the SAPHIRE I[16] and II,[17] PEARL II,[18] III,[19] and IV,[19] and TURQUOISE II[20] Phase 3 clinical trials of the OBT/PTV/r+DSB±RBV regimen. Data from the telaprevir clinical trial publications, namely ADVANCE[21] and REALIZE,[22] were used to present data for the PegIFN+RBV regimen in treatment-naïve and treatment-experienced patients with HCV GT1 infection (Table 1).

Effectiveness and Safety

Treatment efficacy data for model inputs were extracted from clinical trials in patients with HCV GT1.[16-20] Importantly, the OBT/PTV/r+DSB±RBV regimen trials in patients with HCV GT1 infection reported SVR rates at post-treatment week 12, separately for patients with HCV GT1a and 1b infection. For patients with cirrhosis, SVR rates were observed at 12 and 48 weeks. The treatment duration for the PegIFN+RBV group was a total of 48 weeks. Table 2 summarizes the clinical data, which were directly applied in the model.

Adverse Events

Each treatment group reported adverse events (AEs); the most common AEs included anemia, rash, depression, neutropenia, and thrombocytopenia (Table 3). The discontinuation rates due to AEs for the OBT/PTV/r+DSB±RBV regimen trials were low and ranged from 0% to <2% for all 12-week regimens. Discontinuation rates for PegIFN+RBV were 3.03% to 7.2%.[9,10]

Treatment-Related Health Utility

Treatment-related health utility reflects the effects of treatment on HRQoL; it is likely largely related to the AEs reported during treatment. Treatment-related health utility was based on EQ-5D-5L20 measurements in the clinical trial for the OBT/PTV/r+DSB±RBV regimen, whereas values for the PegIFN+RBV regimen were extracted from the NICE appraisal TA 252 for telaprevir.[30]

For all treatments, including the OBT/PTV/r+DSB±RBV regimen and comparators, treatment-related health utility reflects a decrement over the duration that a patient was on therapy (eg, 12, 24, or 48 weeks). Table 4 reflects the values applied in the model.

It is likely that the lower treatment-related health utility decrement of the OBT/PTV/r+DSB±RBV regimen compared with PegIFN+RBV stems from its exclusion of PegIFN and correspondingly, significantly fewer AEs arising from its use, as well as the shorter treatment duration of the OBT/PTV/r+DSB±RBV regimen (12 weeks) compared with the PegIFN+RBV regimen (48 weeks).

Cost analysis

Cost data for different disease stages were extracted from a study conducted locally from a referral center for hepatitis C follow-up treatment from health clinics, district hospitals, and private clinics in the northern region of Malaysia. The data on the healthcare sector resources consumed in outpatient and inpatient settings (length of hospitalization, outpatient consultation,

Table 1. Model inputs.

Variable	Base case value	Source(s)
Demographics		
Treatment-naïve		
Mild (F0-F1)	50.00%	[23]
Moderate (F2-F3)	37.80%	[23]
CC (F4)	12.20%	[23]
Age (in years)*	46	[24]
Male	60.10%	[16-20]
Treatment-experienced		
Mild (F0-F1)	50.00%	[23]
Moderate (F2-F3)	37.80%	[23]
CC (F4)	12.20%	[23]
Age (in years)*	46	[23]
Male	65.10%	[16-20]
Transition probabilities†		
Fibrosis progression, annual transition probabilities†, F0-F1 to F2-F3	0.047	[12] Adjusted to replicate the prevalence of CC at 20 years (ie, 16% [14%, 19%]) at age 43 and 62% male.
Fibrosis progression, annual transition probabilities†, F2-F3 to F4	0.047	[12] Adjusted to replicate the prevalence of CC at 20 years (ie, 16% [14%, 19%]) at age 43 and 62% male.
Non-fibrosis disease progression transition probabilities†		
Recovered, no HCV history of CC to HCC	0.012	[25]
CC to DCC	0.039	[9]
CC to HCC (first year)	0.014	[9]
DCC to HCC (first year)	0.014	[9]
DCC to liver death‡	0.13	[9]
HCC first year to liver death‡	0.43	[9]
HCC subsequent years to liver death‡	0.43	[9]
Health state utilities		
Mild (F0-F1)	0.77	[9]
Moderate (F2-F3)	0.66	[9]
CC (F4)	0.55	[9]
Recovered, no HCV, history of F0-F1	0.82	[9]
Recovered, no HCV, history of F2-F3	0.71	[9]
Recovered, no HCV, history of F4	0.6	[11]
DCC	0.45	[9]
HCC (first year)	0.45	[9]
HCC (subsequent years)	0.45	[9]
Health State Costs		
Mild fibrosis, CHC (F0-F1)	MYR 1893.24	[24]
Moderate fibrosis, CHC (F2-F3)	MYR 1893.24	[24]
CC (F4)	MYR 2762.99	[24]
Recovered, no HCV, history of F0-F1	MYR 1454.48	[24]
Recovered, no HCV, history of F2-F3	MYR 1454.48	[24] using assumption from Backx et al,[26] that mild and moderate recovered have the same costs
Recovered, no HCV, history of F4	MYR 1883.60	[24] using ratio from Backx et al,[26] between noncirrhotic and recovered (CC)
DCC	MYR 16 002.12	[27]
HCC (first year)	MYR 18 339.69	[27]
HCC (subsequent years)	MYR 18 339.69	[27]; based on Hartwell et al[9] assumption
Drug Costs (per day)		
OBT/PTV/r+DSB± RBV regimen	MYR 1846.43	Model assumption
Pegylated Interferon (PegIFN)	MYR 117.81	[28]
Ribavirin (RBV)	MYR 90.00	[28]
Treatment duration§	Varies	
Monitoring costs	MYR 0.00	Model assumption
AE Costs		
Anemia	MYR 0.00	[24]

continued on next page

Table 1. Continued

Variable	Base case value	Source(s)
Rash	MYR 0.00	[24] Estimated cost of rash from treatment to be minimal
Depression	MYR 1878.86	[24]
Grade 3/4 neutropenia	MYR 672.61	[24]

AE indicates adverse event; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MYR, Malaysian Ringgit; OBT/PTV/r+DSB±RBV, ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavarin.
*Note that compared with the phase III trials,[16-20] as well as epidemiology data from other countries, the average age of patients with HCV infection in Malaysia is lower. There are other sources of evidence to support this.[29]
†We report transition probabilities to 3 decimal places. Note that in the model, the transition probability from Cardoso[25] was 0.123 (to 4 decimal places).
‡As a small percentage of patients progress to liver transplant, the difference in these transition probabilities in models with and without liver transplant would be small. Liver transplant does not occur in Malaysia; thus, applying transition probabilities (HCC to liver death and DCC to liver death) from Hartwell et al[9] would be (slightly) conservative.
§Total drug costs are derived from the duration of a therapy in days for each regimen drug multiplied by the daily cost of each regimen. We extracted data for treatment duration from trial publications or from the clinical study report.

laboratory monitoring, imaging, procedures, antiviral medications, and non-antiviral medications) were obtained retrospectively from patients' medical records, including the electronic hospital information system and manual documentation in the Gastroenterology Clinic of the hospital.[24]

Analyses

The SVR rates, direct medical costs, liver outcomes, and quality-adjusted life-years (QALYs) of each regimen were estimated. Data from treatment-naïve and treatment-experienced patients with HCV GT1 with and without cirrhosis were analyzed and stratified by sub-genotypes (ie, GT1a, GT1b) and severity of fibrosis, namely, mild/moderate/CC (ie, METAVIR score F0-F1/F2-F3/F4). These patient groups reflected the licensed indications for the OBT/PTV/r+DSB±RBV regimen.

Incremental cost-effectiveness ratios analysis

Incremental cost-effectiveness ratios (ICERs) of OBT/PTV/r+DSB±RBV regimen versus PegIFN+RBV were computed based on the following formulation:

Difference in Cost ÷ Difference in QALY = (total direct cost of OBT/PTV/r+DSB±RBV regimen − total direct cost of PegIFN+RBV) ÷ (OBT/PTV/r+DSB±RBV regimen QALY − PegIFN+RBV QALY)

Because no explicit CE threshold has been set by the Malaysian authorities, we inferred the threshold based on the standard of care (PegIFN+RBV) for the condition evaluated. Thus, our model estimates the ICERs of PegIFN+RBV versus no treatment in these patient segments to infer the CE threshold. Because treatment-experienced patients with cirrhosis are currently not treated, we were unable to compute an ICER for this patient segment. Table 6 presents the calculations to derive a weighted ICER across relevant patient segments. To obtain the weighted average ICER, we weighed each ICER by the relative size of its population. We inferred the willingness to pay (WTP) per QALY from the derived weighted ICER was MYR 384 503/QALY.

Sensitivity Analyses

Sensitivity analyses were conducted to test the robustness of the results of the model with respect to input parameters. A deterministic sensitivity analysis (DSA) was performed using 1-way and multivariate sensitivity analysis, where one parameter or group of related parameters was varied relative to its base case value. The impact of patient characteristics, regimen attributes (including SVR rates and regimen duration), costs, utilities, transition probabilities, discounting rates, time horizon, and the rate of mortality on the ICER were tested in 1-way DSA. SVR rates were assumed to vary based on ± 1.96 times their standard deviations. For SVR rates, values of 100% were not varied in the DSA. The size of the impact (ie, change in the ICER from the base case) was then ranked and the most influential disease model parameters and treatment attributes were calculated for each patient segment and comparator.

Several parameters were tested in a multi-way sensitivity analysis, including SVR rates, non-fibrosis progression rates, costs, and health utilities.

Table 2. Inputs for treatment efficacy in treatment-naïve and treatment-experienced patients with HCV GT1 infection using clinical trial data.

Treatment status	Therapy	SVR F0-F1	SVR F2-F3	SVR F4
Treatment-naïve	OBT/PTV/r+DSB±RBV	97.3%	97.3%	94.8%
Treatment-naïve	PegIFN+RBV	45.6%	43.5%	33.3%
Treatment-experienced*	OBT/PTV/r+DSB±RBV	97.3%	97.3%	95.3%
Treatment-experienced*	PegIFN+RBV	10.4%	13.8%	NA
Treatment-experienced*	No treatment	NA	NA	0.0%

GT indicates genotype; HCV, hepatitis C virus; NA, not applicable; OBT/PTV/r+DSB±RBV, ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavarin; PegIFN+RBV, pegylated interferon and ribavirin; SVR, sustained virological response.
*Treatment-experienced was computed using a weighted average of null responders, partial responders, and prior relapsers.

Table 3. Inputs for adverse events in treatment-naïve and treatment-experienced patients with genotype 1 hepatitis C virus using clinical trial data.

AEs	Treatment-naïve, F0-F3		Treatment-naïve, F4		Treatment-experienced,* F0-F3		Treatment-experienced,* F4	
	OBT/PTV/r+DSB± RBV	PegIFN+RBV	OBT/PTV/r+DSB± RBV	PegIFN+RBV	OBT/PTV/r+DSB± RBV	PegIFN+RBV	OBT/PTV/r+DSB± RBV	PegIFN+RBV
Anemia	3.8%	19.4%	7.7%	19.4%	3.6%	15.2%	8.6%	0.0%
Rash	7.8%	24.4%	11.1%	24.4%	6.2%	18.9%	12.2%	0.0%
Depression	0.0%	21.9%	3.8%	21.9%	0.0%	14.4%	4.9%	0.0%
Neutropenia†	0.2%	14.7%	0.5%	14.7%	0.0%	14.4%	0.9%	0.0%
Thrombocytopenia‡	0.2%	0.6%	1.0%	0.6%	0.0%	3.0%	0.6%	0.0%

AE indicates adverse events; OBT/PTV/r+DSB±RBV, ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavarin; PegIFN+RBV, pegylated interferon and ribavirin.
*Treatment-experienced included patients with null/partial response and prior relapse. Patients who were not treated do not experience any treatment-related AEs.
†Only Grade 3-4 (<1 x 10^9/L) neutropenia was reported.
‡Only Grade 3-4 (<50 x 10^9/L) thrombocytopenia was reported.

A probabilistic sensitivity analysis (PSA) was also undertaken in the analysis of all patient segments (treatment-naïve and treatment-experienced patients with HCV GT1 infection, with and without cirrhosis) for the currently reimbursed PegIFN+RBV and the OBT/PTV/r+DSB±RBV regimen. For each PSA, 500 simulations were drawn from the variables' distributions.

Results

Across all patient populations, the OBT/PTV/r+DSB±RBV regimen was associated with significant improvements in health outcomes, including reductions in long-term complications such as DCC and liver-related mortality when compared with PegIFN+RBV treatment.

Comprehensive Outcome Analysis

The OBT/PTV/r+DSB±RBV regimen exhibited superior clinical outcomes versus treatment with PegIFN+RBV (Table 5). For the OBT/PTV/r+DSB±RBV regimen, the lifetime risk of DCC in treatment-naïve and treatment-experienced patients without cirrhosis was 0.2%, and the risk of hepatocellular carcinoma was 0.1%. QALYs were higher in treatment-naïve and experienced patients with HCV GT1 without cirrhosis treated with the OBT/PTV/r+DSB±RBV regimen (9.2 and 9.1) versus treatment with PegIFN+RBV (8.4 and 7.9).

In treatment-naïve and treatment-experienced patients with cirrhosis, the lifetime risk of reaching DCC with the OBT/PTV/r+DSB±RBV regimen was 2% and 1.8%, respectively; versus treatment with PegIFN+RBV, this risk increased to 25.4% and 37.8% in treatment-naïve and treatment-experienced patients with cirrhosis, respectively. QALY values were higher with the OBT/PTV/r+DSB±RBV regimen (6.5 and 6.4) compared with the PegIFN+RBV regimen and no treatment in treatment-naïve and treatment-experienced patients with cirrhosis (5.5 and 5.1).

ICER Analyses

Compared with PegIFN+RBV, the OBT/PTV/r+DSB±RBV regimen is cost-effective (with a higher cost and better QALY outcomes) and well below the threshold of Malaysian Ringgit (MYR) 384 503/QALY. Table 6 illustrates the ICERs of the OBT/PTV/r+DSB±RBV regimen compared with PegIFN+RBV in treatment-naïve and treatment-experienced patients with and without cirrhosis.

Sensitivity Analyses

Even though the differences in SVR between the intervention and comparator efficacy rates are relatively large, other factors, such as health state health utilities, have a greater influence on ICERs in DSA. In all patient segment, health utilities in different health states are the most influential variables among all the disease model parameters. For both treatment-naïve and treatment-experienced cirrhotic patients, among transition probabilities for the disease progression of recovered, history of CC to HCC was one of the most influential variables on ICERs, too.

PSA results showed that in treatment-naïve patients with HCV GT1 without cirrhosis, the OBT/PTV/r+DSB±RBV regimen is more

Table 4. Annual treatment-related health utility changes by patient segments.

Health state	OBT/PTV/r+DSB± RBV	PegIFN+RBV*	No treatment†
Treatment-naïve, F0-F3	−0.003	−0.101	NA
Treatment-naïve, F4	−0.007	−0.101	NA
Treatment-experienced, F0-F3	−0.008	−0.116	NA
Treatment-experienced, F4	−0.009	NA	0.000

NA indicates not applicable; OBT/PTV/r+DSB± RBV, ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavarin; PegIFN+RBV, pegylated interferon and ribavirin.
Sources: Data on file: For the ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavarin regimen, utility data was taken directly from internal data from the respective clinical study report.
*This is assumed to be the same as patients with HCV GT1 of the PegIFN+RBV arm in the ADVANCE (treatment-naïve) and REALIZE (treatment-experienced) trials.
†Patients who were not treated did not experience treatment-related utility decrements.

Table 5. Model outputs by clinical outcomes for treatment-naïve and treatment-experienced patients with hepatitis C virus genotype 1 with and without cirrhosis.

Patient type	Intervention/ comparator	Cost (MYR)/ patient	LYs/ patient	QALYs/ patient	Reached CC, %	Reached DCC, %	Reached HCC, %	Had liver-related death, %
Treatment-naïve patients: no cirrhosis	OBT/PTV/ r+DSB±RBV	176 773	11.9	9.2	0.80	0.20	0.10	0.20
	PegIFN+RBV	77 794	11.8	8.4	16.80	4.50	1.90	3.70
Treatment-naïve patients: cirrhosis	OBT/PTV/ r+DSB±RBV	187 626	11	6.5	100.00	2.00	16.70	15.60
	PegIFN+RBV	96 293	10.1	5.5	100.00	25.40	16.40	29.80
Treatment-experienced patients: no cirrhosis	OBT/PTV/ r+DSB±RBV	176 668	11.8	9.1	0.80	0.20	0.10	0.20
	PegIFN+RBV	74 222	11.6	7.9	26.00	6.90	2.80	5.70
Treatment-experienced patients: cirrhosis	OBT/PTV/ r+DSB±RBV	238 156	10.9	6.4	100.00	1.80	16.50	15.30
	No treatment	48 975	9.5	5.1	100.00	37.80	16.10	37.00

CC indicates compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LY, life-year; MYR, Malaysian Ringgit; OBT/PTV/r+DSB± RBV, ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavarin; PegIFN+RBV, pegylated interferon and ribavirin.

cost-effective compared with PegIFN+RBV in all simulations at a value of at least MYR 188 056/QALY. Similarly, in treatment-experienced patients with HCV GT1 without cirrhosis, the OBT/PTV/r+DSB±RBV regimen is more cost-effective versus PegIFN+RBV in all simulations at a value of at least MYR 161 191/QALY, which is well below the inferred WTP threshold of MYR 384 503/QALY. The OBT/PTV/r+DSB±RBV regimen is cost-effective in 95% to 97% of simulations at a WTP threshold of MYR 384 503/QALY in treatment-naïve and treatment-experienced patients with GT1 HCV with cirrhosis.

Discussion

Treatment with PegIFN+RBV is the current standard for treatment of chronic HCV in Malaysia. Nevertheless, with the recent licensing of DAAs, there is a gap in evidence on its cost-effectiveness for public reimbursement in Malaysia. The current analysis fills this gap by assessing the CE of the OBT/PTV/r+DSB±RBV regimen versus PegIFN+RBV or no treatment in treatment-naïve patients with HCV GT1 with and without cirrhosis and treatment-experienced patients with HCV GT1 with and without cirrhosis.

Successful treatment of HCV infection results in an SVR and is thought to be tantamount in treating the disease. The economic model projected that higher SVR rates observed with the OBT/PTV/r+DSB±RBV regimen compared with PegIFN+RBV led to fewer HCV-related complications and deaths and to increased survival and quality-adjusted survival in all patient subgroups examined in the analysis. In addition, fewer costly liver disease complications resulted in reductions in lifetime HCV-related costs. The model results demonstrated that the OBT/PTV/r+DSB±RBV regimen is cost-effective compared with PegIFN+RBV. The OBT/PTV/r+DSB±RBV regimen yields better outcomes at a higher cost, which is still well below the implied WTP threshold of MYR 384 503/QALY.

Sensitivity analyses indicated that the model results were robust to input parameter uncertainty. An important strength of the study is its use of recent cost estimates pertinent to the Malaysian population; as a result, the outcome is relevant to healthcare decision makers in treating HCV infection in Malaysia.

The model adhered to ISPOR best practices for CE analysis. To assess external validity of the model, the model's estimates of CC in untreated patients (ie, setting treatment to "no treatment") and with mild disease (ie, setting the "initial fibrosis distribution" to 100% mild) were generated. The base case used fibrosis rates

Table 6. Incremental costs and effectiveness across patient segments.

Patient segment	Weights	ICER (PegIFN+RBV versus no treatment)	ICER (OBT/PTV/r+DSB±RBV versus PegIFN+RBV
Treatment-naïve: no cirrhosis	72%	MYR 112 473/QALY	MYR 132 326/QALY
Treatment-naïve: cirrhosis	10%	MYR 120 755/QALY	MYR 91 760/QALY
Treatment-experienced: no cirrhosis	18%	MYR 1 619 832/QALY	MYR 89 405/QALY
Treatment-experienced: cirrhosis	0%	N/A*	MYR 138 113/QALY

ICER indicates incremental cost-effectiveness ratio; MYR, Malaysian Ringgit; OBT/PTV/r+DSB±RBV, ombitasvir/paritaprevir/ritonavir and dasabuvir ± ribavarin; PegIFN+RBV, pegylated interferon and ribavirin; QALY, quality-adjusted life-year.
*Since no treatment is the standard of care in treatment-experienced patients with cirrhosis, we are unable to derive the ICER, as there is no alternative treatment to compare it against. We re-computed the distribution of patients based on the 3 segments for which we have ICERs; thus the weight of treatment-experienced patients with cirrhosis is zero.

based on Thein et al.[12] The base case model, applied to the current model using Malaysian life tables, estimated that 14.2% of patients would have a history of CC 20 years after HCV infection. The estimate of cumulative CC in Malaysia falls within the lower end of the range, as mortality in Malaysia is relatively high across all ages compared with the United Kingdom.

Although the results from this study confirm the favorable CE profile of OBT/PTV/r+DSB±RBV documented in other patient populations,[7,8] there are a number of limitations to note. First, the costs were measured from a Malaysian payer's perspective and included only direct medical expenses. Indirect costs such as work and productivity loss and extrahepatic manifestations were not included in the model, which may underestimate the CE of the OBT/PTV/r+DSB±RBV regimen. Future studies and analyses may look into these aspects for a more comprehensive cost-effectiveness analysis to quantify the true value of OBT/PTV/r+DSB±RBV regimen.

Second, this CE analysis only focuses on a comparison between the OBT/PTV/r+DSB±RBV regimen and PegIFN+RBV. It is important to note that after the initiation of this study, several other DAAs have been licensed and are available; however, they could not be included in this study because OBT/PTV/r+DSB±RBV was the first DAA to be licensed in Malaysia and the rest of the DAAs were too new in the market, which restricted the possibility of data collection. Comparison with other available treatment options for HCV represents important future work and will help decision makers understand the comparative efficacy, safety, and CE of DAAs in the treatment of patients with HCV infection.

Third, we recognized that comparability is an important issue for CEA on DAA treatment. Although there is likely some uncertainty regarding the true SVR achieved for treatment efficacy, the data used in the current study were comparable in terms of the patient population. Also, these data were used and accepted by health technology assessment agencies including NICE (UK) and CADTH (Canada), as well as the local clinical experts. In addition, the baseline efficacy data used in the current study were relatively comparable to the CADTH's efficacy data, which used network meta-analysis model to estimate the baseline probability of achieving SVR, especially in treatment-naïve noncirrhotic and cirrhotic patients, as well as treatment-experienced cirrhotic patients.[31]

Finally, the incremental benefit of the OBT/PTV/r+DSB±RBV regimen may be overestimated in the current study especially for the treatment-experienced non-cirrhosis patients. This is because the SVR probability for the PegIFN+RBV treatment arm for the treatment-experienced non-cirrhosis patients was around 2 times lower than that reported in the CADTH's analysis, which was generated based on the network meta-analysis model.[31]

Conclusion

Based on this CE analysis, the OBT/PTV/r+DSB±RBV regimen provides superior clinical outcomes versus the standard of care (ie, PegIFN+RBV and no treatment) with fewer patients treated with the OBT/PTV/r+DSB±RBV regimen experiencing HCV-related complications of CC, DCC, HCC, and liver-related deaths. In turn, patients treated with the OBT/PTV/r+DSB±RBV regimen have favorable CE profile with higher numbers of LYs gained and QALYs than patients treated with the standard of care. More studies are needed to determine the CE and efficacy of all currently approved DAAs for the treatment of HCV in Malaysia.

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Supplementary Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2019.09.005.

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