Cost-effectiveness of new antiviral treatments for non-genotype 1 hepatitis C virus infection in China: a societal perspective

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ABSTRACT

Objective This study aimed to estimate the cost-effectiveness of direct-acting antivirals (DAAs) among patients with non-genotype 1 for the eradication of hepatitis C virus (HCV) infection in China.

Methods A decision-analytic Markov model was developed to estimate the lifetime costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for DAAs and pegylated interferon plus ribavirin (PEG-RBV) from a societal perspective. The model inputs were derived from the literature, a patient survey, HCV expert opinions and a specialised drug price database available in China. Sensitivity analysis was conducted to evaluate the model robustness and calculate reasonable prices of DAAs.

Results For patients infected with HCV genotype 2, the pan-genotypic regimen sofosbuvir/velpatasvir (SOF/VEL) was the most cost-effective strategy compared with PEG-RBV, with an ICER of US$563/QALY. For genotype 3, the combination of sofobuvir plus dacatasvir (SOF-DCV) was the most cost-effective approach, with an ICER of US$314/QALY. All DAA regimens for genotype 6 were cost-saving, and sofosbuvir plus ribavirin (SOF-RBV) was the optimal regimen. One-way sensitivity analysis demonstrated that the ICERs were most sensitive to the utility values, discount rate and drug costs. Probabilistic sensitivity analysis indicated that using a threshold equal to one time the gross domestic product (GDP) per capita in China (US$9769/QALY, 2018), the probability of SOF/VEL, SOF-DCV and SOF-RBV being cost-effective was 58%, 83% and 71% for genotype 2, 3 and 6, respectively. Threshold analysis showed that the price of DAAs should be reduced by some degree to achieve better affordability.

Conclusions DAAs were cost-effective compared with traditional treatments. A reasonable reduction in the price of DAAs will increase drug affordability and is of great significance as a global strategy to eradicate viral hepatitis.

INTRODUCTION

Hepatitis C virus (HCV) infection has become a global public health issue, and the relevant long-term complications, such as liver cirrhosis or hepatocellular carcinoma, have imposed large health and economic burdens on patients. There are around 71 million patients infected with HCV worldwide, leading to approximately 399 000 deaths each year. In China, the incidence of HCV infection increased sharply in the last decade, and...
the estimated number of patients reached 9.8 million in 2015. However, in the same period, the diagnosis rate was only 2%, and the treatment rate was less than 1% in China, far below the global average. Liver cirrhosis and hepatocellular carcinoma are the leading causes of death from HCV. The mortality rate of liver cirrhosis caused by HCV in China was 0.2 per 100 000 people, and that of hepatocellular carcinoma was 0.4 per 100 000 people in 2016.

The primary aim of HCV infection treatment is to achieve sustained virologic response (SVR), which can significantly reduce the risk of progression to liver cirrhosis or hepatocellular carcinoma. Pegylated interferon plus ribavirin (PEG-RBV) was the standard of care in China before the introduction of direct-acting antivirals (DAAs) in 2017. Compared with the suboptimal efficacy and severe adverse events of PEG-RBV, DAAs have drastically decreased morbidity and mortality attributable to HCV infection. However, patients still have limited access to such treatments in China since several DAAs, such as asunaprevir, daclatasvir, sofosbuvir, sofosbuvir/ledipasvir, elbasvir/grazoprevir and sofosbuvir/velpatasvir (SOF/VEL), were not approved through priority review procedure until 2017. In addition, DAAs were more costly than traditional PEG-RBV therapy, and PEG-RBV was the only treatment on the national drug reimbursement list until the end of 2019.

Although the most prevalent HCV genotype in China is genotype 1, patients with non-genotype 1 still account for 43.2%. Unlike the diverse options for patients with genotype 1, they can only be treated with limited types of DAAs. Among those patients, genotypes 2 (15.8%), 3 (8.7%) and 6 (5.7%) are the majority, as well as genotypes 4 and 5 with nearly no report. Significant regional differences exist in the genotype distribution. Genotypes 2 and 3 are more prevalent in western China, and genotype 6 is more prevalent in southern China.

At present, scant evidence is available on the cost-effectiveness of DAAs for patients with non-genotype 1. Hence, this study aimed to estimate the cost-effectiveness of all treatment regimens for patients with non-genotype 1 and provide insights for the eradication of viral hepatitis in China and globally.

METHODS
Model structure and assumptions
A decision-analytic Markov model was developed based on the results of previous studies. The primary aim of HCV infection treatment is to achieve sustained virologic response (SVR), which can significantly reduce the risk of progression to liver cirrhosis or hepatocellular carcinoma. Pegylated interferon plus ribavirin (PEG-RBV) was the standard of care in China before the introduction of direct-acting antivirals (DAAs) in 2017. Compared with the suboptimal efficacy and severe adverse events of PEG-RBV, DAAs have drastically decreased morbidity and mortality attributable to HCV infection. However, patients still have limited access to such treatments in China since several DAAs, such as asunaprevir, daclatasvir, sofosbuvir, sofosbuvir/ledipasvir, elbasvir/grazoprevir and sofosbuvir/velpatasvir (SOF/VEL), were not approved through priority review procedure until 2017. In addition, DAAs were more costly than traditional PEG-RBV therapy, and PEG-RBV was the only treatment on the national drug reimbursement list until the end of 2019.

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Transition probabilities
Since large-sample epidemiological research is rare in China, this study used transition probabilities from other countries. Transition probabilities were assumed comparable among the three genotypes. The probabilities of liver fibrosis progression between F0 and F4 states were derived from a meta-analysis using Markov maximum likelihood estimation. Patients in F4 state could progress to DC and HCC, and the respective probabilities were obtained from Dienstag et al. Only patients with DC and HCC would receive a liver transplant, and the corresponding probabilities were derived from Townsend et al. and Planas et al. After achieving SVR, patients in F4 state could progress to advanced liver disease but typically experience a lower risk than those who did not achieve SVR. The mortality rates associated with DC, HCC, LT and PLT were derived from the literature. Age-specific all-cause mortality rates were extracted from the life tables of the WHO member states. It was assumed that F0–F3 patients had the same mortality rates as the general population after achieving SVR. F4 patients achieving SVR and F0–F4 patients who did not achieve SVR had 1.4 and 2.37 times the background mortality, respectively. The mortality rates were not adjusted for patients older than 65 due to the significantly higher general mortality.

Cost inputs
The societal perspective was adopted in this study. All costs were converted to US$ using official exchange rates of 2018 (US$1=¥6.62) and inflated to 2018 prices using the China Consumer Price Index. All costs were listed in online supplemental table 1.

The direct medical costs consisted of the drug, monitoring and annual liver-related health state costs. Drug costs were regimen-specific, with different drug prices and treatment duration. Additionally, drug prices were obtained from a local database reporting the price of drugs in each province of China. Due to the societal perspective adopted, this study used the median prices of different provinces paid by patients only or by patients and payers together with drug reimbursement. According to the latest guidelines for HCV infection in China, patients should undergo genotyping and liver
fibrosis tests to assess the severity of liver disease before treatment, as well as routine surveillance to monitor the efficacy and safety of the cure during treatment. Routine surveillance was carried out every 3 months during treatment, including plasma HCV RNA, complete blood count and liver ultrasound, among others; the number of times patients were tested varied depending on the treatment duration. Based on local charges of tests and consultation with HCV experts, the costs of genotyping, liver fibrosis test and routine surveillance were set at US$63, US$21 and US$302, respectively. Annual liver-related health state costs associated with F0–F4, DC and HCC were obtained from a study addressing the main hospitals in eight cities in Mainland China. For LT and PLT, costs were derived from a disease burden study for Chinese liver transplant patients. Patients in F0–F3 states with SVR would not incur direct medical costs any more, and patients in F4 state with SVR need less health resource utilisation, 0.709 times of those in F4 state without SVR.41

Due to limited research on direct non-medical and indirect costs of patients with HCV in China, data on these aspects were obtained from a patient survey conducted in Tianjin for centralised and standardised patient management. Adult patients with HCV receiving PEG-RBV or DAAs in the past few years were invited by telephone to participate in the survey. A total of 155 patients receiving PEG-RBV and 145 patients receiving DAAs were investigated in 2018–2019. Based on the characteristics of the HCV treatment, the direct non-medical costs were the transportation and nutrition costs of patients and their family members, and the indirect costs were the productivity loss of patients and their family members. The human capital approach was used to calculate the productivity loss based on working time lost and the per capita disposable income of China in 2018. Combined with treatment duration, the direct non-medical costs and indirect costs were calculated for each regimen.

Utility inputs
Utility inputs consisted of three parts, as shown in online supplemental table 1. Since Chinese utility values were not available, this study used data from the international literature. Utility values of chronic HCV states were derived from systematic reviews of the quality of life of patients with HCV. Patients would experience a utility decrease during treatment due to treatment-related adverse events, with utility decreasing by 0.11 under PEG-RBV and by 0.03 under DAAs treatment. Utility values after achieving SVR for F0–F4 states were obtained from Wright et al.5

Model analysis
The proposed model was developed in Microsoft Excel 2016 software (Microsoft). The future costs and QALYs were discounted at an annual rate of 5%. The willingness-to-pay was set at US$9,769/QALY adopting the threshold of one time the GDP per capita of 2018 in China. Lifetime costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) were illustrated as efficiency frontiers.

One-way sensitivity analysis was conducted to assess the influence of changes in individual parameters on the model results. The costs, SVR, transition probabilities, utilities and discount rate were tested under the range defined in the inputs table. The 95% CI of each parameter was used as the lower and upper values for the one-way sensitivity analysis. In case, the 95% CI was not available, the parameter varied by ±25%. In addition, the discount rate ranged between 0% and 8%. The results were shown as tornado diagrams.

Monte Carlo simulation was performed in probabilistic sensitivity analysis to test the robustness of the model results when all parameters varied simultaneously. A total of 1000 Monte Carlo iterations were run by repeatedly sampling from the distributions assigned to all the uncertain parameters (gamma distribution for costs, and beta or uniform distribution for SVR, utilities and transition probabilities). The results were shown as cost-effectiveness acceptability curves, which reflected the probabilities of the treatment regimens being cost-effective at different willingness-to-pay thresholds.

Additionally, threshold analysis was performed to improve affordability for patients. Keeping all the other parameters constant, the study estimated the threshold price, where the treatment regimen showed equal economic efficiency compared with the optimal DAA regimen for each genotype.

Patient and public involvement
This study did not involve any direct patient and public involvement.

RESULTS
Base-case analysis
The base-case results were presented in table 1 and figure 2. For patients infected with HCV genotype 2, DAAs gained more QALYs compared with PEG-RBV but with higher costs. The efficiency frontier consisted of PEG-RBV and SOF/VEL. SOF-RBV and SOF-DCV were above the efficiency frontier due to lower effectiveness or higher costs. The ICERs of SOF/VEL, SOF-RBV and SOF-DCV versus PEG-RBV were US$5,553, US$7,999 and US$10,680/QALY, respectively. SOF/VEL was the most cost-effective regimen and reduced the greatest cumulative probabilities of DC and HCC by 4.29% and 3.22%, respectively. The results were similar for genotype 3. SOF-DCV was the most cost-effective regimen, with the ICER of US$3314/QALY, which reduced the cumulative probabilities of DC and HCC by 8.09% and 6.26%, respectively. Three DAA regimens for genotype 6 were cost-saving; SOF-RBV was the most cost-saving approach due to its outstanding health benefits.

Sensitivity analysis
In one-way sensitivity analysis, the most cost-effective regimen compared with PEG-RBV was analysed for each
The tornado diagrams of the 10 most sensitive parameters were shown in figure 3. The ICERs were most sensitive to the utility of patients in F0–F3 states after achieving SVR, while the other factors, including the discount rate, drug costs, and SVR, were slightly different. For genotypes 2 and 3, the adjustment of some parameters, such as the discount rate, could make the optimal regimen no longer cost-effective. For genotype 6, changes in the parameters had no fundamental influence on base-case results.

The probability sensitivity analysis also used the most cost-effective regimen for comparison. The cost-effectiveness acceptability curves showed that under a threshold of US$9769/QALY, the probability of SOF/VEL and SOF/DCV being cost-effective was 58%, 83% and 71% for genotypes 2, 3 and 6, respectively, as shown in figure 4. If the threshold was increased to three times the Chinese GDP per capita (US$29,307), the corresponding probability would increase to 86%, 93% and 72%, respectively.

Threshold analysis
We chose the optimal DAA regimen for comparison in threshold analysis for each genotype. For genotype 2, the price reduction needed for sofosbuvir and daclatasvir to achieve the same economic efficiency as the optimal regimen SOF/VEL was 8% and 41%, respectively. To achieve cost-saving for all regimens for genotype 2, sofosbuvir, daclatasvir and SOF/VEL need a price reduction of 28%, 63% and 25%, respectively. For genotype 3, the price reduction of sofosbuvir and SOF/VEL should be 31% and 10%, respectively, compared with the optimal regimen SOF/DCV. To achieve further cost-saving, sofosbuvir and SOF/VEL need to cut price by 45% and 25%, respectively. Since all regimens for genotype 6 were cost-saving, sofosbuvir, daclatasvir and SOF/VEL need to reduce their price by 31%, 31% and 20% to achieve the same economic efficiency as SOF-RBV. The threshold analysis results were reported in table 2.

DISCUSSION
Few studies investigated the cost-effectiveness of treatment regimens for patients infected with non-genotype 1 HCV, especially genotype 6, in China.47 48 This study assessed the cost-effectiveness of all available DAs and PEG-RBV for patients infected with genotypes 2, 3 and 6 in China. Base-case results demonstrated that SOF/VEL and SOF/DCV were more cost-effective than PEG-RBV, while the ICER of SOF-DCV exceeded the willingness-to-pay threshold for genotype 2. For genotype 3, SOF-DCV and SOF/VEL were more cost-effective than PEG-RBV, while SOF-RBV was not cost-effective. SOF-RBV, SOF/VEL and SOF-DCV were all economically dominant relative to PEG-RBV for genotype 6, as the treatment duration of genotypes 2 and 3 with PEG-RBV was only half that of genotype 6. Sensitivity analysis demonstrated that the base-case results were robust. More importantly, the prices of DAA drugs need to be reduced by a range of 8%–63% compared with the most cost-effective DAA regimen for each genotype.

Several cost-effectiveness analyses have been conducted in China. However, most studies focused on patients infected with genotype 1 HCV.11 39 49 Among these
studies, Chen H et al\(^4\) and Chen GF et al\(^3\) compared DAAs with PEG-RBV for genotype 1; however, their results might have potential limitations in the Chinese setting because information on drug costs was obtained from other countries (DAAs were not available in China at that time). Another study evaluated the pan-genotypic SOF/VEL with other DAAs, indicating that a lower price of SOF/VEL would make it more cost-effective; however, the generality of this study’s findings was limited because only genotype 1 was considered.\(^14\) Wu et al are the only researchers who evaluated the cost-effectiveness of SOF-RBV and SOF-DCV for Chinese patients with non-genotype 1, showing that SOF-RBV was a cost-effective alternative for genotypes 2 and 3 and a cost-saving alternative for genotype 6 relative to PEG-RBV.\(^14\) However, the pan-genotypic SOF/VEL, which simplified the treatment, was not included in their study. To the authors’ knowledge, no cost-effectiveness study included all available DAAs for the treatment of patients with non-genotype 1 in China. Hence, this study is likely to represent the first economic evaluation in this field.

The societal perspective was adopted in several studies mainly conducted in the USA. Two American studies compared the cost-effectiveness of DAAs, DAAs plus PEG-RBV and PEG-RBV using a similar Markov model.\(^5\)\(^2\) The results showed that SOF-based treatment was cost-effective, while affordability was to be considered. However, only drug-related and liver-disease-related costs were included, and only patients with genotype 1 were addressed. Another study estimating DAA regimens with PEG-RBV indicated that the novel treatments were cost-effective compared with standard care for genotype 1 and probably genotype 3 but not for patients with genotype 2 in the American setting.\(^2\)\(^5\) Similarly, only direct medical costs were included, while indirect costs due to productivity loss or non-medical costs were not calculated. When the costs of absenteeism, presenteeism and patient/
caregiver time were included, the DAAs were found to be cost-saving relative to no treatment in another American study.\textsuperscript{32} SOF-RBV was cost-effective relative to PEG-RBV in patients with genotype 2, considering costs of the productivity loss in the Japanese scenario,\textsuperscript{36} in line with our results.

DAAs offer more effective, shorter and better-tolerated treatment options for patients; hence, a comparison among DAAs is needed. When compared with the optimal DAA regimen for each genotype, other DAAs need a price reduction to achieve equal economic efficiency. Since the use of SOF/VEL creates an opportunity to simplify the care pathway by removing the need for genotyping, extra direct non-medical costs such as transportation costs can be saved.\textsuperscript{49} This aspect is of particular significance for primary healthcare institutions, where genotyping tests cannot be accessed to manage patients with HCV. In this study, SOF/VEL was found to be cost-effective for all genotypes, while it needed a price reduction of 10% and 20% compared with SOF-DCV in genotype 2 and SOF-RBV in genotype 6, respectively.

The present analysis has several limitations. First, some SVR rates were derived from separate clinical trials due to the scarcity of head-to-head trials comparing those treatment regimens, which may result in biased results. Second, transition probabilities were derived from international research in the absence of domestic information sources. Future studies should update the analysis when these data are available in China. Third, utility values from other countries were assigned to health states due to the unavailability of Chinese-specific utility data, which may affect the accuracy of our results. In addition, the sample size of our patient survey needs to be increased to improve the generality of direct non-medical costs and indirect costs. Finally, our results may differ from the final discounted prices after price negotiation in 2019 as the drug costs were obtained from market prices, and some newly approved regimens, such

Figure 4 Cost-effectiveness acceptability curve in three genotypes. GDP, gross domestic product; PEG-RBV, pegylated interferon plus ribavirin; QALY, quality-adjusted life year; SOF-DCV, sofosbuvir plus daclatasvir; SOF-RBV, sofosbuvir plus ribavirin; SOF/VEL, sofosbuvir/velpatasvir.

| Genotype | Comparator | DAA drugs          | Threshold price (US$) | Price reduction (%) |
|----------|------------|--------------------|-----------------------|---------------------|
| Genotype 2 | SOF/VEL   | Sofosbuvir        | 2723                  | 8                   |
|          |            | Daclatasvir        | 391                   | 41                  |
|          |            | To be cost-saving | Sofosbuvir            | 2127                | 28           |
|          |            |                    | Daclatasvir            | 247                 | 63           |
|          |            |                    | Sofosbuvir/velpatasvir| 2622                | 25           |
| Genotype 3 | SOF-DCV   | Sofosbuvir        | 2055                  | 31                  |
|          |            | Sofosbuvir/velpatasvir | 3141              | 10                  |
|          |            | To be cost-saving | Sofosbuvir            | 1642                | 45           |
|          |            |                    | Sofosbuvir/velpatasvir| 2613                | 25           |
| Genotype 6 | SOF-RBV   | Sofosbuvir        | 2056                  | 31                  |
|          |            | Daclatasvir        | 457                   | 31                  |
|          |            | Sofosbuvir/velpatasvir | 2798              | 20                  |

DAA, direct-acting antiviral; SOF-DCV, sofosbuvir plus daclatasvir; SOF-RBV, sofosbuvir plus ribavirin; SOF/VEL, sofosbuvir/velpatasvir.
as glecaprevir/pibrentasvir, should be considered in the future.

CONCLUSION

DAAs were cost-effective compared with traditional treatments for Chinese patients with non-genotype 1 HCV, but the ICERs of DAAs were different. To globally eradicate viral hepatitis by 2030, DAAs’ prices need to be reduced by some degree to improve economic efficiency and increase the affordability of these drugs, especially in developing countries.

Contributors L-Y contributed to the design, acquisition and interpretation of the data and revisions, X-W contributed to the modelling and drafting the manuscript and J-Z polished the manuscript.

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Patient consent for publication Not required.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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