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Cost-effectiveness analysis of sofosbuvir plus ribavirin in patients with genotype 2 chronic hepatitis C: an analysis with real world outcomes from a multicentre cohort in Japan

Ataru Igarashi,[1,2] Norihiro Furusyo,[3] Eiichi Ogawa,[3] Hideyuki Nomura,[4] Kazufumi Dohmen,[5] Nobuhiko Higashi,[6] Kazuhiro Takahashi,[7] Akira Kawano,[8] Koichi Azuma,[9] Takeaki Satoh,[10] Makoto Nakamuta,[11] Toshimasa Koyanagi,[12] Masaki Kato,[13] Shinji Shimoda,[14] Eiji Kajiwara,[15] Jun Hayashi[16]

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For numbered affiliations see end of article.

Correspondence to
Dr Ataru Igarashi;
atarui1@mac.com

ABSTRACT

Objectives A number of publications have demonstrated the cost-effectiveness of sofosbuvir plus ribavirin (SOF+RBV) compared with the former standard therapy with interferon (IFN)-containing regimens. Unlike these cost-effective analyses, where efficacy parameters were obtained from registration trials for drug approval, this analysis is a cost-effectiveness analysis of SOF+RBV for genotype (GT) 2 non-cirrhosis (NC) and compensated cirrhosis (CC) patients using efficacy parameters obtained from a multicentre cohort study (Kyushu University Liver Disease Study; KULDS) in Kyushu area in Japan in order to reflect real-world clinical practice in Japan.

Method A Markov model followed 10 000 patients (62 years old) over their lifetime. Four populations were followed: treatment-naïve (TN)-NC, treatment-experienced (TE)-NC, TN-CC and TE-CC. Comparators were Peg-IFNα2b+RBV for TN-NC and CC patients and telaprevir (TVR)+Peg-IFNα2b+RBV for TE-NC patients. The sustained virological response (SVR) rates of SOF+RBV were taken from KULDS and those of comparators were obtained from systematic literature reviews. There were nine states (NC, CC, decompensated cirrhosis [DC], hepatocellular carcinoma [HCC], SVR [NC], SVR [CC], liver transplantation [LT], post-LT and death) in this model, and an increase in the progression rate to HCC due to ageing was also considered. The analysis was conducted from the perspective of a public healthcare payer, and a discount rate of 2% was set for both cost and effectiveness.

Results Incremental cost-effectiveness ratios (ICERs) of SOF+RBV versus Peg-IFNα2b+RBV were ¥323 928 / quality-adjusted life year (QALY) for TN-NC patients, ¥92 256/QALY for TN-CC patients and ¥1 519 202/QALY for TE-CC patients. The ICER of SOF+RBV versus TVR+Peg-IFNα2b+RBV was ¥849 138/QALY for TE-NC patients. The robustness of the results was determined by sensitivity analysis.

Conclusions The results of this analysis strongly demonstrate the robustness of our previous findings that SOF+RBV regimens are cost-effective in the real world and clinical trial settings for Japanese GT2 NC and CC patients.

Strengths and limitations of this study

- ► Cost-effectiveness of sofosbuvir plus ribavirin (SOF+RBV) was evaluated in Japanese clinical practice (Initial age: 62 years old).
- ► The sustained virological response of SOF+RBV was obtained from a multicentre cohort study (Kyushu University Liver Disease Study) in Japan.
- ► In addition to cost-effectiveness evaluation, health outcomes (the number of patients that avoided decompensated cirrhosis or hepatocellular carcinoma (HCC) were evaluated.
- ► Study limitation includes the use of assumptions in the setting of the age-related increase in the progression rate to HCC although sensitivity analysis showed that the impact of the adjustment of the progression rate to HCC was small.

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) leads to progression of liver fibrosis, which is life-threatening. Sibley *et al* reported that the number of newly HCV infected patients in 2014, based on expert consensus, was 3300, and that 1.014 million patients suffered from HCV infection in Japan. The proportion of genotype (GT) 2 in Japan is approximately 34%, thus the number of patients was estimated to be 345 000 in 2014.[1]

Sofosbuvir (SOF) 400 mg is an oral, interferon (IFN)-free direct-acting antiviral, and launched in May 2015 for the treatment of patients with chronic GT2 HCV infection as a drug administered with ribavirin (RBV) in Japan.[2] SOF is the first antiviral drug in the world with an inhibiting effect on nucleic acid type HCV non-structural protein 5B polymerase which has polymerase activity for

RNA replication of viruses.[2] In a phase III trial in Japan, sustained virological response (SVR), defined as the absence of quantifiable HCV RNA in serum (<25 IU/mL), at 12 weeks after the end of therapy (SVR12) was 97% for all GT2 chronic hepatitis non-cirrhotic (NC) patients, 98% for treatment-naïve (TN) patients and 96% for treatment-experienced (TE) patients. In liver cirrhosis (CC) patients, SVR12 was 94% for all patients, 100% for TN patients and 89% for TE patients; in brief, high SVR and efficacy were reported.[3]

In Japan, the pilot introduction of economic evaluation was started in April 2016 and incorporated into the medical policy,[4] thus the attention to cost-effectiveness of medical technologies has increased. Although Igarashi *et al* reported a cost-effectiveness analysis (CEA) of SOF+RBV for GT2 Japanese patients using the clinical efficacy SVR rate,[5] obtained from registration trials for drug approval, the clinical question remains whether these results reflect clinical practice. To address this clinical question, this CEA was conducted using demographic and efficacy parameters from a real-world large cohort study, the Kyushu University Liver Disease Study (KULDS),[6] a study led by Kyushu University founded in 2004 to conduct a multicentre large cohort study of chronic hepatitis, in line with the methodological guideline for cost-effectiveness evaluation by the Japanese health authority, the Ministry of Health, Labour and Welfare (MHLW)[4 7] for health technology assessment. An analysis using efficacy data evaluated in the phase III trial[8] was also conducted; however, in this article, the former analysis is reported and results based on the phase III trial is shown in the Appendices.

METHOD

Overview

This analysis was conducted in line with the methodological guideline for cost-effectiveness evaluation by MHLW.[4 7] Comparators were chosen based on the recommendations in the methodological guideline in order to reflect changes in clinical practice when SOF was introduced. Comparators in this analysis were examined by taking into account changes in the first-line treatment in the Japanese Society of Hepatology Guidelines for the Management of Hepatitis C Virus Infection before and after SOF introduction.[9 10] In the treatment guideline before SOF was on the market, treatment by an HCV RNA viral load is recommended. For GT2 NC patients with a high viral load, Peg-IFNα2b+RBV was recommended as the first-line therapy for TN patients. For TN-NC patients with a low viral load, Peg-IFNα2a without RBV for 24–48 weeks or conventional IFN monotherapy for 24 weeks was recommended. The proportion of patients with a high viral load is higher in clinical trials in Japan,[11–14] therefore, Peg-IFNα2b+RBV was set as the comparator for TN-NC patients. For TE-NC patients with GT2, the first-line therapy was telaprevir (TVR)+Peg-IFNα2b+RBV. Thus, TVR+Peg-IFNα2b+RBV was set as the comparator for those patients. For CC patients, the first-line therapy before SOF was on the market was Peg-IFN+RBV for both TN and TE patients. Both Peg-IFNα2a+RBV and Peg-IFNα2b+RBV show indications for CC, but the used amount of Peg-IFNα2b+RBV, estimated by the amount of sales, is larger. Therefore, Peg-IFNα2b+RBV was selected as the comparator for both TN and TE patients.

The analysis was conducted from the perspective of public healthcare payers, and quality-adjusted life year (QALY) and life year (LY) were used as economic outcomes. The number of cases that avoided decompensated cirrhosis (DC) or hepatocellular carcinoma (HCC) was used for the health outcome. A discount rate of 2% was set, and lifetime simulation (up to 105 years old) was conducted.

Model structure

A Markov model based on a model evaluated by the National Institute of Health and Care Excellence was developed to evaluate the cost-effectiveness of SOF+RBV (figure 1). Patients start antiviral therapy at the NC or CC state and move forward to the SVR health state ('SVR [NC]' or 'SVR [CC]') after 24 weeks from the end of treatment. Patients who failed to achieve SVR are sent back to the 'NC' or 'CC' state, and progress to advanced liver disease stages: DC, HCC, liver transplant (LT), 'post-LT' and 'death'. The model also included a small risk of progression for patients with SVR (CC) to HCC and DC. Transition probabilities were extracted from the literature and natural mortality[15] from every state was also considered.

Initial age was set 62 years old based on the median age in KULDS.[6] To consider the treatment period and SVR evaluation period in each treatment regimen, the cycle length was set at 3 months from the start of analysis. After 2 years, cycle length was set at 1 year. Parameters used for the analysis prioritised Japanese evidence[4 7]

Clinical evidence—efficacy (SVR)

The SVR of SOF+RBV in patients aged 65 years or older was obtained from the KULDS report.[6] SVR rates of the comparators were obtained from the results of a systematic literature review (SLR). The target population of the SLR was patients aged 18 or older with GT2 HCV infection. Target treatments were SOF+RBV and the comparators, Peg-IFNα2b+RBV, Peg-IFNα2a and TVR+Peg-IFNα2b+RBV. Eligibility criteria and exclusion criteria for the SLR are summarised in online supplementary appendix 1.

We did not take the tolerability of treatments into account for several reasons; (1) no information is available for the timing of treatment interruption, (2) it could be conservative for SOF/RBV arms as more patients would have to quit treatment in Peg-IFN arms than in SOF/RBV arms.

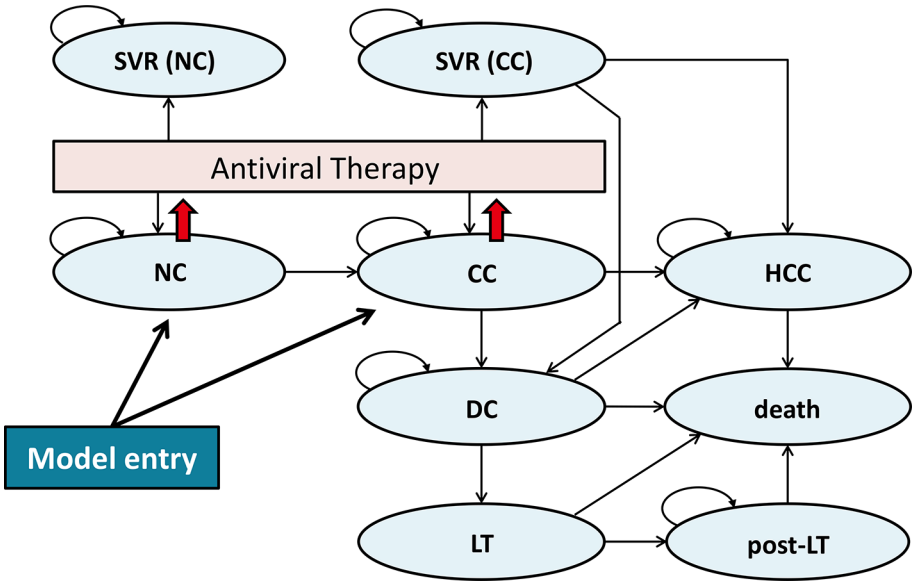

Figure 1 Model structure. CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; NC, non- cirrhosis; SVR, sustained virological response.

Model inputs

Transition probabilities

Relevant transition probabilities after antiviral therapy were extracted from a natural history model for HCV in Japan by Ishida *et al*,[16] which was developed as part of long-term research on economic evaluation of viral hepatitis control and prevention funded by the Health Labour Sciences Research Grant. The transition probabilities that were not reported by Ishida *et al*, eg, CC to HCC, were set by either Tanaka *et al*,[17] which contained data corresponding with the initial age of this analysis, or Cardoso *et al*,[18] which was used in a previous study on CEA in Japan.[5]

Several studies have reported a risk increase for HCC with age.[19–26] Although transition probabilities to HCC used in this analysis were targeted to patients aged 60–69 years, it was expected that the probabilities increase with the patients' ageing in a lifetime simulation. Thus, the transition probabilities related to the onset of HCC (NC-CC, CC-DC, CC-HCC, SVR(CC)-DC, SVR(CC)-HCC and DC-HCC) were adjusted by multiplying the base setting by 1.86 times in the all HCC-related transition probabilities after the age of 70 in this model.[19 27] The transition probabilities used in the analysis are listed in online supplementary appendix 2.

Costs

Monitoring costs during treatment, each health state and post-treatment hepatitis C (SVR achieved) were calculated using commercially available claims data (Japan Medical Data Center Co.) from January 2010 to December 2015. Those costs were defined by the disease, procedure and drugs described on claims data (online supplementary appendix 3). For each health state, medical costs were calculated as the sum of receipt scores of patients whose disease code met the defined definition. If patients could be followed-up for 12 months or shorter, medical costs in the follow-up period were assumed to be the annual medical cost. For patients followed-up for over 12 months, the average medical cost per month is multiplied by 12 for the annual medical cost. Medical costs lower than the fifth percentile and higher than the 95th percentile were excluded as outliers. The results are presented in online supplementary appendix 4. Drug costs were derived from the National Drug Tariff on April 2016[28] and calculated based on approved dosage.

Utility

Utilities related to each health state were obtained from a report by Sugimori *et al*[29] and Ishida and Yotsuyanagi,[30] in which Japanese utility values related to HCV health status were reported. Those studies were selected based on Section 8.4 in the Methodological guideline.[4 7]

Utilities during the treatment period of the target and comparator drugs were quoted from a previous CEA study by Leleu *et al*.[31]

Model outcomes

The incremental cost-effectiveness ratio (ICER) was calculated by dividing incremental costs by incremental QALYs or LYs between SOF+RBV and each comparator for each target population. In addition, an integrated ICER (¥/QALY), which derives from weighted-average incremental costs and weighted-average incremental QALYs by the proportion of each population in all GT2 patients, was calculated.

$$\text{Integrated ICER} = \frac{\sum_i (w_i \times \Delta cost_i)}{\sum_i (w_i \times \Delta QALY_i)}$$

where w is the proportion of each population, Δ costs is incremental cost, ΔQALY is incremental QALY and i represents a patient category considered in

the analysis, namely TN-NC: 61%, TE-NC: 9%, TN-CC: 26% and TE-CC: 4%, data on file. The numerator represents the total of incremental costs for all GT2 patients by choosing a SOF+RBV regimen over a comparator treatment regimen, whereas the denominator represents the total of incremental cost-effectiveness (in terms of QALY) for all GT2 patients. In Japan, the threshold for ICER, that is, the threshold to be judged as cost-effective, has not been clearly established. In this analysis, ICERs below the range of ¥5-6 million/QALY were evaluated to be cost-effective, according to reports describing the expected range of willingness-to-pay (WTP) in the Japanese general population.[32 33]

The number of cases that avoided DC or HCC was simulated for each treatment group, and proportion of cases avoided to DC or HCC for SOF+RBV compared with each comparator was calculated. The Number Needed to Treat (NNT) of SOF+RBV compared with each comparator was also calculated.

Sensitivity analysis

Both one-way sensitivity analysis (one-way SA) and probabilistic sensitivity analyses (PSA) were conducted to explore the uncertainty around model input parameters. The range for the SVR in one-way SA was set from phase III trials for each drug.[8 32–34] Basically, the range of each transition probability referred to the reported value by Ishida *et al*.[16] For variables whose range is not reported, it was set as ±25% of each variable.

In the PSA, beta distribution was applied to transition probabilities and utilities, and gamma distribution was applied to cost parameters. The setting values in the sensitivity analysis are listed in table 1 and online supplementary appendices 2, 4 and 5.

Model validation

We validated our simulation model using the cumulative number of HCC patients estimated from the annual incidence of HCC per 100 000 NC patients of the observational study by Omata and Yoshida (27 568–31 014 per 100 000 patients).[35] The estimated value in our model was 16 966–49 321 patients, and we evaluated it is within a reasonable range considering individual difference in disease progression.

Patient and public involvement

Patients and public were not involved in this study.

RESULTS

SLR

Seventy-two articles were extracted and the work process of the SLR is summarised in the flowchart recommended by the PRISMA statement (online supplementary appendix 6).

The SVR in Japanese patients aged 65 or older reported by Kainuma *et al*[36] was selected for Peg-IFNα2b+RBV. There was no report of the SVR in Japanese patients aged 65 or older for TVR+Peg-IFNα2b+RBV. Thus, the result of a phase III trial of TVR+Peg-IFNα2b+RBV evaluating TE-NC patients aged 60 or older was used.[34] Kainuma *et al* reported the SVR only in a population of mixed TN/TE-NC/CC patients. Thus, the SVR rates for the four target populations in Peg-IFNα2b+RBV were assumed to be the same (table 1).

Base-case analysis

The results of base-case analysis are reported in table 2. ICERs were ¥323 928/QALY for TN-NC patients, ¥92 256/QALY for TN-CC patients and ¥1 519 202/QALY for TE-CC patients in the analysis using Peg-IFNα2b+RBV as the comparator. As for TVR+Peg-IFNα2b+RBV, the ICER was ¥849 138/QALY for TE patients with NC. In all populations examined, the ICER did not exceed hypothetical threshold, or ¥5-6 million/QALY.

The number of patients that progressed to DC or HCC of SOF+RBV and comparators in each population is shown in figure 2. The proportion of cases avoided to both DC and HCC was 93.6% for SOF+RBV compared with Peg-IFNα2b+RBV in TN-NC patients, and 75.9% for SOF+RBV compared with TVR+Peg-IFNα2b+RBV in TE-NC patients. The proportion of cases avoided to DC

Table 1 Sustained virological response

Drug	NC/CC	TN/TE	SVR rate	Range*	Distribution	Reference
SOF+RBV	NC	TN	97.8%	97.6%–97.8%	Beta(89.08,2.00)	6
		TE	95.7%	95.7%–96.3%	Beta(45.43,2.04)	
	CC	TN	100%	–	–	
		TE	80.0%	80.0%–88.9%	Beta(20.00,5.00)	
Peg-IFNα2b+RBV	NC	TN	65.6%	65.6%–88.9%	Beta(40.00,20.98)	35
	CC	TN	65.6%	65.6%–85.7%	Beta(40.00,20.98)	
		TE	65.6%	65.6%–66.7%	Beta(40.00,20.98)	
TVR+Peg-IFNα2b+RBV	NC	TE	82.1%	82.1%–84.7%	Beta(46.06,10.04)	34

CC, compensated cirrhosis; IFN, interferon; NC, non-cirrhosis; RBV, ribavirin; SOF, sofosbuvir; SVR, s ustained virological response; TE, treatment-experienced; TN, treatment-naïve; TVR, telaprevir.
*Range of SVR for each drug was set based on the phase III trial.

Table 2 Results of base-case analysis

NC/CC	TN/TE	Drug	Total costs (¥)	Δ costs (¥)	LY	Δ LY	QALY	Δ QALY	ICER (cost/LY)	ICER (cost/QALY)
NC	TN	Peg-IFNα2b+RBV	4 439 479	–	18.140	–	15.026	–	–	–
		SOF+RBV	4 868 269	428 790	19.083	0.943	16.349	1.324	454 618	323 928
	TE	TVR+Peg-IFNα2b+RBV	4 498 788	–	18.624	–	15.676	–	–	–
		SOF+RBV	4 999 315	500 527	19.020	0.396	16.266	0.589	1 262 428	849 138
CC	TN	Peg-IFNα2b+RBV	9 414 101	–	14.349	–	10.295	–	–	–
		SOF+RBV	9 556 876	142 775	15.899	1.550	11.842	1.548	92 137	92 256
	TE	Peg-IFNα2b+RBV	9 414 101	–	14.349	–	10.295	–	–	–
		SOF+RBV	10 338 928	924 827	14.839	0.490	10.903	0.609	1 887 694	1 519 202

CC, compensated cirrhosis; ICER, incremental cost-effectiveness ratio; IFN, interferon; LY, life year; NC, non-cirrhosis; QALY, quality-adjusted life year; RBV, r ibavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; TVR, telaprevir.

or HCC for SOF+RBV compared with Peg-IFNα2b+RBV were 37.7% and 12.1% for TN-CC patients, and the rates were 15.2% and 4.6% for TE-CC patients. The NNT of SOF+RBV to avoid one DC or HCC progression in TN-NC patients were estimated as 11.3 (100 000/8811) and 6.3 (10 000/15 877), respectively, and those in TE-NC patients were estimated as 26.9 (100 000/3717) and 14.9 (100 000/6698), respectively. Similarly, the NNT to avoid one DC or HCC progression in TN-CC and TE-CC patients were estimated as 11.6 (100 000/8639) and 28.6 (100 000/3493) in DC and 14.7 (100 000/6784) and 39.0 (100 000/2567) in HCC.

Figure 2 Summary of health outcome. CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; IFN, interferon; NC, non- cirrhosis; RBV, ribavirin; SOF, sofosbuvir; TE, treatment-experienced; TN, treatment-naïve; TVR, telaprevir.

For all GT2 patients, the integrated ICER (¥/QALY) was calculated using the proportion of each population in GT2 (TN-NC: 61%, TE-NC: 9%, TN-CC: 26%, TE-CC: 4%, data on file). The integrated ICER of SOF+RBV versus Peg-IFN+RBV was ¥270 000/QALY for all GT2 patients, and SOF+RBV was evaluated to be cost-effective for the overall GT2 patient population in Japan.[37 38]

Sensitivity analysis

There was no variable exceeding the range of ¥5-6 million/QALY within the setting range of the analysis (online supplementary appendix 7).

The probability of the ICER of SOF+RBV versus each comparator being below ¥5 million/QALY was 100% in TN-NC patients, 94.7% in TE-NC patients, 100% in TN-CC patients and 78.4% in TE-CC patients (online supplementary appendix 8).

DISCUSSION

This is the first analysis to evaluate the cost-effectiveness of SOF+RBV in GT2 NC and CC patients (median age 62 years old) using real world evidence. When analysing using the data of phase III trials, sensitivity analysis should be conducted to consider divergence from the real world setting because subjects in clinical trials might be biased by patient's selection criteria and limits on the number of cases. In this analysis, those uncertainties of data were expected to be reduced by using real world data obtained in KULDS, and we are convinced that this robust analysis could contribute for Japanese policymaking. Our analysis showed that SOF+RBV was evaluated as cost-effective in any of the target populations, and the integrated ICER of SOF+RBV versus Peg-IFNα2b+RBV, weighted by the proportion of each population, was estimated as ¥270 000/QALY for all GT2 patients and ¥850 000/QALY for all TE-GT2 patients. The robustness of these results was confirmed by sensitivity analyses.

Igarashi *et al* conducted a CEA on GT2 HCV patients in Japan.[5] Their model structures and analysis conditions were similar with this analysis; however, there are some differences in the target population classification, comparators and clinical evidence used for the SVR. Although the results of these analyses cannot be directly compared, SOF+RBV was evaluated to be cost-effective in both analyses. In addition, as the analysis based on the result of the phase III study of the SVR of each drug showed similar results (online supplementary appendices 9, 10), it was suggested that SOF+RBV was cost-effective regardless of the age at treatment initiation.

Although the productivity loss of the target patients was not considered in this analysis, chronic infection with HCV leads to disease progression to DC and HCC and productivity loss in patients themselves and their caregivers. From the results of a questionnaire survey on productivity loss in approximately 5000 patients, Sato estimated that the annual productivity losses of a patient aged 65 years old with DC or HCC was approximately ¥1.9-million and ¥1.6-2.3 million, respectively.[39] SOF+RBV treatment is expected to mitigate this economic impact.

There were a few limitations to this analysis. First, populations whose SVRs were used in this analysis were not entirely matched to target populations. Although four target populations were set, reflecting subgroups of treatment guidelines, the SVR of Peg-IFNα2b+RBV was not distinguished between TN-NC, TN-CC and TE-CC. Therefore, the same rate of the SVR was used for each population. As for TVR+Peg-IFNα2b+RBV, there was no SVR data in patients aged 65 years or older. Thus, SVR data in populations aged 60 years or older was used. The SLR conducted in this analysis suggested that data distinguished by target populations are still insufficient in clinical practice in Japan, compared with clinical trials which are pre-designed and high quality. More real-life cohort studies and data accumulation are necessary in Japan. Second, several assumptions were set in the model structure. Some studies reported that the incidence rate of HCC becomes higher with ageing, so progression rate to HCC was adjusted in this analytical model. However, there have been no reports about attribution of higher progression rates to HCC in each state. Therefore, all transition probabilities related to HCC incidence (NC-CC, CC-DC, CC-HCC, SVR[CC]-DC, SVR[CC]-HCC and DC-HCC) were adjusted by the same rate. It should be noted that sensitivity analysis of the adjustment of the progression rate to HCC showed that the impact was small. Third, it was not clear whether the proportion that used the estimation of the integrated ICER (¥/QALY) reflects clinical practice. The proportion used in this analysis was quoted from a survey for patients using SOF+RBV. Data on the proportion of each population in clinical practice is needed. Another limitation is that we could not conduct age-stratified analyses, since no data was available for SVR rates, classified by age. Given that age-dependent reduction of the SVR rate are only reported for the IFN, cost-effectiveness of SOF/RBV would possibly be better for aged population, further research should be conducted.

CONCLUSION

The results of the CEA showed that SOF+RBV was cost-effective compared with Peg-IFNα2b+RBV and TVR+Peg-IFNα2b+RBV among GT2 NC and CC patients in Japan. Based on the CEA, SOF+RBV yields the best overall health outcomes for all GT2 patients when compared with Peg-IFNα2b+RBV and TVR+Peg-IFNα2b+RBV. This analysis strongly demonstrates the robustness of our previous findings that SOF+RBV regimens are cost-effective in the real world and clinical trial settings for Japanese GT2 patients.

Author affiliations
[1]Department of Health Economics and Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Bunkyo, Tokyo, Japan
[2]Unit of Public Health and Preventive Medicine, Yokohama City University School of Medicine, Yokohama, Kanagawa, Japan

[3]Department of General Internal Medicine, Kyushu University Hospital, Fukuoka, Japan
[4]The Center for Liver Disease, Shin-Kokura Hospital, Kitakyushu, Japan
[5]Department of Internal Medicine, Chihaya Hospital, Fukuoka, Japan
[6]Department of Hepatology, Steel Memorial Yawata Hospital, Kitakyushu, Japan
[7]Department of Medicine, Hamanomachi Hospital, Fukuoka, Japan
[8]Department of Medicine, Kitakyushu Municipal Medical Center, Kitakyushu, Japan
[9]Department of Medicine, Kyushu Central Hospital, Fukuoka, Japan
[10]Center for Liver Disease, National Hospital Organization Kokura Medical Center, Kitakyushu, Japan
[11]Department of Gastroenterology, Kyushu Medical Center, National Hospital Organization, Fukuoka, Japan
[12]Department of Medicine, Fukuoka City Hospital, Fukuoka, Japan
[13]Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[14]Department of Medicine and Biosystemic Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[15]Kajiwara Clinic, Kitakyushu, Japan
[16]Kyushu General Internal Medicine Center, Haradoi Hospital, Fukuoka, Japan

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