

Regular Article*Highlighted Paper selected by Editor-in-Chief***Cost-Outcome Description of PEG-IFN- α 2b+RBV for Hepatitis C: Results Based on the Interferon Database**Maiko Akutagawa,^a Yohei Kawasaki,^{*a,b} Atsuko Kawasaki,^a Kazuki Ide,^{a,b} Hiroshi Yamada,^a and Naohiko Masaki^c

^aDepartment of Drug Evaluation & Informatics, Graduate School of Pharmaceutical Sciences, University of Shizuoka; 52-1 Yada, Suruga-ku, Shizuoka 422-8526, Japan; ^bDepartment of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University; Yoshida-konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan; and ^cLaboratory Testing Department, National Center for Global Health and Medicine; Tokyo 162-8655, Japan.

Received October 10, 2016; accepted February 7, 2017; advance publication released online February 15, 2017

Economic evaluation of drugs is used in decision-making on medical care and public policy. Recently, real-world data (RWD) have been used in the analysis. In this study, we discuss the risk and benefits of using RWD for economic evaluation. We conducted a cost-outcome description with RWD from a nationwide registry providing information on hepatitis treatment in Japan and estimated the utility of the analysis. We evaluated the cost-outcome description of peginterferon plus ribavirin (PEG-IFN- α 2b+RBV) treatment in hepatitis C virus (HCV)-infected patients. Simulations were based on a Markov model. The cohorts were set using data from the registry and we assumed a societal perspective for the calculation of costs. The dose and drug cost were chosen based on the Japanese Guidelines for the Management of Hepatitis C Virus Infection or package inserts. Model details and parameters were as described in previous studies. The simulations were performed for a period of 10 years with no discount rate. We estimated 2.5 million JPY per Quality Adjusted Life Year (QALY) in 48-week PEG-IFN- α 2b+RBV treatment for a period of 10 years. The results of this study are in agreement with previous HCV treatment economic evaluation studies in Japan. We analyzed the statistics of the HCV-infected patients at each disease stage using the data in our registry and calculated the costs. The results of this study more closely reflect a real-world clinical situation compared to the widely used randomized clinical trial method, which estimates clinical trial results and scenarios.

Key words economic evaluation; registry; real-world data; hepatitis c virus; peginterferon; ribavirin

Economic evaluation of drugs is used for decision-making on medical care and public policy mainly in Europe and America^{1,2)} and was introduced in Japan in a trial conducted in 2016.³⁾ A representative evaluation method is the simulation based on the results of randomized clinical trials (RCTs) or research papers.⁴⁾ However, there are differences between endpoints measured in cost-effectiveness analyses and clinical trials. The endpoints of cost-effectiveness studies require a comprehensive evaluation of the outcome in a broad sense, whereas the endpoints of a clinical trial refer to target outcomes of the trial.²⁾

This study focused on a patient registry with clinical real-world data (RWD) for conducting an economic evaluation. A patient registry can be defined as “an organized system that uses observational study methods to collect uniform data (clinical and other), to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.”⁵⁾ Using Real-World Data for Coverage and Payment Decisions: The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Real-World Data Task Force Report states: “While RCTs remain the gold standard for demonstrating clinical efficacy in restricted trial settings, other designs contribute to the evidence base. In some situations, RWD may provide clear advantage for understanding outcomes of treatment, for example, for patients excluded from trials, patients in actual clinical practice settings (vs. research settings), and patients whose treatment is not determined by trial protocol or practice guidelines.”⁶⁾

However, this report indicated selection bias as a limitation of RWD.⁶⁾ In addition, benefits of using a patient registry, as proposed by Dang and Angle,⁷⁾ are as follows: mergers with other databases, access to data of a large number of patients, which makes registries useful in analyzing rare diseases and orphan drugs, access to data collected over a long period of time, and access to information on how a drug or therapy is accepted in a real-world setting.⁸⁾

It could be hypothesized that RWD would be applicable for economic evaluation. Therefore, the aim of the present study was to perform a cost-outcome description using registry data. The patient registry used in this study was the hepatitis treatment registry of Japan. We analyzed the cost-outcome description of peginterferon plus ribavirin (PEG-IFN- α 2b+RBV) treatment in hepatitis C virus (HCV)-infected patients. Several treatment regimens are available for HCV, with different efficacy, onset of adverse events, and cost.⁹⁾

METHODS

Registry We set the cohorts for this analysis model using data from the hepatitis treatment registry of Japan. The data (38 prefectures included) were collected by The Hepatitis Information Center of the National Center for Global Health and Medicine (Chiba, Japan) from December 2009 to August 2015¹⁰⁾ and 25989 patients were registered. The registry recorded information on the patient background (e.g., prefecture, age, sex, and genotype) and treatment (e.g., date of treatment start/end, drugs, and treatment-related adverse events). The

* To whom correspondence should be addressed. e-mail: kawasaki.yohei.2r@kyoto-u.ac.jp

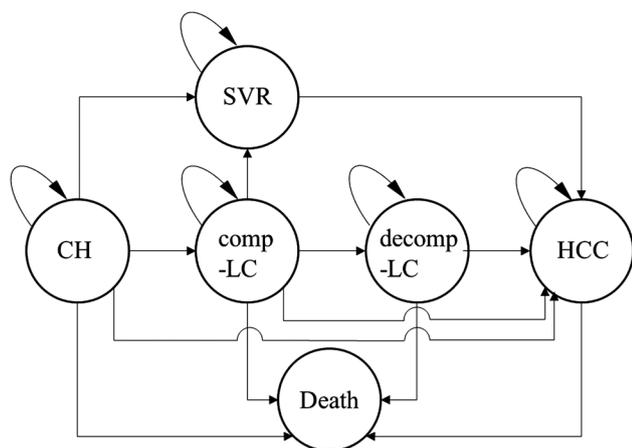


Fig. 1. Modeling the Natural History and Cost-Effectiveness of Hepatitis (MONARCH) Simulation Model

Table 1. Disease Transition Rates

Transition	Mean	Source
CH to comp-LC	0.065	Nakamura <i>et al.</i> ¹⁵⁾
CH to HCC	0.016	Nakamura <i>et al.</i> ¹⁵⁾
comp-LC to decomp-LC	0.021	Imazeki <i>et al.</i> ¹⁶⁾
comp-LC to HCC	0.043	Hayashida <i>et al.</i> ¹⁷⁾
decomp-LC to HCC	0.083	Nakamura <i>et al.</i> ¹⁵⁾
decomp-LC to death	0.153	Nakamura <i>et al.</i> ¹⁵⁾
HCC to death	0.200	Nakamura <i>et al.</i> ¹⁵⁾
comp-LC SVR to HCC	0.018	Arase <i>et al.</i> ¹⁸⁾
CH/comp-LC to SVR	0.080	Broglio <i>et al.</i> ¹⁹⁾

Table 2. Health State Costs and Utilities

Health state	Mean cost (¥)	Source	Mean utility	Source
SVR CH (first year only)	57224	McEwan <i>et al.</i> ¹³⁾	0.960	Ishida <i>et al.</i> ²⁰⁾
SVR comp-LC (first year only)	122873	McEwan <i>et al.</i> ¹³⁾	0.960	Ishida <i>et al.</i> ²⁰⁾
CH monitoring	119576	McEwan <i>et al.</i> ¹³⁾	0.920	Ishida <i>et al.</i> ²⁰⁾
CH care	97610	McEwan <i>et al.</i> ¹³⁾		
comp-LC monitoring	171090	McEwan <i>et al.</i> ¹³⁾	0.860	Okita ²¹⁾
comp-LC care	174177	McEwan <i>et al.</i> ¹³⁾		
decomp-LC	1561085	McEwan <i>et al.</i> ¹³⁾	0.670	Okita ²²⁾
HCC	2086469	Nakamura <i>et al.</i> ¹⁵⁾	0.380	Ishida <i>et al.</i> ²²⁾
Death	0	Assumed	0.000	Assumed

original study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan (#738; October 1, 2009).¹⁰⁾

The patient selection criteria of this study were HCV infection, genotype 1, and PEG-IFN- α 2b+RBV treatment.

Drug Treatment Costs We assumed a societal perspective for the calculation of costs. We calculated the drug treatment costs for PEG-IFN- α 2b+RBV using costs of drugs, the doses of drugs, and medical costs. Costs of drugs were based on Japanese medical fees. The doses were determined according to the Japanese Guidelines for the Management of Hepatitis C Virus Infection or package inserts. The following treatment scenario was considered: patient weight of 60kg (based on average weight of 67.7 and 51.2kg for 20-year-old Japanese men and women, respectively¹¹⁾) and duration of treatment of 48 weeks for chronic hepatitis (CH) or compensated cirrhosis of the liver (comp-LC). Medical costs were estimated according to McEwan *et al.*¹²⁾

Model and Parameters The simulation in this study used a Markov model. The model and parameters were based on the model described by McEwan *et al.*,^{12,13)} “modeling the natural history and cost-effectiveness of hepatitis” (MONARCH), defined as the standard method in the review of HCV cost-effectiveness studies (published in the period of 2000–2011).¹⁴⁾ In addition, Kamae *et al.*⁹⁾ suggested several points to consider when using the MONARCH model in Japanese patients. Firstly, liver transplantation is rarely performed in patients with decompensated cirrhosis (decomp-LC) in Japan; therefore, these cases should not be considered. However, cases of

Table 3. Demographics

		CH (n=7101)		comp-LC (n=270)	
		n	%	n	%
Treatment	First time	5407	77.07	172	64.18
	Retreatment	1609	22.93	96	35.82
	N/A	85		2	
Fibrosis	0	107	4.31	—	—
	1	1047	42.17	3	2.38
	2	790	31.82	6	4.76
	3	539	21.71	10	7.94
	4	—	—	107	84.92
	N/A	4618		144	

Note: When proportion is calculated, the denominator is the number of patients excluded N/A.

CH progressing to hepatocellular carcinoma (HCC) and comp-LC patients who achieve a sustained virological response (SVR) and progress to HCC in Japan should be considered. Additionally, CH disease stage (fibrosis) cannot be defined because of limited data on this disease in Japan. The analysis model is presented in Fig. 1. Utilities are described by Quality Adjusted Life Year (QALY). QALYs and transition probabilities are similar to previous HCV treatment economic evaluation studies in Japan^{15–22)} (Tables 1, 2).

The simulation was performed using the Tree Age Pro Healthcare 2016 v2.1 (Tree Age Software, Inc., Williamstown, MA, U.S.A.) for a period of 10 years with no discount rate.

Table 4. Drug Dose and Cost

		Drug ²⁴⁾	Duration	Cycle ^{25,26)}	Dose ^{25,26)}	Cost ²⁷⁾
PEG-IFN	CH	Pegintron	48 weeks	1 time/week	100 µg/0.5 mL	30607JPY/vial
	comp-LC				50 µg/0.5 mL	15924JPY/vial
RBV		Rebetol	48 weeks	everyday	3 capsules	580.10JPY/capsule

Scenario: weight=60 kg.

RESULTS

Registry We extracted registry data on 7371 patients (CH: 7101, comp-LC: 270) who met the required criteria and used these data in the model. The cohort demographics are presented in Table 3. The majority of the CH and comp-LC patients (77 and 64%, respectively) were seeking treatment for the first time. The most frequent stage of fibrosis was F1 for CH and F4 for comp-LC.

Drug Costs Drug dose and costs are presented in Table 4. We speculated that PEGINTRON[®] powder for injection is used as a PEG-IFN- α 2b drug and REBETOL[®] capsules 200mg as RBV based on the guidelines.²³⁾ The doses were as follows: PEGINTRON[®] powder for injection=1 vial/week (CH; 100 µg/0.5 mL, comp-LC; 50 µg/0.5 mL) (source: package insert (May 2015 revised)²⁴⁾); and REBETOL[®] capsules 200mg, 3 capsules/d (package insert (July 2016 revised)²⁵⁾). The drug costs were as follows: PEGINTRON[®] powder for injection 100 µg/0.5 mL=30607 JPY/vial, 50 µg/0.5 mL=15924 JPY/vial, REBETOL[®] capsules 200mg=580.1 JPY/capsule (Japanese medical fee in April 2016²⁶⁾). Drug costs for a treatment period of 48 weeks were 2053877 and 1349093 JPY for CH and comp-LC patients, respectively.

Cost-Outcome Description We estimated the PEG-IFN- α 2b+RBV 48-week treatment cost and effectiveness for a period of 10 years. The resulting cumulative cost was 16 million JPY with effectiveness of 6.42 QALY. Therefore, the cost per QALY was 2.5 million JPY. These results were obtained from the registry-based cohort.

DISCUSSION

We estimated the cost of PEG-IFN- α 2b+RBV treatment for HCV patients per QALY at 2.5 million JPY. This result is in agreement with previous HCV treatment economic evaluation studies in Japan. Teramukai *et al.*²⁷⁾ reported that incremental cost-effectiveness ratios (ICERs) of consensus interferon treatment and PEG-IFN- α 1 are 1.32 and 2.47 million JPY per QALY, respectively, compared to non-PEG-IFN treatment. Ishida *et al.*²²⁾ have shown that PEG-IFN- α 2b+RBV 24-week treatment prolonged survival for 1.6 QALY more and cost 12000 JPY less than PEG-IFN retreatment. The cohorts of previous studies did not reflect the statistics of HCV-infected patients at each disease stage. In this study, the statistics can be obtained from the registry and costs calculated at each disease stage, allowing results to reflect the real world setting in Japan. However, the genotype of patients in this registry differs from general Japanese population. The majority (70–80%) of Japanese CH patients are genotype 1,^{28–30)} compared to 56% of CH patients in this study. In our study, most genotype 2 or 3 patients had high viral RNA levels (CH: 91%, comp-LC: 85%). PEG-IFN- α 2a+RBV treatment is not recommended for

genotype 2 and patients with high viral RNA levels in Japan. Patients with these characteristics receive the treatment we analyzed, resulting in the observed lower proportion of genotype 1 patients in this study, compared to previous studies.

As a sensitivity analysis, considering a treatment scenario of patient weight >60 kg, the cost per QALY was 2.7 million JPY.

The future directions of our research include comparisons with other treatments, calculating ICER, and making use of other data contained in the registry.

CONCLUSION

This study analyzed the usefulness of patient registries for cost-outcome description analysis by estimating the cost and QALYs of PEG-IFN- α 2b+RBV treatment in HCV-infected patients. The results of this approach are in agreement with previous studies and offer an improved representation of the real-world clinical setting compared to the widely used method of estimating randomized clinical trial results and scenarios. This study shows that patient registry data can be effectively applied for cost-effectiveness analysis.

Acknowledgments This work was supported by a Grant-in-Aid from the Ministry of Health, Labour and Welfare of Japan (Research on Hepatitis: 2009–2014) and a Grant-in-Aid from the National Center for Global Health and Medicine (27A1301) to NM. The authors wish to thank Ms. Mikako Kajio and Ms. Asako Horiara for their technical assistance during data analysis. We would also like to acknowledge the great contributions of the 38 prefectural members and all the medical staff engaged in the long-term interferon treatment and data collection.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES

- 1) Igarashi A. Economic evaluation in medicines. *J. Natl. Inst. Public Heal.*, **62**, 605–612 (2013).
- 2) Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, Luce BR, ISPOR Task Force on Good Research Practices--Modeling Studies. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value Health*, **6**, 9–17 (2003).
- 3) Ministry of Health, Labour and Welfare. <<http://www.mhlw.go.jp/file/05-Shingikai-12404000-Hokenkyoku-Iryouka/0000044418.pdf>>, cited 2016-03-01.
- 4) National Institute for Health and Clinical Excellence. "The guidelines manual. 7.2 Modelling approaches." <<https://www.nice.org.uk/article/pmg6/chapter/7-assessing-cost-effectiveness#modelling>>

- approaches, cited 2016-03-01.
- 5) "Registries for Evaluating Patient Outcomes: A User's Guide: 3rd Edition - Research Report - Final | AHRQ Effective Health Care Program." <<http://www.effectivehealthcare.ahrq.gov/ehc/products/420/1897/registries-guide-3rd-edition-vol-1-140430.pdf>>, cited 2016-03-01.
 - 6) Garrison LP Jr, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: The ISPOR real-world data Task Force report. *Value Health*, **10**, 326–335 (2007).
 - 7) Dang A, Angle VS. Utilizing Patient Registries as Health Technology Assessment (HTA) tool. *Sys. Rev. Pharm.*, **6**, 5–8 (2015).
 - 8) Kennedy L, Craig A-M. Global registries for measuring pharmaco-economic and quality-of-life outcomes: focus on design and data collection, analysis and interpretation. *Pharmacoeconomics*, **22**, 551–568 (2004).
 - 9) Kamae I, Kumada H, Kobayashi M, Ward T, Webster S, Yuan Y, Kalsekar A, Inoue S, Tang A, McEwan P. Epidemiology, treatment and health economics of hepatitis C in Japan (Review). *Japan Soc. Hepatol.*, **55**, 589–603 (2014).
 - 10) Masaki N, Yamagiwa Y, Shimbo T, Murata K, Korenaga M, Kanto T, Mizokami M, prefectural members contributing to the Japanese Interferon Database. Regional disparities in interferon therapy for chronic hepatitis C in Japan: a nationwide retrospective cohort study. *BMC Public Health*, **15**, 566 (2015).
 - 11) Ministry of Health, Labour and Welfare. <<http://www.mhlw.go.jp/bunya/kenkou/eiyoudl/h25-houkoku-05.pdf>>, cited 2016-02-06.
 - 12) McEwan P, Ward T, Webster S, Yuan Y, Kalsekar A, Broglio K, Kamae I, Quintana M, Berry SM, Kobayashi M, Inoue S, Tang A, Kumada H. Kristine Broglio, Kamae I, Quintana M, Scott M, Kobayashi M, Inoue S, Tang A, Kumada H. Estimating the long-term clinical and economic outcomes of daclatasvir plus asunaprevir in difficult-to-treat Japanese patients chronically infected with hepatitis C genotype 1b. *Value Heal. Reg. Issues*, **3**, 136–145 (2014).
 - 13) McEwan P, Ward T, Webster S, Yuan Y, Kalsekar A, Kamae I, Kobayashi M, Tang A, Kumada H. Estimating the cost-effectiveness of daclatasvir plus asunaprevir in difficult to treat Japanese patients chronically infected with hepatitis C genotype 1b. *Hepatol. Res.*, **46**, 423–433 (2016).
 - 14) Townsend R, McEwan P, Kim R, Yuan Y. Structural frameworks and key model parameters in cost-effectiveness analyses for current and future treatments of chronic hepatitis C. *Value Health*, **14**, 1068–1077 (2011).
 - 15) Nakamura J, Terajima K, Aoyagi Y, Akazawa K. Cost-effectiveness of the national screening program for hepatitis C virus in the general population and the high-risk groups. *Tohoku J. Exp. Med.*, **215**, 33–42 (2008).
 - 16) Imazeki F, Yokosuka O, Fukai K, Kawai S, Kanda T, Kojima H, Saisho H. Lower incidence of hepatic failure than hepatocellular carcinoma in Japanese patients with chronic hepatitis C. *Liver Int.*, **25**, 772–778 (2005).
 - 17) Hayashida K, Nagasue I, Fukuda T, Gunji A. The natural history model of hepatitis C virus infection and the economic evaluation of alpha interferon treatment. *J. Epidemiol.*, **12**, 22–32 (2002).
 - 18) Arase Y, Kobayashi M, Suzuki F, Suzuki Y, Kawamura Y, Akuta N, Kobayashi M, Sezaki H, Saito S, Hosaka T, Ikeda K, Kumada H, Kobayashi T. Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. *Hepatology*, **57**, 964–973 (2013).
 - 19) Broglio KR, Daar ES, Quintana M, Yuan Y, Kalsekar A, Spellberg B, Lewis RJ, van den Akker D, Detry MA, Le T, Berry SM. A meta-analysis platform methodology for determining the comparative effectiveness of antihepatitis C virus regimens. *J. Comp. Eff. Res.*, **4**, 101–114 (2015).
 - 20) Ishida H, Terai S, Sakaida I, Inoue Y. Cost-effectiveness of telaprevir with peginterferon and ribavirin for treatment-naïve patients chronically infected with HCV of genotype 1 in Japan. *Value Health*, **15**, A328 (2012).
 - 21) Okita K. *Cost Effectiveness of Hepatocellular Carcinoma Treatment by Disease Stage: Life Expectancy and Cost-Effectiveness of Single Tumor by Markov Model: Report of MHLW Urgent Measures Against Hepatitis Research Grant*. Ministry of Health, Labour and Welfare, Tokyo, Japan (2007).
 - 22) Ishida H, Inoue Y, Wong JB, Okita K. Cost-effectiveness of ribavirin plus interferon alpha-2b for either interferon relapsers or non-responders in chronic hepatitis C: a Japanese trial. *Hepatol. Res.*, **28**, 125–136 (2004).
 - 23) Drafting Committee for Hepatitis Management Guidelines, the JS of H. JSH guidelines for the management of hepatitis C virus infection: A 2014 update for genotype 1. *Hepatol. Res.*, **44** (Suppl. S1), 59–70 (2014).
 - 24) Package insert (PEGINTRON® Powder for Injection). <<http://database.japic.or.jp/pdf/newPINS/00050436.pdf>>, cited 2016-10-21.
 - 25) Package insert (REBETOL® Capsules 200mg). <<http://database.japic.or.jp/pdf/newPINS/00048359.pdf>>, cited 2016-10-21.
 - 26) "Ministry of Health, Labour and Welfare." <<http://www.mhlw.go.jp/topics/2016/04/tp20160401-01.html>>, cited 2016-10-21.
 - 27) Teramukai S, Ishida H, Inoue Y. Cost-effectiveness of interferon acon-1 (Consensus Interferon) in chronic hepatitis C patients with genotype 1b and high-titer in Japan. *Jpn. J. Pharmacoepidemiol.*, **7**, 1–11 (2002).
 - 28) Shiratori Y, Kato N, Yoshida H, Nakata R, Ihori M, Imazeki F, Yokosuka O, Kawase T, Katamoto T, Unuma T, Nakamura A, Ikegami F, Hirota K, Omata M. Sustained viral response is rarely achieved in patients with high viral load of HCV RNA by excessive interferon therapy. *Dig. Dis. Sci.*, **45**, 565–574 (2000).
 - 29) Yoshizawa K, Ota M, Saito S, Maruyama A, Yamaura T, Rokuhara A, Orii K, Ichijo T, Matsumoto A, Tanaka E, Kiyosawa K. Long-term follow-up of hepatitis C virus infection: HLA class II loci influences the natural history of the disease. *Tissue Antigens*, **61**, 159–165 (2003).
 - 30) Matsumura H, Moriyama M, Goto I, Tanaka N, Okubo H, Arakawa Y. Natural course of progression of liver fibrosis in Japanese patients with chronic liver disease type C-a study of 527 patients at one establishment. *J. Viral Hepat.*, **7**, 268–275 (2000).