Regular Article

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Cost-Outcome Description of PEG-IFN-α2b+RBV for Hepatitis C: Results Based on the Interferon Database

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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-α2b+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-α2b+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-α2b+RBV) treatment in hepatitis C virus (HCV)-infected patients. Several treatment regiments 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 2015[10] 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

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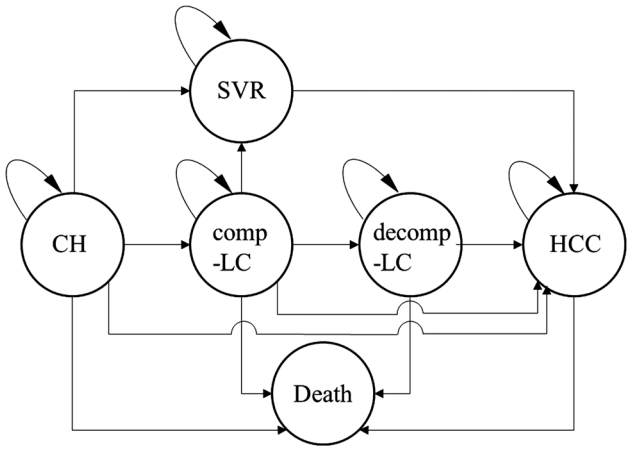

Fig. 1. Modeling the Natural History and Cost-Effectiveness of Hepatitis (MONARCH) Simulation Model

Table 1. Disease Transition Rates

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

Table 2. Health State Costs and Utilities

Health state	Mean cost (¥)	Source	Mean utility	Source
SVR CH (first year only)	57224	McEwan *et al.*[13]	0.960	Ishida *et al.*[20]
SVR comp-LC (first year only)	122873	McEwan *et al.*[13]	0.960	Ishida *et al.*[20]
CH monitoring	119576	McEwan *et al.*[13]	0.920	Ishida *et al.*[20]
CH care	97610	McEwan *et al.*[13]		
comp-LC monitoring	171090	McEwan *et al.*[13]	0.860	Okita[21]
comp-LC care	174177	McEwan *et al.*[13]		
decomp-LC	1561085	McEwan *et al.*[13]	0.670	Okita[22]
HCC	2086469	Nakamura *et al.*[15]	0.380	Ishida *et al.*[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-α2b+RBV treatment.

Drug Treatment Costs We assumed a societal perspective for the calculation of costs. We calculated the drug treatment costs for PEG-IFN-α2b+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 60 kg (based on average weight of 67.7 and 51.2 kg for 20-year-old Japanese men and women, respectively[11]) 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 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 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.

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-α2b drug and REBETOL® capsules 200 mg 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 200 mg, 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 200 mg=580.1 JPY/capsule (Japanese medical fee in April 2016[26]). 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-α2b+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-α2b+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-αn1 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-α2b+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-α2a+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-α2b+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.

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Conflict of Interest The authors declare no conflict of interest.

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