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Original Article

Cost-effectiveness analyses of anti-hepatitis C virus treatments using quality of life scoring among patients with chronic liver disease in Hiroshima prefecture, Japan

Terumi Kaishima,[1] Tomoyuki Akita,[1] Masayuki Ohisa,[1] Kazuaki Sakamune,[1] Akemi Kurisu,[1] Aya Sugiyama,[1] Hiroshi Aikata,[2] Kazuaki Chayama[2] and Junko Tanaka[1]

Departments of [1]Epidemiology, Infectious Disease Control and Prevention, and [2]Gastroenterology and Metabolism, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

Aim: We estimated the cost-effectiveness of direct-acting antiviral treatment (DAA) compared to triple therapy (simeprevir, pegylated interferon-α [Peg-IFN], and ribavirin [RBV]) (scenario 1), Peg-IFN + RBV (scenario 2), and non-antiviral therapy (scenario 3).

Methods: Cost-effectiveness was evaluated as incremental cost-effectiveness ratios (ICERs) using direct costs and indirect costs, which included loss of wages during the patient's lifetime due to early death caused by viral hepatitis infection. Quality of life (QOL) scores were determined by EQ-5D-3L questionnaire survey on 200 HCV patients in Hiroshima.

Results: The QOL scores for chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma were estimated as 0.871, 0.774, and 0.780, respectively. The follow-up period that the ICER of scenario 1 becomes shortest (cost <¥6 million) was 25 years after treatment in men and women who started treatment at the age of 20–60. In contrast, those of scenarios 2 and 3 was 10 years after treatment in patients who started treatment at age <80 years. Based on the sensitivity analysis in scenario 1, the most significant factor affecting the value of ICER is the QOL score after sustained virologic response (SVR), followed by the SVR rate of DAA or follow-up period.

Conclusions: Direct-acting antiviral treatment was estimated to be cost-effective from 10 to 25 years after treatment, depending on the SVR rate of the drugs and the age of onset of treatment. In order to increase the cost-effectiveness of DAA treatment, measures or effort to improve the QOL score of patients after SVR are necessary.

Key words: cost-effectiveness analysis, direct acting antiviral, EQ-5D, hepatitis C virus, incremental cost-effectiveness ratio, loss of productivity, Markov model, QALY

INTRODUCTION

THE WORLD HEALTH Organization has reported that approximately 2 billion people are infected with the hepatitis B virus (HBV) and approximately 270 million people are persistent HBV carriers. Furthermore, approximately 130–150 million people are persistently infected with the hepatitis C virus (HCV), and >1 million deaths each year are thought to be caused by liver diseases that are associated with HBV and HCV infections.[1] In Japan, approximately 1.9–2.3 million people have persistent HCV infections,[2] and hepatitis-related diseases are widespread. At the 69th World Health Assembly (May 2016), the Global Strategy on Viral Hepatitis 2016–2020 was unanimously adopted, with a goal of eliminating hepatitis B and C by 2030. The main targets are to reduce the annual number of deaths by 65% and to increase the treatment rate to 80% by 2030.[3] Gilead Sciences Co. Ltd. supplies inexpensive direct acting antiviral treatment (DAA) to low- and middle-income countries, such as Cuba, Pakistan, the Philippines, and Egypt, which increases local access to chronic hepatitis C treatment.[4]

Japan has developed interventions to target HBV and HCV carriers, which include prevention and control measures. Furthermore, hepatitis testing has been carried out and promoted since the 1990s. Since the 2000s, each

Correspondence: Professor Junko Tanaka, Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551 Japan. Email: jun-tanaka@hiroshima-u.ac.jp
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Japanese prefecture and district has implemented measures that are based on the "Basic Act on Hepatitis Measures", which aim to increase the rates of examination, diagnosis, and treatment using free-of-charge hepatitis testing, reimbursement for some hepatitis-related medical expenses, and regional hospitals that specialize in treating liver disease. The countermeasure should focus on the effective treatment and follow-up after screening, and Japan has shifted from screening to treatment.[5] In addition, several highly effective, albeit expensive, direct-acting antiviral (DAA) treatments have been developed to eliminate HCV infection by directly affecting the enzymatic activity of the HCV. Many clinical studies reported effectiveness, safety, and impact on patients' quality of life (QOL) of DAA.[6–9] However, concerns have been raised regarding the cost-effectiveness of expensive medical technologies, and their burden on Japan's health insurance system. Therefore, the present study examined the cost-effectiveness of DAA and triple therapy (simeprevir [SMV], pegylated interferon-α [Peg-IFN], and ribavirin [RBV]).

The target population was defined as HCV carriers in the Hiroshima prefecture, which has had a screening system since 1992 but still has a high mortality rate for hepatocellular carcinoma (HCC).[10] Hiroshima currently serves as a model district for Japan, and has introduced advanced countermeasures that include carrier surveillance and early releases of new hepatitis treatments. Thus, we collected data regarding the epidemiology of HCV infections, as well as the carrier rate, rate of receiving antiviral therapy, and disease states (HCC, liver cirrhosis [LC], and chronic hepatitis [CH]). Furthermore, QOL scores for patients in Hiroshima were estimated according to their disease state. This cost-effectiveness study might help facilitate region-specific hepatitis control measures.

METHODS

Ethical considerations

THIS STUDY'S PROTOCOL was approved by our institutional ethics committee (Epi E-43). The main objectives were explained to all participants and informed consent was obtained after confirming that the participants understood these objectives.

Patients and study design

The QOL scores were estimated using data from 212 patients who were treated as outpatients or inpatients at Hiroshima University Hospital (Hiroshima, Japan) between August and September 2015. The required sample size was calculated using the following formula,[11] with absolute accuracy of 0.03 and a QOL standard deviation of 0.1:

$$N = 4\times1.96^2\ S^2/W^2.$$

In that equation, S denotes the QOL standard deviation, W denotes the absolute accuracy, and 1.96 is the cut-off for the upper 2.5% of the normal distribution. The required sample size was calculated to be 129 (43 cases each for CH, LC, and HCC), and we ultimately targeted 215 cases based on an assumed response rate of 60%. The patients were categorized according to their liver disease state, and they provided information regarding their age and sex before self-administering the Japanese version of the EQ-5D-3 L questionnaire (mobility, self-care, usual activities, pain, and anxiety).[12] The average health-related QOL scores were calculated according to disease state based on the conversion table.[12]

Model structure

The Markov model (Fig. 1) was used to simulate the cumulative disease states (asymptomatic carriers [AC], CH, LC,

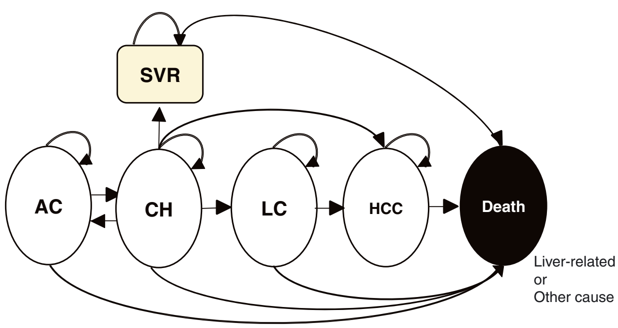

Figure 1 Markov model for the natural course of hepatitis C virus infection. The Markov model for this study consisted of six liver disease states, namely asymptomatic carrier (AC), chronic hepatitis (CH), liver cirrhosis (LC), hepatocellular carcinoma (HCC), sustained virologic response (SVR), and death, and transition probabilities. The arrows indicate a transition between liver disease states over 1 year. [Color figure can be viewed at wileyonlinelibrary.com]

HCC, sustained virologic response [SVR], and death) among HCV carriers with or without treatment. This model included the SVR rates for DAA, triple therapy, and Peg-IFN + RBV, the rates of receiving antiviral therapy, the mortality rate for all causes, and annual transition probability matrixes.[13] Three treatment strategies were assumed in scenario 1 (DAA vs. triple therapy), scenario 2 (DAA vs. Peg-IFN + RBV) and scenario 3 (DAA vs. non-antiviral treatment). The following assumptions were made: (i) the six liver disease states (AC, CH, LC, HCC, SVR, and death) are mutually exclusive and collectively exhaustive; (ii) the rates of visiting a medical institution are 100% for the first time, 65% for the next time for CH, 80% for LC, and 95% for HCC (Table 1); (iii) only CH is eligible for anti-HCV treatment; (iv) the targeted age range for anti-HCV treatment is 20–90 years; (v) the rate of receiving antiviral therapy is 65% for CH (Table 1); (vi) if patients with CH do not respond to antiviral treatment (non-SVR), the transition from CH to AC is zero; (vii) the SVR rate for each age group is constant (0% for non-antiviral treatment in scenario 3, 45% for Peg-IFN + RBV in scenario 2, 88.6% for triple therapy in scenario 1, and 100% for DAA);[14] (viii) the model is limited by an age of 100 years; (ix) the annual discount rates for costs and quality-adjusted life years (QALY) are 2%.[15]

Model development

Model population

The numbers of untreated patients in Hiroshima prefecture were estimated using the following formula (Table 1):

$$UP_{ijd} = P_{ij} \times HCV_{ij} \times 0.7 \times LDS_{ijd}.$$

In that equation, i denotes sex (1 for men, 2 for women), j denotes age (1 for 20–24 years, 2 for 25–29 years, 17 for ≥100 years), d denotes the disease state at the start of follow-up (1 for AC, 2 for CH, 3 for LC), UP_{ijd} denotes the estimated number of untreated HCV carriers in Hiroshima, P_{ij} denotes the population of Hiroshima,[16] HCV_{ij} denotes the anti-HCV positivity rate in Hiroshima,[17] 0.7 is the proportion of HCV carriers among anti-HCV positive individuals,[17] and LDS_{ijd} denotes the proportion of each liver disease state (e.g., LDS_{111} is the proportion of AC among male 20–24-year-old HCV carriers).[18]

Base setting value

In the base setting value, treatment is started at the age of 50 years, the discount rate is 2%, the rate of receiving antiviral therapy is 65%,[10] the SVR rate after DAA treatment is

Table 1 Number of hepatitis C virus (HCV) carriers in Hiroshima prefecture, Japan

Age, years	Population of Hiroshima (2010)†			Estimated no. of HCV carriers‡			Diagnosed in men§				Diagnosed in women§			
	Total	Men	Women	Total	Men	Women	AC	CH	LC	HCC	AC	CH	LC	HCC
20–24	137 098	69 684	67 414	120	54	66	19	35	0	0	44	22	0	0
25–29	153 042	77 217	75 825	134	59	75	21	38	0	0	50	25	0	0
30–34	178 636	89 808	88 828	263	126	137	45	81	0	0	91	46	0	0
35–39	216 329	108 188	108 141	318	152	166	54	98	0	0	111	55	0	0
40–44	184 012	91 510	92 502	972	525	447	183	338	4	0	260	187	0	0
45–49	168 328	83 426	84 902	888	478	410	167	308	3	0	239	171	0	0
50–54	167 126	82 409	84 717	1501	813	688	329	477	7	0	360	325	3	0
55–59	191 535	94 642	96 893	1719	933	786	378	547	8	0	411	371	4	0
60–64	232 762	113 986	118 776	2931	1444	1487	505	867	36	36	766	699	22	0
65–69	189 386	90 135	99 251	2386	1143	1243	400	685	29	29	640	584	19	0
70–74	151 666	69 745	81 921	3595	1685	1910	590	1011	42	42	983	898	29	0
75–79	133 626	56 550	77 076	3161	1365	1796	478	819	34	34	925	844	27	0
80–84	103 132	39 509	63 623	2437	954	1483	334	572	24	24	764	697	22	0
85–89	61 669	19 156	42 513	1455	464	991	162	278	12	12	510	466	15	0
90–94	27 347	6735	20 612	643	163	480	57	98	4	4	247	226	7	0
95–99	8439	1649	6790	198	40	158	14	24	1	1	82	74	2	0
≥100	1395	190	1205	32	5	27	2	3	0	0	14	13	0	0
Total				22 753	10 403	12 350	3738	6279	204	182	6497	5703	150	0

†Vital Statistics in Japan (2010), Ministry of Health, Labour and Welfeare.
‡Tanaka J *et al*. Intervirology 2004; 47: 32–42.
§Mizui M *et al*. Hepatol Res 2007; 37: 994–1001.

100%,[19] triple therapy is 88.6% and Peg-IFN + RBV is 45%, the QOL score after SVR is 1.000, and the drug costs are set according to the National Drug Tariff (April 2016).

Mortality rate

The annual mortality rates were assumed to be 0.225 for HCC[20] and 0.061 for LC.[21] Mortality rates for all causes of death in Hiroshima prefecture were calculated according to 2010 mortality data (Table 2).[22]

Direct costs

Direct costs include the cost of treatment and drugs. The total costs[23] of HCV antiviral treatment for CH were estimated to be ¥4 603 000 for DAA (12 weeks) and ¥1 837 000 for triple therapy (24 weeks for Peg-IFN + RBV, and 12 weeks for SMV), ¥1 470 000 for Peg-IFN + RBV (48 weeks) based on the National Drug Tariff (April 2016). The total costs of non-antiviral treatment for CH, LC, and HCC were estimated using an insurance and clinical practice survey that was published by the Ministry of Health, Labour, and Welfare in June 2011.[24] The numbers of CH, LC, and HCC cases were calculated based on the 2014 Patient Survey in Japan,[25] using codes for viral hepatitis (International Classification of Diseases and Related Health Problems, 10th revision [ICD-10] codes: B15–B19), liver cirrhosis except alcoholic cirrhosis (ICD-10: K74.3–K74.6), and malignant neoplasm of the liver and intrahepatic bile duct (ICD-10: C22). Based on these factors, the per-capita medical costs were estimated to be ¥540 000 for CH, ¥527 000 for LC, and ¥2 160 000 for HCC. These medical costs included consultations, treatment, radiographic imaging, pathological testing, surgery, hospital charges, and nutritional support for inpatients (Table 2).

Indirect costs

Indirect costs include loss of productivity, which was defined as the "loss of wages during the patient's lifetime due to early death caused by viral hepatitis infection," and was estimated using the human capital valuation method:[15]

$$L_D = \sum_{i=D}^{D+LE_D-1} \frac{E_i \times W_i}{(1+r)^{i-1}}$$

In that equation, D denotes age at death, L_D denotes the loss of wages during the patient's lifetime due to early death at age D, LE_D denotes life expectancy at age D, i denotes the index of age, r denotes the discount rate (2%)[15] and E_i and W_i denote the employment rate and annual wages at age i, respectively. The employment rate was based on the 2015 Labour Force Survey[26] the annual income was based on the 2015 Basic Survey on Wage Structure.[27] Life expectancy was based on the 2010 Life Table.[22]

Table 2 Parameters and costs of each stage of anti-hepatitis C virus treatments in patients with chronic liver disease in Hiroshima prefecture, Japan

Item		Value	Ref.
QOL scores	AC	1.000	
	SVR	1.000	
	CH	0.871	
	LC	0.774	
	HCC	0.780	
Direct costs, ¥1000	DAA	4603	23†
	Triple therapy	1837	23‡
	Peg-IFN + RBV	1470	23§
	CH	540	24
	LC	527	24
	HCC	2610	24
Indirect costs	Loss of wages during the patient's lifetime due to early death caused by viral hepatitis infection		¶
Rate of receiving antiviral therapy		65%	10
Rate of visits to medical institutions	CH (for the first time)	100%	
	CH (for the second time)	65%	
	LC	80%	
	HCC	95%	
Rate of SVR	DAA	100%	
	Triple therapy	88.6%	
	Peg-IFN + RBV	45.0%	
Death rate	LC	0.061	21
	HCC	0.225	20
	Others	Death rate in Hiroshima	22

†Ledipasvir + sofosbuvir [LDV + SOF] for 12 weeks.
‡Pegylated interferon + ribavirin [Peg-IFN + RBV] for 24 weeks + simeprevir [SMV] for 12 weeks.
§Peg-IFN + RBV for 48 weeks.
¶Loss by early death = $\Sigma_{i=D}^{D+LE-1}$ {(operation rate in age i * annual wage in age i)} / $(1 + r)^{i-1}$
AC, asymptomatic carrier; CH, chronic hepatitis; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; LC, liver cirrhosis; QOL, quality of life; SVR, sustained virologic response.

Model outcomes

The total costs and QALYs for DAA, triple therapy (scenario 1), Peg-IFN + RBV (scenario 2), and non-antiviral treatment (scenario 3) were used to calculate the incremental cost-effectiveness ratios (ICERs), based on the guidelines for Economic Evaluation of Health Care Technology in Japan,[15] to compare the treatments for 5-year increments ranging from 5 years to 50 years after starting treatment:

$$ICER = \frac{Total\ costs_{DAA} - Total\ costs_{triple\ therapy\ or\ Peg-IRN+RBV\ or\ non-antiviral\ treatment}}{QALYs_{DAA} - QALYs_{triple\ therapy\ or\ Peg-IFN+RBV\ or\ non-antiviral\ treatment}}$$

In our study, the cut-off ICER value for determining cost-effectiveness was set to ¥5 million or ¥6 million.[28]

Sensitivity analysis

In scenario 1, sensitivity analyses were carried out to assess the influence of specific input parameters on the cost-effectiveness results: patient age (±10 years), discounting (±2%), patient sex (male/female), follow-up period (±10 years), HCC treatment cost (±20%), DAA cost (±20% based on the 2015 National Drug Tariff), DAA SVR (100–95%), QOL scores after SVR (1.000–0.871), and the rate of receiving DAA therapy (65–85%).

RESULTS

Quality of life scores

AMONG THE 212 eligible patients, 200 patients (94.3%) responded to the QOL questionnaires (105 men [52.5%] and 95 women [47.5%]). The largest age subgroups were 60–69 years old (65 patients, 32.5%) and 70–79 years old (62 patients, 31.0%). The disease states were CH for 108 patients (54.0%), LC for 24 patients (12.0%), and HCC for 68 patients (34.0%) (Table 3). The results from the EQ-5D-3L questionnaires are summarized in Table 3. The average QOL scores for patients in Hiroshima prefecture were estimated to be 0.871 for CH, 0.774 for LC, and 0.780 for HCC (Table 4).

Table 3 Number of respondents to each dimension of the EQ-5D-3L questionnaire among 200 hepatitis C virus (HCV) patients in Hiroshima prefecture, Japan

	HCV disease stage			
EQ-5D dimension	CH *n* = 108	Comp-LC *n* = 20	Decomp-LC *n* = 4	HCC *n* = 68
Mobility				
No problem	93 (86.1)	14 (70.0)	1 (25.0)	42 (61.8)
Some problems	15 (13.9)	5 (25.0)	3 (75.0)	26 (38.2)
Extreme problems	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)
Self-care				
No problem	105 (97.2)	19 (95.0)	2 (50.0)	57 (83.8))
Some problems	2 (1.9)	1 (5.0)	2 (50.0)	9 (13.2)
Extreme problems	1 (0.9)	0 (0.0)	0 (0.0)	2 (3.0)
Usual activities				
No problem	90 (83.3)	11 (55.0)	1 (25.0)	40 (58.8)
Some problems	17 (15.7)	9 (45.0)	3 (75.0)	24 (35.3)
Extreme problems	1 (1.0)	0 (0.0)	0 (0.0)	4 (5.9)
Pain/discomfort				
No pain/discomfort	80 (74.1)	12 (60.0)	1 (25.0)	38 (55.9)
Moderate pain/discomfort	23 (21.3)	8 (40.0)	2 (50.0)	29 (42.6)
Extreme pain/discomfort	5 (4.6)	0 (0.0)	1 (25.0)	1 (5.9)
Anxiety/depression				
No anxiety/depression	85 (78.7)	16 (80.0)	3 (75.0)	50 (73.5)
Moderate anxiety/depression	20 (18.5)	4 (20.0)	0 (0.0)	17 (25.0)
Extreme anxiety/depression	3 (2.8)	0 (0.0)	1 (25.0)	1 (1.5)

Data are shown as *n* (%).
CH, chronic hepatitis; Comp-LC, compensated liver cirrhosis; Decomp-LC, decompensated liver cirrhosis; HCC, hepatocellular carcinoma.

Table 4 Quality of life (QOL) scores among HCV patients in Hiroshima prefecture, Japan, with chronic hepatitis (CH), liver cirrhosis (LC), or hepatocellular carcinoma (HCC)

Condition of liver disease	No. of patients	QOL scores	95% CI
CH	108	0.871	(0.824–0.917)
LC	24	0.774	(0.649–0.900)
Comp-LC	20	0.824	(0.718–0.930)
Decomp-LC	4	0.524	(0.000–1.00)
HCC	68	0.780	(0.723–0.837)
HCC	14	0.750	(0.619–0.881)
HCC – early	23	0.838	(0.759–0.917)
HCC – intermediate	15	0.786	(0.681–0.891)
HCC – advanced	16	0.716	(0.540–0.892)

CI, confidence interval; Comp-, compensated; Decomp-, decompensated.

Cost-effectiveness analyses

Incremental cost-effectiveness ratios in the base setting value

In the base setting value, treatment is started at the age of 50 years. In scenario 1 (DAA vs. triple therapy), the ICERs for direct costs (treatment and drug costs) after 25 years of follow-up (i.e., ≥75 years old) were estimated according to disease state (Table 5) and were ¥5 671 000/QALY for men and ¥6 075 000/QALY for women. The ICERs for both direct and indirect costs (loss of productivity) after 25 years follow-up were ¥5 018 000/QALY for men and ¥5 712 000/QALY for women (Table 6). In scenario 2 (DAA vs. Peg-IFN + RBV) and scenario 3 (DAA vs. non-antiviral treatment), the ICERs for direct costs after 10 years of follow-up were ¥2 863 000/QALY for men and ¥3 467 000/QALY for women, and ¥1 715 000/QALY for men and ¥2 203 000/QALY for women, respectively.

Incremental cost-effectiveness ratios according to sex and age at the start of treatment

In scenario 1, ICERs for direct costs according to sex and age at the start of treatment were estimated (Fig. 2a). In scenario 1, the case of DAA treatment started at age of 50 years old for men (¥5 671 000/QALY) and 60 years old for women (¥5 959 000/QALY); the ICER values reach cost-effectiveness within shortest period at 25 years. In men who started treatment at the age of 20 years, the follow-up period that the ICER <¥6 million was 35 years after treatment (¥5 124 000/QALY), compared to 30 years after treatment in men who started

Table 5 Incremental cost-effectiveness ratios (ICER) of anti-hepatitis C virus treatments among patients with chronic liver disease in Hiroshima prefecture, Japan, based on direct costs

		DAA		Triple therapy				
Gender	Follow-up period, years	Total direct costs, ¥1000	QALYs	Total direct costs, ¥1000	QALYs	ΔCost	ΔQALY	ICER, ¥1000 /QALY
Male	15	4 752 748	20 795	2 604 635	20 611	2 148 113	184	11 675
	20	5 002 159	25 728	2 944 215	25 460	2 057 944	268	7679
	25	5 190 272	29 657	3 210 960	29 308	1 979 312	349	5671
	30	5 324 428	32 546	3 406 851	32 125	1 917 577	421	4555
	35	5 412 403	34 400	3 537 064	33 926	1 875 339	474	3956
	40	5 463 135	35 362	3 611 630	34 858	1 851 505	504	3674
	45	5 487 622	35 726	3 646 502	35 210	1 841 120	516	3568
	50	5 494 229	35 800	3 655 621	35 281	1 838 608	519	3543
Female	15	3 785 994	18 159	1 964 920	18 023	1 821 074	136	13 390
	20	4 086 326	22 753	2 300 698	22 547	1 785 628	206	8668
	25	4 320 535	26 637	2 595 171	26 353	1 725 364	284	6075
	30	4 500 572	29 790	2 838 717	29 428	1 661 855	362	4591
	35	4 635 424	32 171	3 028 487	31 738	1 606 937	433	3711
	40	4 731 779	33 736	3 165 130	33 251	1 566 649	485	3230
	45	4 795 454	34 535	3 253 182	34 023	1 542 272	512	3012
	50	4 817 268	34 748	3 282 634	34 229	1 534 634	519	2957

ΔCost = Total direct costs $_{DAA}$ − total direct costs $_{\text{triple therapy}}$
ΔQALY = QALYs $_{DAA}$ − QALYs $_{\text{triple therapy}}$
In the base setting value, treatment is started at the age of 50 years, the rate of receiving antiviral therapy is 65%, and the discount rate is 2%.
DAA, direct-acting antiviral; QALY, quality-adjusted life years; Triple therapy, simeprevir, pegylated interferon-α, and ribavirin.

Table 6 Incremental cost-effectiveness ratios (ICERs) of anti-hepatitis C virus treatments among patients with chronic liver disease in Hiroshima prefecture, Japan, based on direct and indirect costs

		DAA		Triple therapy				
Gender	Follow-up period, years	Total (direct + indirect) costs, ¥1000	QALYs	Total (direct + indirect) costs, ¥1000	QALYs	ΔCost	ΔQALY	ICER, ¥1000 /QALY
Male	15	6 098 843	20 795	4 134 893	20 611	1 963 950	184	10 674
	20	6 482 333	25 728	4 638 818	25 460	1 843 515	268	6879
	25	6 726 978	29 657	4 975 742	29 308	1 751 236	349	5018
	30	6 885 152	32 546	5 202 079	32 125	1 683 073	421	3998
	35	6 977 282	34 400	5 338 396	33 926	1 638 886	474	3458
	40	7 017 941	35 362	5 401 593	34 858	1 616 348	504	3207
	45	7 022 646	35 726	5 413 119	35 210	1 609 527	516	3119
	50	6 377 164	35 800	4 672 814	35 281	1 704 350	519	3284
Female	15	4 163 061	18 159	2 402 963	18 023	1 760 098	136	12 942
	20	4 576 630	22 753	2 877 379	22 547	1,699 251	206	8249
	25	4 882 626	26 637	3 260 462	26 353	1 622 164	284	5712
	30	5 106 768	29 790	3 558 784	29 428	1 547 984	362	4276
	35	5 264 248	32 171	3 776 858	31 738	1487,390	433	3435
	40	5 369 764	33 736	3 925 156	33 251	1444,608	485	2979
	45	5 433 145	34 535	4 013 165	34 023	1 419 980	512	2773
	50	5 156 710	34 748	3 685 173	34 229	1 471 537	519	2835

ΔCost = Total (direct + indirect) costs $_{\text{DAA}}$ − total (direct + indirect) costs $_{\text{triple therapy}}$
ΔQALY = QALYs $_{\text{DAA}}$ - QALYs $_{\text{triple therapy}}$
In the base setting value, treatment is started at the age of 50 years, the rate of receiving antiviral therapy is 65%, the discount rate is 2%, including direct and indirect costs.
DAA, direct-acting antiviral; QALY, quality-adjusted life years; Triple therapy, simeprevir, pegylated interferon-α, and ribavirin.

treatment at the age of 30 years (¥5 587 000/QALY), 40 years (¥4 799 000/QALY), or 60 years (¥5 651 000/QALY).

In women who started treatment at the age of 20, the follow-up period that the ICER becomes <¥6 million was 40 years after treatment (¥5 041 000/QALY), compared to 30 years after treatment in those who started treatment at the age of 40 years (¥5 619 000/QALY) or 50 years (¥4 591 000/QALY).

In both men and women who started treatment at the age of ≥80 years, the ICER values did not reach cost-effectiveness (<¥6 million) before 100 years of age; however, the ICER values decreased slightly.

In scenario 2, the follow-up period after treatment that the ICER becomes <¥6 million was 10 years for men and women who started treatment at the age of under 80 (Fig. 2b). That is, in men who started treatment at the age of 20 years (¥3 357 000/QALY), 30 years (¥3 369 000/QALY), 40 years (¥3 118 000/QALY), 50 years (¥2 863 000/QALY), 60 years (¥2 403 000/QALY), 70 years (¥2 885 000/QALY), or 80 years (¥4 493 000/QALY), the follow-up time to an ICER of <¥6 million was 10 years after treatment.

In women who started treatment at the age of 20 years (¥3 997 000/QALY), 30 years (¥3 884 000/QALY), 40 years (¥3 802 000/QALY), 50 years (¥3 467 000/QALY), 60 years (¥3 064 000/QALY), 70 years (¥3 314 000/QALY), or 80 years (¥4 305 000/QALY), the follow-up time to an ICER of <¥6 million was 10 years after treatment.

In scenario 3, the follow-up period after treatment that the ICER becomes <¥6 million was also 10 years for men and women who started treatment at age <80 years. Although in patients who started treatment at the age of 90 years the ICER values did not reach cost-effectiveness (<¥6 million), the value decreased remarkably (Fig. 2c).

Sensitivity analyses

The results of the sensitivity analyses are shown in Figure 3 and Table 7. In the case of changing QOL score after SVR from 1.0 (base setting value; base) to 0.871, the ICERs in men were ¥4 555 000 (base)–11 552 000/QALY and the ICERs in women were ¥4 591 000 (base)–12 130 000/QALY. In the case of changing the SVR rate of DAA treatment from 100% (base) to 95%, the ICERs in men were ¥4 555 000 (base)–9 502 000/QALY and the ICERs in

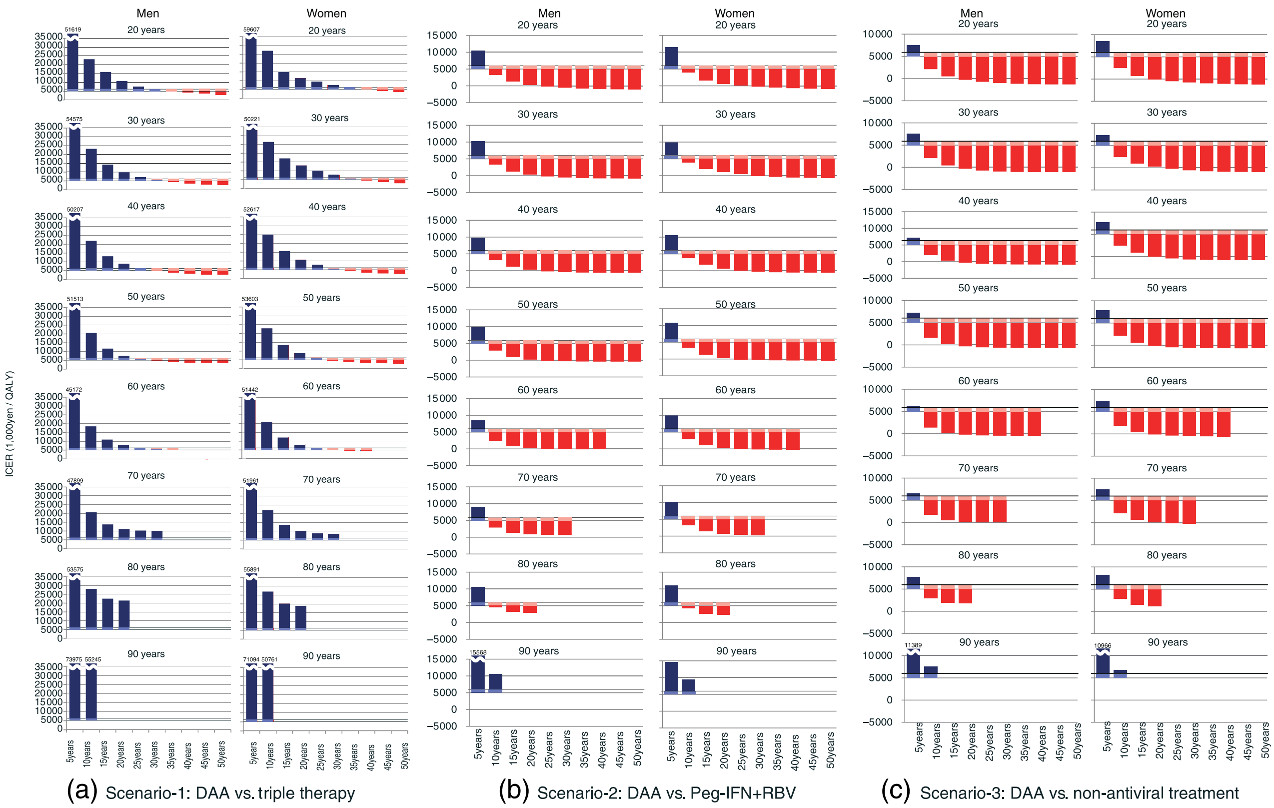

Figure 2 Incremental cost-effectiveness ratios (ICERs) of anti-hepatitis C virus treatments among patients with chronic liver disease in Hiroshima prefecture, Japan, classified by treatment starting age, sex, and follow-up period. The assumptions were a 65% rate of receiving antiviral therapy and a 2.0% discount rate. The sustained virologic response rates were 88.6% for triple therapy (simeprevir + pegylated interferon-α [Peg-IFNα], and ribavirin [RBV]) in scenario 1, 45% for Peg-IFN + RBV in scenario 2, 0% for non-antiviral treatment in scenario 3, and 100% for direct-acting antiviral (DAA) treatment. (a) Scenario 1, DAA vs. triple therapy. (b) Scenario 2, DAA vs. Peg-IFN + RBV. (c) Scenario 3, DAA vs. non-antiviral treatment. [Color figure can be viewed at wileyonlinelibrary.com]

women were ¥4 591 000 (base)–9 582 000/QALY. In the case of changing the DAA costs from −20% (¥3 682 000) to +20% (¥5 524 000), the ICERs in men were ¥2 435 000–6 675 000/QALY and the ICERs in women were ¥2 468 000–6 713 000/QALY. In the case of changing the follow-up period from 20 years to 40 years, the ICERs in men were ¥7 679 000–3 674 000/QALY and the ICERs in women were ¥8 668 000–3 230 000/QALY. In the case of changing the rate of receiving DAA therapy from 65% (base) to 85%, the ICERs in men were ¥4 555 000 (base)–1 865 000/QALY and the ICERs in women were ¥4 591 000 (base)–1 858 000/QALY.

DISCUSSION

DECLINING BIRTH RATES and prolonged lifespans have been associated with remarkable increases in national health-care costs, as the introduction of expensive but innovative drugs can create drastic changes in medical care. These treatments must be evaluated for safety, effectiveness, and cost-effectiveness, which highlights the need for new criteria that incorporate direct and indirect costs, as well as the resulting changes in QOL.[29] Other countries have developed specialized cost-effectiveness evaluations for depression[30] and cancer treatments[31] and a Japanese cost-effectiveness subcommittee was established in 2012. One pilot study in Japan was completed in 2016, and a full-scale study is planned for 2018.[32]

There are several recently published reports that are related to our study, that is, cost-effectiveness of DAA.[33,34] McEwan *et al.* showed the cost-effectiveness of DAA treatment (daclatasvir + asunaprevir) compared to simeprevir + Peg-IFN + RBV or telaprevir + Peg-IFN + RBV using transition probabilities through all ages, based on other published reports.[33] Tanaka *et al.* analyzed the cost-effectiveness of antiviral treatment for HCV patients based

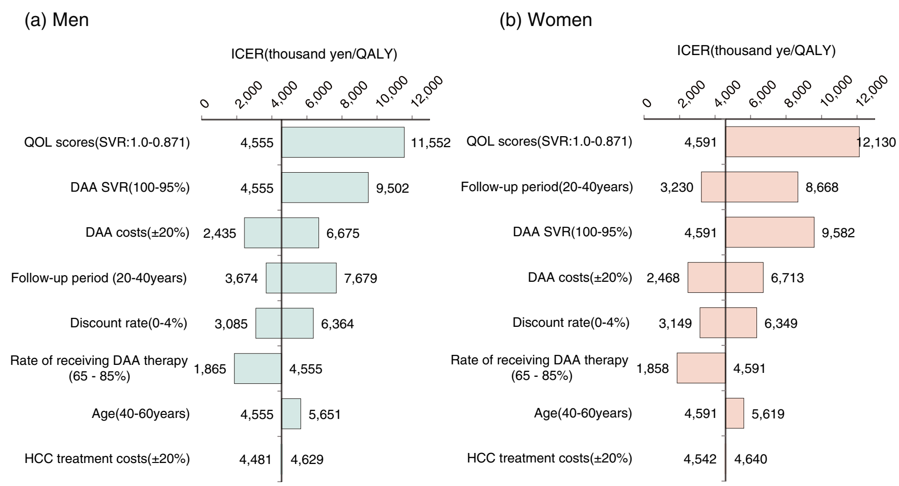

Figure 3 Univariate sensitivity analyses of the base setting value of incremental cost-effectiveness ratios (ICERs) of antihepatitis C virus treatments among patients with chronic liver disease in Hiroshima prefecture, Japan. Bars indicate the change in the ICERs for each parameter. DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; QALY, quality-adjusted life years; QOL, quality of life; SVR, sustained virologic response. [Color figure can be viewed at wileyonlinelibrary.com]

Table 7 Univariate sensitivity analysis of base-case

		DAA (LDV + SOF) vs. triple therapy (Peg-IFN + RBV + SMV)					
		Men			Women		
Scenario		Incremental cost, ¥1000	Incremental QALY	ICER, ¥1000 /QALY	Incremental cost, ¥1000	Incremental QALY	ICER, ¥1000 /QALY
Direct cost	Base case†	1 917 577	421	4555	1 661 855	362	4591
	Age (+10 years)	2 622 153	464	5651	3 066 868	625	4907
	Age (−10 years)	1 151 718	240	4799	949 663	169	5619
	Discount rate (0%)	1 795 368	582	3085	1 618 349	514	3149
	Discount rate (4%)	1 991 965	313	6364	1 676 073	264	6349
	Follow-up period (+10 years)	1 851 505	504	3674	1 566 649	485	3230
	Follow-up period (−10 years)	2 057 944	268	7679	1 785 628	206	8668
	HCC treatment costs (+20%)	1 886 459	421	4481	1 644 106	362	4542
	HCC treatment costs (−20%)	1 948 695	421	4629	1 679 603	362	4640
	DAA costs (+20%)	2 809 980	421	6675	2 430 284	362	6713
	DAA costs (−20%)	1 025 174	421	2435	893 425	362	2468
	DAA costs (2015 National Drug Tariff)	3 580 296	421	8504	3 093 587	362	8546
	DAA SVR (95%)	2 252 024	237	9502	1 945 160	203	9582
	QOL scores for SVR (0.871)	1 917 577	166	11 552	1 661 855	137	12 130
	Receival rate of anti-virus therapy (+20%)	2 867 682	1538	1865	2 495 492	1343	1858
Direct + indirect cost	Base case†	1 683 073	421	3998	1 547 984	362	4276
	HCC death rate (+5%)	1,698 504	431	3941	1 561 108	368	4242
	HCC death rate (−5%)	1 659 733	407	4078	1 529 987	355	4310

†In the base treatment scenario, age at the start of treatment is 50 years, follow-up period is 30 years, discount rate is 2%, the receival rate of antiviral therapy is 65%, direct-acting antiviral (DAA) sustained virologic response (SVR) is 100%, quality of life (QOL) scores for SVR is 1.00, and the drug cost is according to the National Drug Tariff (April 2016).
HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; Peg-IFNα, pegylated interferon-α; LDV, ledipasvir; QALY, quality-adjusted life years; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.

on disability-adjusted life-years as an index of cost-effectiveness, and it was concluded that the elimination model promoting DAA treatment is the most cost-effective as DAA treatment can reduce the cost per year of disability to the lowest level.[34]

In this study, we could estimate ICERs as an index of cost-effectiveness classified by sex and age groups applying transition probabilities calculated from a Japanese cohort study. We were also able to report, for the first time, the cost-effectiveness of DAA treatment by age of starting treatment and by follow-up period after SVR. Furthermore, this study pointed out the importance of evaluating the cost-effectiveness of DAA treatment according to different medical subsidies systems, hepatitis virus examination rates, medical institution receiving rates, and HCV carrier rates for each administrative district.

The present study estimated QOL scores among HCV carriers specifically residing in Hiroshima prefecture using the EQ-5D-3L questionnaire. Because every prefecture has its own parameters, such as the QOL scores, estimated number of HCV carriers in 2010, the rates of receiving antiviral treatments, and the mortality rate, the ICER value might also vary in every prefecture. As the reference model for other prefectures, using prefecture-specific parameters, we simulated age- and sex-specific ICER values in Hiroshima prefecture for DAA treatment compared to triple therapy, Peg-IFN + RBV, or non-antiviral treatment.

The EQ-5D tool was developed by the EuroQol Group, which was established in 1987, and has been translated into >170 languages as the international standard for calculating QALYs.[35] The Japanese version of EQ-5D-3L was released in 1997 and has been certified by the EuroQol Group.[36] However, the QOL scores using for cost-effectiveness analyses have typically been calculated using the EQ-5D tool, which assigns a score of 0 to death and a score of 1 to healthy status.[37] We used ICERs to evaluate cost-effectiveness, which reflect the cost to achieve 1 QALY. According to Shiroiwa *et al.*,[28,38] the willingness-to-pay threshold is ¥5–6 million/QALY, which has been considered as a reference of cut-off value for determination of cost-effectiveness in Japan; this value was applied in this study.

The direct costs showed a decreasing trend for ICERs in both sexes and every age group after treatment, although men tended to have lower ICERs than women during the early follow-up period after treatment. In scenario 1, that is, compared to triple therapy, DAA treatment was cost-effective for patients who started treatment at the age of 20–60 years, followed by 25–35 years after treatment. However, DAA treatment was not relatively cost-effective if DAA treatment was started at >70 years, even for survival to age 100 years, which is likely related to the high all-cause mortality rate. In this analysis, we assumed the discount rate was 2%, that is, values of QALY and costs in future were discounted by length of follow-up period. The discount rate (2%) is used to calculate future value discounted to the present. For example, ¥1 million after 10 years will be ¥836 000 for the current value, and QALY 1 after 10 years will be 0.84 of the current value. QALY is associated with the progress of hepatitis. In younger generation, the period until liver pathology progresses to LC/HCC is longer than elderly. The treatment costs are same for each generations. However due to the adaptation of the discount rates, the QALY in the distant future becomes lower as a current value. Therefore in younger generation ΔQALY estimated lower than the elderly generation. For this reason, if the discount rate is 0%, DAA treatment is more cost-effective in scenario 1 after 25 years of treatment for all generations who started treatment at age <70 years.

Furthermore, in scenarios 2 or 3, that is, compared to Peg-IFN + RBV or non-antiviral treatment, DAA treatment was estimated to be cost-effective after 10 years of treatment in all age patients, excluding those who started treatment at the age of 90 years. Even in patients who started treatment at the age of 90 years, the ICER values decreased remarkably after 10 years of treatment, but did not reach <¥6 million. In our study, elderly people in Japan have little or no income, and there is no difference in indirect costs between treated patients with SVR and untreated patients. From our analysis, it means indirect costs may not significantly affect the ICER in some populations where most HCV patients are elderly.

The Ministry of Health, Labour, and Welfare guidelines[15] indicate that public nursing costs and indirect costs (loss of productivity) should not be included in the preliminary evaluation of cost-effectiveness, although they should be considered in subsequent evaluations. This may be because loss of productivity among HCV carriers is generally related to "loss of incomes/wages due to HCV-related early death" and "loss due to a decline in the job performance" (i.e., absenteeism).[39] Thus, the present study estimated loss of productivity due to "a loss of income caused by early death due to HCV infection," but excluded indirect costs due to absenteeism in order to prevent double counting of absenteeism.[40]

In scenario 1 (DAA vs. triple therapy), based on the sensitivity analysis, QOL scores after SVR had significantly greater effects on the ICER values than the receiving rate of DAA treatment or SVR rate of DAA treatment. It indicates that, in order to increase cost-effectiveness of DAA treatment, measures or effort to improve the QOL score of patients after SVR are important. Therefore, in order to avoid the risk of carcinogenesis after SVR, which is reported by some clinical research, it is considered that patients after SVR need to visit medical institutions periodically. It is important to explain the follow-up system currently being maintained in each prefecture to patients and obtain their understanding. By encouraging patients to register in this system, regular check-ups will be possible. Providing information on health promotion (e.g., exercise and nutrition) using the system to registrants might assist in maintaining and improving their QOL.

Because of their relatively short life expectancy, DAA treatment did not show cost-effectiveness for patients who started treatment at the age >80 years. However, in Japan, the HCV carrier rate among older people is higher than that among young people;[41] for example, approximately 50% of HCV carriers in Hiroshima were over the age of 80 years (Table 2). Furthermore, the new HCV infection rate in Japan is very low (0.7/100 000 person-years [95% confidence interval, 0.6–0.9]).[13] However, the cause of HCV infection is unclear in up to 60% of new hepatitis C cases, and the incidence of HCV infection in women is highest among the age groups 50–60 years and 20–30 years.[13] Therefore, DAA treatment for HCV carriers aged >60 years might still be effective for preventing new HCV infections.

This study has several limitations. First, the incidence of HCC after SVR was assumed to be zero in this study, but there are some reported cases that have developed HCC after starting DAA treatment, which might have increased the ICER estimates. Second, method to determine the cut-off value of ICER for determining cost-effectiveness is not unique.[42] For example, if we apply the cut-off based on three times of the gross domestic product per capita, cut-off value becomes ¥12 573 000,[43–45] instead of willingness-to-pay, DAA treatment would be evaluated as more cost-effective. Finally, we should consider the high SVR rate as a benefits of DAA treatment, which may help prevent new infections.[46]

Although the cost of DAA treatment remains high in developed countries, DAA was cost-effective compared to triple therapy, PEG-IFN + RBV, and non-antiviral treatment, even for elderly patients.

In terms of HCV infection prevention, DAA treatment should be recommended to elderly patients. To improve the cost-effectiveness of DAA treatment, strategies to increase the QOL scores of HCV patients after SVR are important.

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