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Research

Drug therapies for chronic hepatitis C infection: a cost-effectiveness analysis

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Abstract

Background: Before 2011, pegylated interferon plus ribavirin was the standard therapy for chronic hepatitis C. Interferon-free direct-acting antiviral agents were then approved. Although these treatments appear to be more effective, they are substantially more expensive. In anticipation of the need for information regarding the comparative cost-effectiveness of new regimens in a recent therapeutic review, we conducted the analysis to inform listing decision in Canada.

Methods: A state-transition model was developed in the form of a cost-utility analysis. Regimens included in the analysis were comprehensive. The cohort under consideration had a mean age of 50 years. The cohort was defined by treatment status and cirrhosis status. Inputs for the model were derived from published sources and validated by clinical experts.

Results: For each genotype 1 population, at least 1 of the interferon-free agents appeared to be economically attractive compared with pegylated interferon–ribavirin, at a willingness-to-pay of $50 000 per quality-adjusted life-year. The drug that was the most cost-effective varied by population. For genotype 2–4 population, the direct-acting antiviral therapies appeared not to be economically attractive compared with pegylated interferon–ribavirin for the treatment-naive; however, there were direct-acting antiviral therapies that appeared to be attractive when compared with no treatment for the treatment-experienced.

Interpretation: Public health policy should be informed by consideration of health benefit, social and ethical values, feasibility and cost-effectiveness. Our analysis assists the development of reimbursements and policies for interferon-free direct-acting antiviral agent regimens for chronic hepatitis C infection by informing the last criterion. Considering the rapid development of treatments for chronic hepatitis C, further update and expanded reviews will be necessary.

Before 2011, pegylated interferon plus ribavirin was the standard therapy for chronic hepatitis C. Since then, substantial advances have been made in the treatment of this disease. Treatment success is measured by a sustained virological response, which is defined as undetectable hepatitis C viral RNA 12 to 24 weeks post-treatment (i.e., effectively a virological cure).[1–4] In patients with advanced fibrosis or cirrhosis at baseline, a sustained virological response is associated with reduced liver-related and all-cause mortality, in addition to reduced incidence of liver failure and liver cancer.[5] Although treatment with pegylated interferon–ribavirin results in sustained virological response in a proportion of patients, the treatment is less than ideal because of its long duration, numerous associated adverse effects and relatively low efficacy.[4] In 2011, the first 2 direct-acting antiviral agents, boceprevir and telaprevir, were approved for use in combination with pegylated interferon–ribavirin for patients with genotype 1 chronic hepatitis C infection. More recently, Health Canada has approved Harvoni (an interferon-free combination of ledipasvir and sofosbuvir),[6–8] Holkira Pak, a combination of a dasabuvir tablet and an ombitasvir, paritaprevir and ritonavir tablet,[9–11] and daclatasvir in combination with sofosbuvir[12] for treating chronic hepatitis C infection. Apart from better tolerability without requiring pegylated interferon–ribavirin, potential benefits of some or all of these regimens are shorter treatment durations and higher efficacy in terms of sustained virological response rates.

Regulatory approvals of these newer regimens have given way to discussions of affordability and accessibility, which pose

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a challenge for public drug programs in Canada, given the prevalence of chronic hepatitis C infection and the high cost of new treatments compared with pegylated interferon–ribavirin regimens. In anticipation of the need and demand for supporting evidence and information regarding the comparative effectiveness of new regimens for chronic hepatitis C infection, the Canadian Agency for Drugs and Technologies in Health (CADTH) has updated its previous Therapeutic Review[13] to include recently approved and emerging regimens for the treatment of chronic hepatitis C infection (genotypes 1–6).

In collaboration with CADTH, the objective of this study was to evaluate the cost-effectiveness of treatment regimens for chronic hepatitis C infection (genotypes 1–4).

Methods

Study design

We developed a state-transition model of the hepatitis C virus to assess the cost-effectiveness of alternative treatment strategies for patients with chronic monoinfection from hepatitis C virus genotypes 1 through 4 in Canada. Detailed methodology is reported in Appendix 1, available at www.cmajopen.ca/content/5/1/E97/suppl/DC1.

Cohort

The cohort under consideration had a mean age of 50 years. A broader age range (40–60 yr) was considered in the sensitivity analyses. Cohorts were defined by age, treatment status (naive v. experienced) and cirrhosis status (no cirrhosis v. cirrhosis).

Strategies

Treatment regimens included in the base-case analysis were those approved in Canada, recommended by major guidelines or considered to have a high likelihood of approval in Canada in the near future. Treatment regimens included: pegylated interferon–ribavirin, boceprevir, telaprevir, simeprevir, sofosbuvir, ledipasvir–sofosbuvir, ombitasvir–paritaprevir–ritonavir and dasabuvir, and daclatasvir–sofosbuvir. Detailed regimens considered for each population are presented in Table 1.

Decision model

In our analysis, we developed a cohort-based, state transition model using TreeAge Pro 2014 software.[14] In our simulations, cohort members move between predefined health states in weekly cycles until all members die. Health states and allowed transitions among health states are shown in Figure 1.

Model parameters

Model parameters (Table 2, Table 3 and Appendix 2, available at www.cmajopen.ca/content/5/1/E97/suppl/DC1) that included disease progression parameters, transition probabilities to advanced liver disease, mortality, epidemiologic variables and direct medical costs were obtained from the published literature (Appendix 1).[5,16–18,20,22–32] All cost data were expressed in Canadian dollars and were inflated to 2015 using the Statistics Canada Consumer Price Index for health care and personal items.[33] Treatment efficacy and safety inputs were generated directly from the network meta-analysis model.[15] Health states utility data were obtained from the most recent and valid Canadian utility study available, conducted by Hsu and colleagues[26] in 2012, using Health Utilities Index Mark 2. The study included 700 patients across different chronic hepatitis C health states.

Economic assumptions

The analysis was conducted from the perspective of a provincial Ministry of Health in Canada and was structured as a cost-utility analysis, with outcomes expressed in quality-adjusted life-years and costs. Future costs and health benefits were discounted at 5% annually.[34]

Results

Model validation

In Appendix 3 (available at www.cmajopen.ca/content/5/1/E97/suppl/DC1), we compared the predicted outcomes of our model against published studies.[20,35,36] These outcomes included: probability of progression to cirrhosis and probability of liver-death. Our model results closely matched the results of the published studies.[20,35,36]

Base-case analysis

Genotype 1, treatment-naive

Table 4 and Appendix 4 (available at www.cmajopen.ca/content/5/1/E97/suppl/DC1) summarize the outcomes associated with the base-case analysis for a cohort of 50-year-old treatment-naive genotype 1 patients without cirrhosis. In this subpopulation, the interferon-free drugs are more costly but more effective than pegylated interferon–ribavirin. Among the interferon-free drugs, paritaprevir–ritonavir plus ombitasvir plus dasabuvir for 12 weeks (PAR/RIT12 + OMB12 + DAS12) was the most cost-effective treatment (incremental cost-utility ratio of $29 354 per quality-adjusted life-year), when compared with pegylated interferon–ribavirin therapy — it was associated with an increase in health (0.996 quality-adjusted life-years) and cost ($29 247) compared with pegylated interferon–ribavirin therapy. Sofosbuvir plus ledipasvir for 12 weeks (SOF12 + LDV12) was the most effective treatment in terms of total quality-adjusted life-years (11.857 quality-adjusted life-years), resulting in an incremental cost utility ratio of $37 951 per quality-adjusted life-year compared with pegylated interferon–ribavirin therapy. For genotype 1, treatment-naive patients with cirrhosis, SOF12 + LDV12 was the most cost-effective treatment (incremental cost utility ratio of $26 261 per quality-adjusted life-year) when compared with pegylated interferon–ribavirin therapy, associated with an increase in health (1.879 quality-adjusted life-years) and cost ($49 344).

Genotype 1, treatment-experienced

For genotype 1, treatment-experienced patients without cirrhosis, paritaprevir–ritonavir plus ombitasvir plus dasabuvir for 12 weeks (PAR/RIT12 + OMB12 + DAS12) was the most cost-effective treatment (incremental cost utility ratio

of $15 506 per quality-adjusted life-year) when compared with pegylated interferon–ribavirin therapy, associated with an increase in health (1.586 quality-adjusted life-years) and cost ($24 597). For patients with cirrhosis, response-guided therapy with simeprevir–pegylated interferon–ribavirin (SIM12 PR24–48 response-guided therapy) was likely to be the most cost-effective option, followed by sofosbuvir plus ledipasvir plus ribavirin for 12 weeks (SOF12 + LDV12 + RBV12), compared with pegylated interferon–ribavirin alone (Table 4).

Genotype 2

Table 4 also summarizes the outcomes associated with the base-case analysis for a cohort of 50-year-old, treatment-naive, genotype 2 patients without cirrhosis. Sofosbuvir plus ribavirin for 12 weeks (SOF12 + RBV12) was associated with an increase in health (0.217 quality-adjusted life-years) and cost ($44 051), resulting in an incremental cost utility ratio of $203 282 per quality-adjusted life-year compared with pegylated interferon–ribavirin therapy. For genotype 2, treatment-naive patients with cirrhosis, SOF12 + RBV12 was associated with an increase

Table 1: Treatment included in the base-case analysis

Treatment comparators	Subgroup				Description
Genotype 1	N/NC	N/C	E/NC	E/C	
PR48	X	X	X	X	Pegylated interferon + ribavirin for 48 wk
SOF24 + RBV24	X	X			Sofosbuvir + ribavirin for 24 wk
SIM12 + SOF12	X	X	X	X	Simeprevir + sofosbuvir for 12 wk
SOF12 + LDV12	X	X	X		sofosbuvir + ledipasvir for 12 wk
PAR/RIT12 + OMB12 + DAS12	X		X		Paritaprevir/ritonavir + ombitasvir + dasabuvir for 12 wk
PAR/RIT12 + OMB12 + DAS12 + RBV12	X		X		Paritaprevir/ritonavir + ombitasvir + dasabuvir + ribavirin for 12 wk
DCV12 + SOF12	X				Daclatasvir and sofosbuvir for 12 wk
T12 PR24–48 RGT q8	X	X			Telaprevir for 12 wk and PR used as RGT for 24 or 48 wk (750 mg every 8 h)
SOF12 + PR12	X	X	X	X	Sofosbuvir + pegylated interferon + ribavirin for 12 wk
SOF12 + PR24–48 RGT	X				Sofosbuvir for 12 wk and PR used as RGT for 24 or 48 wk
SIM12 + PR24–48 RGT	X	X	X	X	Simeprevir for 12 wk and PR used as RGT for 24 or 48 wk
B24 + PR28–48 RGT	X	X			Boceprevir for 24 wk and PR used as RGT for 28 or 48 wk
SIM12 + SOF12 + RBV12	X		X		Simeprevir + sofosbuvir+ ribavirin for 12 wk
SIM12 + PR48			X	X	Simeprevir for 12 wk and PR for 48 wk
B32 PR36–48 RGT			X	X	Boceprevir for 32 wk and PR used as RGT for 36 or 48 wk
SOF24 + LDV24				X	Sofosbuvir + ledipasvir for 24 wk
SOF12 + LDV12 + RBV12				X	Sofosbuvir + ledipasvir + ribavirin for 12 wk
T12 PR48 q8			X	X	Telaprevir for 12 wk and PR for 48 wk (750 mg every 8 h)
Genotype 2					
SOF12 + RBV12	X	X	X	X	sofosbuvir + ribavirin for 12 wk
SOF12 + PR12	X		X	X	Sofosbuvir + pegylated interferon + ribavirin for 12 wk
PR24	X	X			Pegylated interferon + ribavirin for 24 wk
SOF16 + RBV16				X	Sofosbuvir + ribavirin for 16 wk
Genotype 3					
PR48	X	X	X	X	Pegylated interferon + ribavirin for 48 wk
DCV12 + SOF12	X		X		Daclatasvir and sofosbuvir for 12 wk
SOF24 + RBV24	X	X	X	X	Sofosbuvir + ribavirin for 24 wk
SOF12 + PR12			X	X	Sofosbuvir + pegylated interferon + ribavirin for 12 wk
Genotype 4					
PR 48	X	X			Pegylated interferon + ribavirin for 48 wk
SOF12 + PR12	X				sofosbuvir + pegylated interferon + ribavirin for 12 wk
SOF24 + RBV24	X	X	X	X	Sofosbuvir + ribavirin for 24 wk

Note: E/C = treatment-experienced with cirrhosis, E/NC = treatment-experienced without cirrhosis, N/C = treatment-naive with cirrhosis, N/NC = treatment-naive without cirrhosis.

in health (0.797 quality-adjusted life-years) and cost ($46 773), resulting in an incremental cost utility ratio of $58 659 per quality-adjusted life-year compared with pegylated interferon–ribavirin therapy.

For genotype 2, treatment-experienced patients without cirrhosis, SOF12 + RBV12 was associated with an increase in health (2.157 quality-adjusted life-years) and cost ($39 355), resulting in an incremental cost utility ratio of $18 247 per quality-adjusted life-year compared with no treatment. For treatment-experienced patients with cirrhosis, sofosbuvir plus pegylated interferon–ribavirin for 12 weeks (SOF12 + PR12) was associated with an increase in health (3.265 quality-adjusted life-years) and cost ($59 508), resulting in an incremental cost utility ratio of $18 226 per quality-adjusted life-year compared with no treatment.

Genotype 3

The outcomes associated with the base-case analysis for a cohort of 50-year-old, genotype 3, treatment-naive patients without cirrhosis are shown in Table 4. Daclatasvir and sofosbuvir for 12 weeks (DCV12 + SOF12) was the most cost-effective regimen of those currently approved, with an incremental cost utility ratio of $97 158 when compared with pegylated interferon–ribavirin. Similarly, for genotype

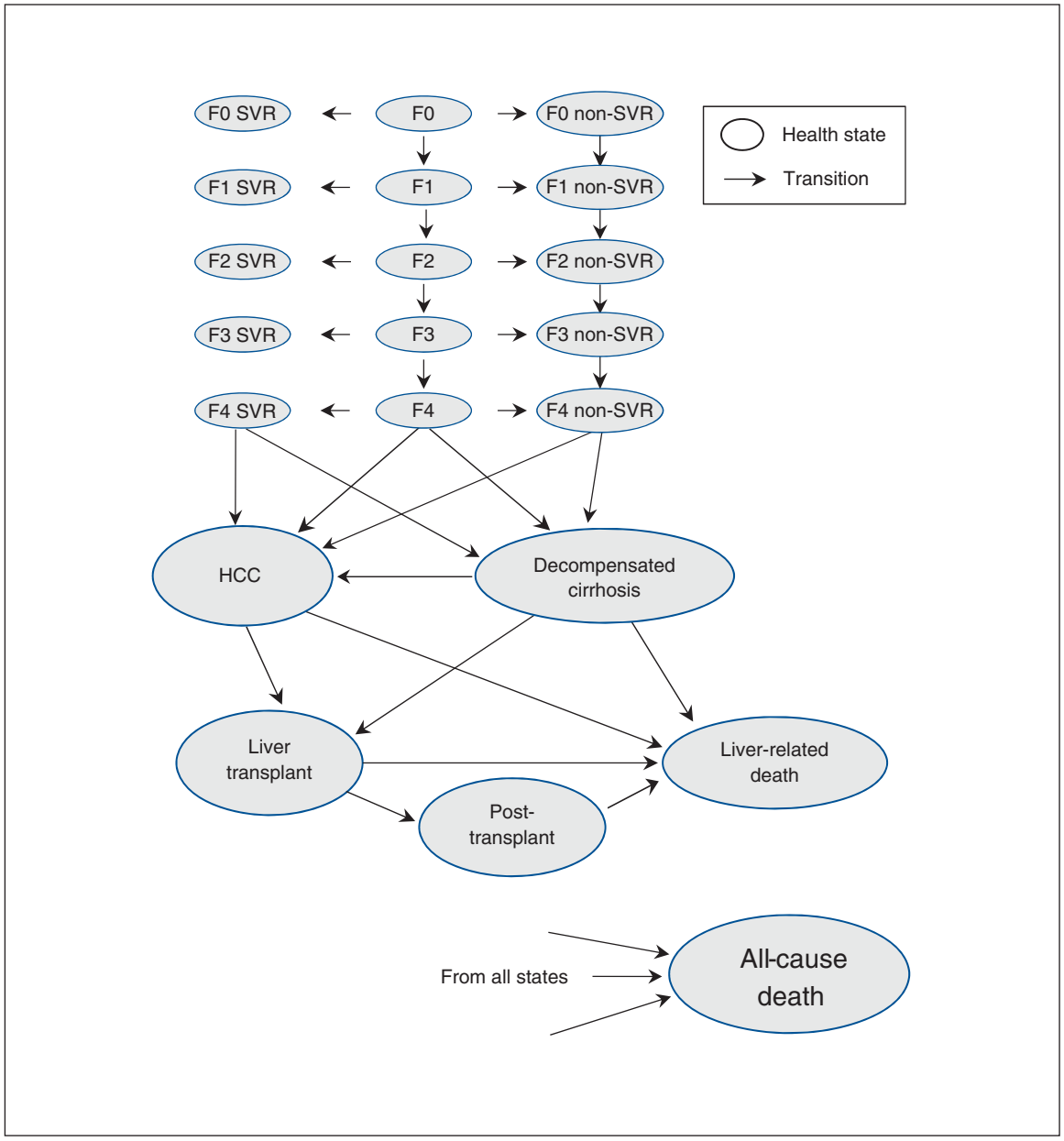

Figure 1: State-transition model of hepatitis C virus infection and progression. F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with rare septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis, HCC = hepatocellular carcinoma, SVR = sustained virological response.

Table 2 (part 1 of 2): Treatment efficacy (sustained virological response) used in the model

Description	Baseline* or RR	Lower limit (95% CrI)	Upper limit (95% CrI)
Genotype 1: treatment-naive			
Noncirrhosis			
Reference baseline PR48	0.4913*	0.4359	0.5456
SOF24 + RBV24	1.634	1.288	1.899
SIM12 + SOF12	1.802	0.8004	2.186
SOF12 + LDV12	1.978	1.78	2.225
PAR/RIT12 + OMB12 + DAS12	1.932	1.337	2.211
PAR/RIT12 + OMB12 + DAS12 + RBV12	1.944	1.748	2.18
T12 PR24–48 RGT q8	1.555	1.312	1.767
SOF12 + PR12	1.769	1.278	2.065
SOF12 + PR24–48 RGT	1.727	1.245	2.055
SIM12 + PR24–48 RGT	1.589	1.411	1.784
B24 PR28–48 RGT	1.538	1.268	1.777
SIM12 + SOF12 + RBV12	1.766	0.8601	2.176
DCV12 + SOF12	1.898	1.276	2.212
Cirrhosis			
Reference baseline PR48	0.3958*	0.3092	0.4906
SOF24 + RBV24	1.757	0.6207	2.571
SIM12 + SOF12	2.175	0.9347	2.949
SOF12 + LDV12	2.408	1.893	3.089
T12 PR24–48 RGT q8	1.43	0.6368	2.195
SOF12 + PR12	2.038	1.125	2.749
SIM12 + PR24–48 RGT	1.695	1.057	2.387
B24 PR28–48 RGT	0.6456	0.1609	1.653
Genotype 1: treatment-experienced			
Noncirrhosis			
Reference baseline PR48	0.2571*	0.2242	0.292
SIM12 + SOF12	1.023	0.04915	3.635
SOF12 + LDV12	3.564	2.992	4.151
PAR/RIT12 + OMB12 + DAS12	3.753	3.204	4.329
PAR/RIT12 + OMB12 + DAS12 + RBV12	3.818	3.345	4.387
T12 PR48 q8	3.038	2.405	3.633
SOF12 + PR12	3.097	2.276	3.768
SIM12 + PR24–48 RGT	2.587	1.757	3.207
SIM12 + PR48	3.045	2.152	3.718
SIM12 + SOF12 + RBV12	2.354	0.2271	3.878
B32 PR36–48 RGT	2.547	1.692	3.328
Cirrhosis			
Reference baseline PR48	0.1691*	0.1165	0.2334
SIM12 + SOF12	4.665	1.796	7.161
SOF24 + LDV24	4.503	1.603	7.215
SOF12 + LDV12 + RBV12	4.626	2.931	7.005
T12 PR48 q8	3.027	1.361	5.425
SOF12 + PR12	2.944	0.3161	6.236
SIM12 + PR24–48 RGT	3.563	1.608	6.091
SIM12 + PR48	2.709	0.8918	5.319
B32 PR36–48 RGT	2.521	0.7132	5.623

3 treatment-experienced patients without cirrhosis, DCV12 + SOF12 was associated with an increase in health (2.612 quality-adjusted life-years) and cost ($79 544), resulting in an incremental cost utility ratio of $28 151 per quality-adjusted life-year, compared with no treatment. In patients with cirrhosis, sofosbuvir and ribavirin for 24 weeks (SOF24

Table 2 (part 2 of 2): Treatment efficacy (sustained virological response) used in the model

Description	Baseline* or RR	Lower limit (95% CrI)	Upper limit (95% CrI)
Genotype 2: treatment-naive			
Noncirrhosis			
SOF12 + RBV12	1.16	1.083	1.244
SOF12 PR12	1.148	0.4762	1.266
Reference baseline PR24	0.8191*	0.7687	0.8619
Cirrhosis			
SOF12 + RBV12	1.375	1.026	1.791
Reference baseline PR24	0.6209*	0.4966	0.7344
Genotype 2: treatment-experienced			
Noncirrhosis			
Reference baseline SOF12 + RBV12	0.9549*	0.9071	0.9829
SOF12 + PR12	1.006	0.8914	1.071
Cirrhosis			
Reference baseline SOF12 + RBV12	0.7331*	0.579	0.8554
SOF12 + PR12	1.286	0.9865	1.643
SOF16 + RBV16	1.052	0.7123	1.414
Genotype 3: treatment-naive			
Noncirrhosis			
Reference baseline PR48	0.7051*	0.6393	0.765
SOF24 + RBV24	1.318	1.177	1.47
DCV12 + SOF12	1.375	1.233	1.525
Cirrhosis			
Reference baseline PR48	0.6021*	0.5584	0.6441
SOF24 + RBV24	1.509	1.142	1.702
Genotype 3: treatment-experienced			
Noncirrhosis			
Reference baseline PR48	0.6082*	0.5786	0.6374
SOF24 + RBV24	1.467	1.315	1.591
SOF12 + PR12	1.384	0.8798	1.62
DCV12 + SOF12	1.544	1.306	1.667
Cirrhosis			
Reference baseline PR48	0.4777*	0.4382	0.5174
SOF24 + RBV24	1.465	1.139	1.789
SOF12 + PR12	1.731	1.09	2.086
Genotype 4: treatment-naive			
Noncirrhosis			
Reference baseline PR48	0.6502*	0.6335	0.6668
SOF24 + RBV24	1.268	0.895	1.465
SOF12 + PR12	1.482	1.269	1.552
Cirrhosis			
Reference baseline PR48	0.3804*	0.3567	0.4052
SOF24 + RBV24	2.27	1.361	2.65
Genotype 4: treatment-experienced			
Noncirrhosis			
Reference baseline SOF12 + RBV12	0.6345*	0.4483	0.7983
SOF24 + RBV24	1.28	0.6814	1.905
Cirrhosis			
Reference baseline SOF12 + RBV12	0.5628*	0.2422	0.8484
SOF24 + RBV24	1.469	0.5728	3.505

Note: Probability distribution based on network meta-analysis.[15] For descriptions or treatment regimens, see Table 1. CrI = credible interval, RR = relative risk.
*Baseline probability.

+ RBV24) was the most cost-effective approved option for both treatment-naïve and treatment-experienced patients.

Genotype 4

Sofosbuvir plus pegylated interferon–ribavirin for 12 weeks (SOF12 + PR12) was the only approved treatment for genotype 4 infection, and was associated with an incremental cost utility ratio of $63 421 per quality-adjusted life-year compared with pegylated interferon–ribavirin for treatment-naive patients without cirrhosis (Table 4). For patients who are treatment-naive with cirrhosis or those who are treatment-experienced, SOF24 + RBV24 was considered the most cost-effective treatment; however it is not currently approved. SOF12 + PR12 could not be evaluated in these subgroups owing to lack of data.

Sensitivity analyses

We performed both 1-way sensitivity analyses and probabilistic sensitivity analyses to explore the impact of the model's parameter uncertainty.

Deterministic sensitivity analyses

The effect of varying parameters related to chronic hepatitis C, treatment-related parameters and heterogeneity parameters for the treatment-naive and treatment-experienced populations based on the incremental cost utility ratio of the most cost-effective treatment is shown in Appendix 4. For all the subpopulations assessed, baseline age, treatment efficacy and cost of antiviral therapy were the most sensitive parameters.

To further measure the effect of the estimates of relative risk of treatment efficacy used in the model, the parameters were

Table 3 (part 1 of 2): Costs, utilities and other important parameters used in the model

Fibrosis distribution				
Treatment status and fibrosis stage	Base estimate	Lower limit (–25%)	Upper limit (+25%)	Probability distribution
Treatment-naive[16]				
F0	0.08	0.06	0.1	Beta (58.8–676.2)
F1	0.20	0.15	0.25	Beta (51–204)
F2	0.35	0.2625	0.4375	Beta (41.25–76.61)
F3	0.21	0.1575	0.2625	Beta (50.35–189.41)
F4	0.16	0.12	0.2	Beta (53.6–281.4)
Treatment-experienced[17]				
F0	0.04	0.03	0.05	Beta (61.4–1473.6)
F1	0.13	0.0975	0.1625	Beta (55.55–371.76)
F2	0.38	0.285	0.475	Beta (39.3–64.12)
F3	0.23	0.1725	0.2875	Beta (49.05–164.21)
F4	0.22	0.165	0.275	Beta (49.7–176.2)
Natural history parameters				
Description	Base estimate	Lower limit (95% CI)	Upper limit (95% CI)	Probability distribution
Annual probability for fibrosis progression				
F0–F1[18]	0.117	0.104	0.13	Beta (285.9–2158.3)
F1–F2[18]	0.085	0.075	0.096	Beta (218.5–2351.6)
F2–F3[18]	0.12	0.109	0.133	Beta (299.8–2198.6)
F3–F4[18]	0.116	0.104	0.129	Beta (281.4–2144.7)
Genotype 3 accelerated fibrosis progression (OR)[19]	1.52	1.12	2.07	Exp [normal (0.419–0.154)]
Annual probability for cirrhosis progression				
F4–decompensated (non-SVR)[5]	0.035	0.027	0.043	Beta (73.8–2036.1)
F4–decompensated (SVR)[5]	0.002	0.0001	0.005	Beta (1.77–884.3)
F4–HCC (non-SVR)[5]	0.024	0.018	0.031	Beta (45.9–1865.3)
F4–HCC (SVR)[5]	0.005	0.001	0.009	Beta (6.21–1236.5)
Annual probability for liver transplantation[20]				
From decompensated cirrhosis	0.033	0.017	0.049	Beta (16.42–481.19)
From HCC	0.033	0.017	0.049	Beta (16.42–481.19)

Table 3 (part 2 of 2): Costs, utilities and other important parameters used in the model

Description	Base estimate	Lower limit (–25%)	Upper limit (+25%)	Probability distribution
Chronic hepatitis C–related mortality				
HCC[21]	0.411	0.31	0.51	Beta (38.6–55.3)
Decompensated cirrhosis[22]	0.216	0.162	0.27	Beta (49.96–181.3)
Liver transplant (first yr)[23]	0.142	0.124	0.159	Beta (213.4–1289.7)
Liver transplant (> 1 yr)[23]	0.034	0.024	0.043	Beta (44.6–1268.1)
Therapy cost, Can$				
PAR/RIT+ OMB + DAS (Holkira Pak) 12 wk[24]	55 860	41 895	69 825	–
LDV + SOF (Harvoni) 12 wk[24]	67 000	50 250	83 750	–
DCV (Daklinza) 12 wk[24]	36 000	27 000	45 000	–
SOF(Sovaldi) 12 wk[24]	55 000	41 250	68 750	–
SIM (Galexos) 12 wk[24]	36 502	27 377	45 628	–
PR 24 wk[24]	9500	7125	11 875	–
Telaprevir (Incivek) Pegylated interferon/ribavirin 24 to 48 wk[24]	44 468–53 968	33 351–40 476	55 585–67 460	–
Boceprevir Pegylated interferon alfa-2b/ribavirin 24 to 44 wk[24]	31 831–59 972	23 873–44 979	39 789 –74 965	–
Chronic hepatitis C–related utilities				
Canadian population average[25]				
Age 45–54 yr	0.86	0.83	0.88	Beta (459.34–74.78)
Utility for CHC infection–related health states[26]				
Non-irrhosis	0.73	0.69	0.77	Beta (358.98–132.77)
Compensated cirrhosis	0.69	0.65	0.73	Beta (368.29–165.46)
Hepatocellular carcinoma	0.69	0.65	0.73	Beta (368.29–165.46)
Decompensated cirrhosis[27]	0.65	0.61	0.69	Beta (369.04–198.71)
Post-transplant	0.75	0.70	0.79	Beta (224.25–74.75)
Noncirrhosis on-treatment (apply only to regimens contains pegylated interferon or ribavirin)	0.71	0.67	0.75	Beta (364.76–148.99)
Noncirrhosis viral clearance	0.80	0.76	0.84	Beta (319.2–79.8)
Compensated cirrhosis on-treatment (apply only to regimens contains pegylated interferon or ribavirin)	0.67	0.63	0.71	Beta (369.67–182.08)
Compensated cirrhosis viral clearance	0.76	0.72	0.80	Beta (345.8–109.2)
One-time disutility associated with adverse event[28,29]				
Anemia	–0.03	–0.0375	–0.0225	–Beta (62.05–2006.28)
Depression	–0.0625	–0.0781	–0.0468	–Beta (59.94–899.06)
Rash	–0.0213	–0.0267	–0.0159	–Beta (62.62–2006.28)

Note: For descriptions of treatment regimens, see Table 1. CI = confidence interval, OR = odd ratio, SVR = sustained viral response.

varied by the 95% credible intervals generated by the network meta-analysis, as indicated in Table 2. In this analysis for genotype 1, treatment-naive, noncirrhosis group, the incremental cost utility ratio varied from $25 988 to $92 392 for the most cost-effective treatment (PAR/RIT12 + OMB12 + DAS12) when compared with pegylated interferon–ribavirin. For the genotype 1, treatment-experienced, cirrhosis group, the incremental cost utility ratio varied from $11 517 to $99 452 for the most cost-effective treatment (SIM12 + PR24–48 RGT) when compared with pegylated interferon–ribavirin, which may not be considered economically attractive. The main conclusions for the other subgroups remained unchanged.

To measure the effect of the cost of antiviral therapies used in the model, these parameters were varied by 25%, as indicated in Table 2. For the genotype 2 and genotype 4 treatment-naive cirrhosis groups, the generated incremental cost utility ratio for the most cost-effective treatments (genotype 2, SOF12 + RBV12; genotype 4, SOF24 + RBV24) may be less than $50 000 when compared with pegylated interferon–ribavirin. The main conclusion for other groups remained unchanged.

To measure the effect of age in the model, instead of the baseline values, a broader age range of 40–60 years was evaluated. Appendix 1 summarizes the results. The cost-effectiveness results changed significantly. For the genotype 2 and genotype 4 treatment-naive cirrhosis groups, the generated incremental cost utility ratio for the most cost-effective treatments (genotype 2, SOF12 + RBV12; genotype 4, SOF24 + RBV24) may be less than $50 000 when compared with pegylated interferon–ribavirin in younger patients. The main conclusion for other groups remained unchanged.

Other parameters were assessed in deterministic sensitivity analysis, including: fibrosis stage distribution; costs related to chronic hepatitis C, utilities, mortality, chronic hepatitis C progression; and different risk for adverse events. Varying

Table 4 (part 1 of 2): Base-case cost-effectiveness results

	Versus pegylated interferon–ribavirin alone					
Treatment	Total cost, $	Total quality adjusted life-years	Incremental cost, $	Incremental quality-adjusted life-years	Incremental cost utility ratio	Sequential incremental cost utility ratio, $
Genotype 1: treatment-naive noncirrhosis*						
(0) No treatment	104 904	9.734	–	–	–	–
(1) PR48	114 132	10.839	–	–	–	8 353
(14) PAR/RIT12 + OMB12 + DAS12	143 379	11.835	29 247	0.996	29 354	48 060
(6) SOF12 + LDV12	152 762	11.857	38 631	1.018	37 951	435 528
Genotype 1: treatment-naive cirrhosis*						
No treatment	101 355	7.043	–	–	–	–
PR48	120 140	8.659	–	–	–	11 628
SOF12 + LDV12	169 483	10.538	49 344	1.879	26 261	26 261
Genotype 1: treatment-experienced noncirrhosis*						
No treatment	104 668	9.596	–	–	–	–
PR48	118 321	10.282	–	–	–	ext. dominated
PAR/RIT12 + OMB12 + DAS12	142 917	11.868	24 597	1.586	15 506	16 836
PAR/RIT12 + OMB12 + DAS12 + RBV12	145 743	11.898	27 422	1.616	16 965	93 872
Genotype 1: treatment-experienced cirrhosis*						
No treatment	101 355	7.043	–	–	–	–
PR48	119 828	7.924	–	–	–	ext. dominated
SIM12 PR24–48 RGT	148 780	9.326	28 953	1.402	20 655	20 774
SOF12 + LDV12 + RBV12	172 976	9.933	53 148	2.009	26 456	39 845
SIM12 + SOF12	193 052	9.966	73 225	2.041	35 870	618 881
Genotype 2: treatment-naive noncirrhosis*						
PR24	99 904	11.532	–	–	–	–
SOF12 + RBV12	143 955	11.749	44 051	0.217	203 282	203 282
Genotype 2: treatment-naive cirrhosis						
No treatment	101 355	7.043	–	–	–	–
PR24	112 767	9.384	–	–	–	4 876
SOF12 + RBV12	159 541	10.181	46 773	0.797	58 659	58 659
Genotype 2: treatment-experienced noncirrhosis*						
No treatment	104 668	9.596	–	–	–	–
SOF12 + RBV12	144 023	11.753	39 355	2.157	18 247	18 247
Genotype 2: treatment-experienced cirrhosis*						
No treatment	101 355	7.043				
SOF12 + PR12	160 863	10.308	59 508	3.265	18 226	18 226

Table 4 (part 2 of 2): Base-case cost-effectiveness results

Treatment	Versus pegylated interferon–ribavirin alone					
	Total cost, $	Total quality adjusted life-years	Incremental cost, $	Incremental quality-adjusted life-years	Incremental cost utility ratio	Sequential incremental cost utility ratio, $
Genotype 3: treatment-naive noncirrhosis*						
No treatment	104 183	9.314	–	–	–	–
PR48	110 387	11.156	–	–	–	3 367
DCV12 + SOF12	175 987	11.832	65 600	0.675	97 158	97 158
Genotype 3: treatment-naive cirrhosis						
No treatment	101 355	7.043	–	–	–	–
PR48	120 843	9.335	–	–	–	8 504
SOF24 + RBV24	215 437	10.362	94 594	1.027	92 117	92 117
Genotype 3: treatment-experienced noncirrhosis*						
No treatment	103 932	9.167	–	–	–	–
PR48	112 301	10.879	8 368	1.712	4 888	4 888
SOF12 + PR12	149 249	11.51	45 316	2.343	19 339	58 535
DCV12 + SOF12	177 476	11.78	73 544	2.612	28 151	104 857
Genotype 3: treatment-experienced cirrhosis						
No treatment	101 355	7.043				-
PR48	120 880	8.936	19 525	1.893	10 317	10 317
SOF12 + PR12	163 647	10.082	62 292	3.039	20 496	37 319
SOF24 + RBV24	214 706	9.661	113 351	2.618	43 292	Dominated
Genotype 4: treatment-naive noncirrhosis*						
No treatment	104 904	9.734	–	–	–	–
PR48	111 493	11.158	–	–	–	4 627
SOF12 + PR12	145 731	11.698	34 239	0.54	63 421	63 421
Genotype 4: treatment-naive cirrhosis						
No treatment	101 355	7.043	–	–	–	–
PR48	120 087	8.608	–	–	–	11 970
SOF24 + RBV24	215 281	10.208	95 194	1.6	59 492	59 492
Genotype 4: treatment-experienced noncirrhosis						
No treatment	104 668	9.596	–	–	–	
SOF24 + RBV24	201 763	11.503	97 095	1.907	50 913	NA
Genotype 4: treatment-experienced cirrhosis						
No treatment	101 355	7.043	–	–	–	NA
SOF24 + RBV24	215 142	10.093	113 787	3.05	37 303	

Note: For description of treatment regimens, see Table 1.
*Refer to Appendix 4 for dominated or extendedly dominated treatments.

these parameters did not significantly change the results of the base-case analysis.

Probabilistic sensitivity analyses

The results of the probabilistic sensitivity analysis for genotype 1 chronic hepatitis C infection suggest that, for treatment-naive patients without cirrhosis, PAR/RIT12 + OMB12 + DAS12 is likely to remain cost-effective at a willingness-to pay-threshold of $50 000 per quality-adjusted life-year. For treatment-naive patients with cirrhosis, SOF12 + LDV12 is likely to remain cost-effective. For treatment-experienced patients without cirrhosis, PAR/RIT12 + OMB12 + DAS12 is likely to remain cost-effective. For treatment-experienced patients with cirrhosis, owing to the large degree of uncer-

tainty around the efficacy data derived from the network meta-analysis on genotype 1 treatment-experienced patients with cirrhosis, there is significant uncertainty associated with the incremental cost utility ratios for this population.

Results of the probabilistic sensitivity analysis also suggest that, for each genotype 2, genotype 3 and genotype 4 treatment-naive population (with or without cirrhosis), pegylated interferon–ribavirin alone is the most cost-effective option at a willingness-to-pay of $50 000 per quality-adjusted life-year. For genotype 2 chronic hepatitis C infection, the probabilistic sensitivity analysis suggests that, for treatment-experienced patients without cirrhosis, SOF12 + RBV12 is likely to remain cost-effective. For treatment-experienced patients with cirrhosis, SOF12 + PR12 is likely to remain cost-effective (< $50 000/quality-adjusted life-year). For genotype 3 chronic hepatitis C infection, the analysis suggests that for treatment-experienced patients with or without cirrhosis, SOF12 + PR12 is likely to remain cost-effective (< $50 000/quality-adjusted life-year). For genotype 4 chronic hepatitis C infection, the analysis suggests that for treatment-experienced patients with cirrhosis, SOF24 + RBV24 is likely to remain cost-effective. For treatment-experienced patients without cirrhosis, no conclusion about the most cost-effective option can be reached owing to uncertainty. Appendix 4 summarizes the results through cost-effectiveness acceptability curves.

Results of multiple 1-way sensitivity analyses and multiple probabilistic sensitivity analyses provided evidence that there were some subpopulations in which the direct-acting antiviral agents would likely remain cost-effective compared with pegylated interferon–ribavirin alone when the uncertainty of the model's parameters are taken into consideration.

Discussion

For each genotype 1 population, at least 1 of the interferon-free therapies appeared to be economically attractive compared with pegylated interferon–ribavirin alone, at a willingness-to-pay of $50 000 per quality-adjusted life-year. The conventional upper limit of applied cost effectiveness thresholds[37–39] varies among countries from $50 000 to $120 000 per quality-adjusted life-year. The drug that was the most cost-effective varied by population. For each genotype 2–4 treatment-naive population, the interferon-free or the pegylated interferon–ribavirin–based direct-acting antiviral therapies appeared not to be economically attractive compared with pegylated interferon–ribavirin alone at a willingness-to-pay of $50 000 per quality-adjusted life-year. For each genotype 2–4 treatment-experienced population, there were interferon-free or pegylated interferon–ribavirin–based direct-acting antiviral therapies that appeared to be attractive at a willingness to pay of $50 000 per quality-adjusted life-year when compared with no treatment.

A number of studies reported incremental cost-effectiveness ratios of about Can$40 000 per quality-adjusted life-year for the interferon-free direct-acting antiviral regimens compared with pegylated interferon–ribavirin–based direct-acting antiviral regimens.[40–43] Most studies concluded that it is cost-effective to treat genotype 1 with interferon-free direct-acting antiviral agents compared with pegylated interferon–ribavirin–based direct-acting antiviral agents. More recently, additional studies have reported incremental cost-effectiveness for other genotypes.[41,42,44–46] Most of the studies concluded that it is not cost-effective to treat genotypes 2–4 with the interferon-free direct-acting antiviral agents at a willingness-to-pay of $50 000 per quality-adjusted life-year.

Limitations

As with all economic models, a number of assumptions were made in this economic evaluation. First, comparative efficacy and adverse events was based on findings for fibrosis subgroups from a network meta-analysis, which have been stratified by cirrhosis and noncirrhosis. Ideally, the network meta-analysis should have been stratified by individual fibrosis stages. Furthermore, there were very few data available in the literature on the disutility associated with adverse events. The costs related to chronic hepatitis C that we used were not fibrosis-specific; they may overestimate the cost of mild or no fibrosis and underestimate the cost of severe fibrosis. The utilities of patients with chronic hepatitis C who have late-stage liver disease (decompensated cirrhosis and hepatocellular carcinoma) used in the model were based on very small sample sizes and may not cover the full spectrum of the severity of the disease. The pharmacoeconomic analyses do not account for any confidential prices potentially negotiated for therapies. Finally, our analyses do not consider patients with coinfections and subsequent treatment of reinfection.

Conclusion

Public health policy should be informed by consideration of health benefit, social and ethical values, feasibility and cost-effectiveness. Our analysis assists the development of hepatitis C virus reimbursements and policies for direct-acting antiviral–based regimens for chronic hepatitis C infection by informing the last criterion. We believe that it offers scientifically valid projections mainly based on Canadian data and a network meta-analysis. The CADTH Canadian Drug Expert Committee has issued a recommendation partly based on our findings.[47]

Considering the rapid pace of development of treatments for chronic hepatitis C, updated and expanded reviews will be necessary. Finally, although shown to be cost-effective, the high cost of direct-acting antiviral agents seriously restricts treatment access in Canada, with further pressure from screening efforts to identify many more patients. To seriously effect the disease, ensure equitable access and help policymakers meet budgetary challenges, fair and efficient screening and treatment strategies are needed.

References

1. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002;347:975-82.
2. Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140:346-55.
3. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001;358:958-65.

4. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009;361:580-93.
5. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012;308:2584-93.
6. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014;370:1483-93.
7. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014;370:1889-98.
8. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014;370:1879-88.
9. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370:1594-603.
10. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;370:1973-82.
11. Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014;370:1604-14.
12. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014;370:211-21.
13. Murphy G, Farah B, Wong WWL, et al. CADTH THERAPEUTIC REVIEW 7: Scientific report: direct acting antiviral agents for chronic hepatitis C Genotype 1. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2014.
14. TreeAge 2014 Professional. Williamstown (MA): TreeAge Software; 2014.
15. Therapeutic review: drugs for chronic hepatitis C infection [clinical report]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2015.
16. Lee SS, Bain VG, Peltekian K, et al. Treating chronic hepatitis C with pegylated interferon alfa-2a (40 KD) and ribavirin in clinical practice. *Aliment Pharmacol Ther* 2006;23:397-408.
17. Sherman M, Yoshida EM, Deschenes M, et al. Peginterferon alfa-2a (40KD) plus ribavirin in chronic hepatitis C patients who failed previous interferon therapy. *Gut* 2006;55:1631-8.
18. Thein HH, Yi Q, Dore GJ, et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008;48:418-31.
19. Probst A, Dang T, Bochud M, et al. Role of hepatitis C virus genotype 3 in liver fibrosis progression — a systematic review and meta-analysis. *J Viral Hepat* 2011;18:745-59.
20. Krahn M, Wong JB, Heathcote J, et al. Estimating the prognosis of hepatitis C patients infected by transfusion in Canada between 1986 and 1990. *Med Decis Making* 2004;24:20-9.
21. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009;27:1485-91.
22. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J Hepatol* 2006;44:217-31.
23. Charlton M, Seaberg E, Wiesner R, et al. Predictors of patient and graft survival following liver transplantation for hepatitis C. *Hepatology* 1998;28:823-30.
24. Therapeutic review: drugs for chronic hepatitis C infection [pharmacoeconomic report]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2015.
25. Maddigan SL, Feeny DH, Johnson JA. Health-related quality of life deficits associated with diabetes and comorbidities in a Canadian National Population Health Survey. *Qual Life Res* 2005;14:1311-20.
26. Hsu PC, Federico CA, Krajden M, et al. Health utilities and psychometric quality of life in patients with early- and late-stage hepatitis C virus infection. *J Gastroenterol Hepatol* 2012;27:149-57.
27. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. *Med Decis Making* 2008;28:582-92.
28. Del Rio RA, Post AB, Singer ME. Cost-effectiveness of hematologic growth factors for anemia occurring during hepatitis C combination therapy. *Hepatology* 2006;44:1598-606.
29. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006;26:410-20.
30. Krajden M, Kuo M, Zagorski B, et al. Health care costs associated with hepatitis C: a longitudinal cohort study. *Can J Gastroenterol* 2010;24:717-26.
31. Taylor MC, Greig PD, Detsky AS, et al. Factors associated with the high cost of liver transplantation in adults. *Can J Surg* 2002;45:425-34.
32. Gao X, Stephens JM, Carter JA, et al. Impact of adverse events on costs and quality of life in protease inhibitor-based combination therapy for hepatitis C. *Expert Rev Pharmacoecon Outcomes Res* 2012;12:335-43.
33. *Table 3260021: Consumer Price Index (CPI) — annual (2002=100) [2005 basket].* Ottawa: Statistics Canada; 2015. Available: www5.statcan.gc.ca/cansim/a26?id=3260021 (accessed 2017 Jan. 9).
34. *Guidelines for the economic evaluation of health Technologies. 3rd ed.* Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006. Available: www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf (accessed 2016 June 1).
35. Salomon JA, Weinstein MC, Hammitt JK, et al. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. *JAMA* 2003;290:228-37.
36. Wong JB, Bennett WG, Koff RS, et al. Pretreatment evaluation of chronic hepatitis C: risks, benefits, and costs. *JAMA* 1998;280:2088-93.
37. Laupacis A, Feeny D, Detsky AS, et al. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ* 1992;146:473-81.
38. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. *Pharmacoeconomics* 2008;26:733-44.
39. Choosing interventions that are cost effective (WHO-CHOICE). Geneva: World Health Organization; 2005.
40. San Miguel R, Gimeno-Ballester V, Blazquez A, et al. Cost-effectiveness analysis of sofosbuvir-based regimens for chronic hepatitis C. *Gut* 2015;64:1277-88.
41. Chhatwal J, Kanwal F, Roberts MS, et al. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med* 2015;162:397-406.
42. Najafzadeh M, Andersson K, Shrank WH, et al. Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. *Ann Intern Med* 2015;162:407-19.
43. Zhang S, Bastian ND, Griffin PM. Cost-effectiveness of sofosbuvir-based treatments for chronic hepatitis C in the US. *BMC Gastroenterol* 2015;15:98.
44. Foster GR, Pianko S, Cooper C, et al. Sofosbuvir plus Peg-IFN/RBV for 12 weeks vs Sofosbuvir/RBV for 16 or 24 weeks in Genotype 3 HCV-Infected Patients and Treatment-Experienced Cirrhotic Patients With Genotype 2 HCV: The BOSON Study. *Proceedings of EASL — The International Liver Congress 2015 50th Annual Meeting of the European Association for the Study of the Liver*; 2015 Apr. 22–26.
45. Linas BP, Barter DM, Morgan JR, et al. The cost-effectiveness of sofosbuvir-based regimens for treatment of hepatitis C virus genotype 2 or 3 infection. *Ann Intern Med* 2015;162:619-29.
46. Moshyk A, Martel MJ, Tahami Monfared AA, et al. Cost-effectiveness of daclatasvir plus sofosbuvir-based regimen for treatment of hepatitis C virus genotype 3 infection in Canada. *J Med Econ* 2016;19:181-92.
47. Drugs for chronic hepatitis C infection: recommendations report. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2015.
48. Rotermann M, Langlois K, Andonov A, et al. *Health Reports: Seroprevalence of hepatitis B and C virus infections: results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey.* Ottawa: Statistics Canada; 2013. Cat. no. 82-003-X.

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