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Hepatitis C Treatment Regimens Are Cost-Effective: But Compared With What?

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Abstract

Background: Numerous economic models have been published evaluating treatment of chronic hepatitis C virus (HCV) infection, but none provide a comprehensive comparison among new antiviral agents. **Objective:** Evaluate the cost-effectiveness of all recommended therapies for treatment of genotypes 1 and 4 chronic HCV. **Methods:** Using data from clinical trials, observational analyses, and drug pricing databases, Markov decision models were developed for HCV genotypes 1 and 4 to compare all recommended drugs from the perspective of the third-party payer over a 5-, 10-, and 50-year time horizon. A probabilistic sensitivity analysis (PSA) was conducted by assigning distributions for clinical cure, age entering the model, costs for each health state, and quality-adjusted life years (QALYs) for each health state in a Monte Carlo simulation of 10 000 repetitions of the model. **Results:** In the lifetime model for genotype 1, effects ranged from 18.08 to 18.40 QALYs and total costs ranged from $88 107 to $184 636. The lifetime model of genotype 4 treatments had a range of effects from 18.23 to 18.43 QALYs and total costs ranging from $87 063 to $127 637. Grazoprevir/elbasvir was the optimal strategy followed by velpatasvir/sofosbuvir as the second-best strategy in most simulations for both genotypes 1 and 4, with drug costs and efficacy of grazoprevir/elbasvir as the primary model drivers. **Conclusions:** Grazoprevir/elbasvir was cost-effective compared with all strategies for genotypes 1 and 4. Effects for all strategies were similar with cost of drug in the initial year driving the results.

Keywords

hepatitis C, cost-effectiveness, cost-utility, genotype 1, genotype 4

Introduction

In late 2013, pharmaceutical advances in the treatment of chronic hepatitis C virus (HCV) with direct acting antivirals (DAAs) changed the landscape of therapy for patients and clinicians.[1] These advances provide a cure for potentially 3 to 4 million Americans with HCV but would require substantial expenditures for the US health care system.[2-4] Previous investigations of the cost-effectiveness of new HCV medications have established the case for the treatment of disease from a societal perspective as curing the disease prevents downstream long-term costs.[5-8]

A search of a combination of the terms "cost-effectiveness analysis" OR "incremental cost-effectiveness ratio" (ICER), and "hepatitis C" in SCOPUS from January 1, 2014 to January 11, 2017 returned 178 articles. At least 30 peer-reviewed economic evaluations of HCV therapies have been published since January 2014, but there is no standard methodology for determining which interventions to include in an analysis (Table 1).[5,8-44] Cost-effectiveness researchers often have good rationale for methodological variations chosen in a given model, but these adjustments may add difficulty when interpreting the results across studies in any one disease state or area.[45,46] Several economic analyses published evaluating DAAs after 2014 included comparisons to older interferon-based regimens or no treatment as base case scenarios. As DAAs continued to be introduced on the market there have been limited direct comparisons that would reflect the current treatment guidelines.[1] Multiple studies were also published in 2016 that included boceprevir or telaprevir-based therapies as comparators, despite the manufacturers voluntarily pulling both drugs from the market in 2014 and 2015.[7,12-14,47,48]

Genotypes 1 and 3 are the most prevalent genetic variations of HCV worldwide; however, regional patterns exist for all genotypes and genotypes 2, 4, and 6 represent about 23% of cases globally.[50] Currently, there are 6 potent oral DAA combinations recommended for initial treatment of genotype 1 infection and 4 DAAs recommended for

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Table 1. Cost-Effectiveness Studies for HCV Treatments From January 1, 2014 to January 11, 2017.

	Treatment Comparators Used in Analysis (Citation Number Listed)										
	LED/SOF	VEL/SOF	DAC+SOF	SIM+SOF	SOF with INF ± RBV	PrO/DAS	GZR/EBR	BOC or TEL-based regimen	INF+RBV	Other regimen	No treatment comparator
LED/SOF			14	14	15			4,5,14	4,5,14-16		5
VEL/SOF											
DAC+SOF					17,18			13	13,18		13
SIM+SOF											
SOF with INF ± RBV			19	20				8,20-28	19-30	26	8,21,22,30
PrO/DAS	31,32			31	32,49			49	49	31,33	31,32
GZR/EBR									34		34
BOC- or TEL-based regimen	6		6	6	6,35	35			36-39		38
INF+RBV					40			41			41,42
Other regimen[a]								12,43,44	43,44		44

Abbreviations: HCV, hepatitis C virus; GZR/EBR, grazoprevir/elbasvir; LED/SOF, ledipasvir/sofosbuvir; PrO/DAS, paritaprevir/ritonavir/ombitasvir plus dasabuvir; SIM+SOF, simeprevir + sofosbuvir; SOF with INF ± RBV, sofosbuvir with either interferon and/or ribavirin; DAC+SOF, daclatasvir + sofosbuvir; VEL/SOF, velpatasvir/sofosbuvir; BOC- or TEL-based regimen, boceprevir- or telaprevir-containing regimens; INF+RBV, interferon + ribavirin.
[a]Other regimen includes combinations with asunaprevir or various other combinations not mentioned previously.

Table 2. Treatment of Chronic HCV Genotypes 1 and 4 With Total Regimen Acquisition Costs.[1,56]

Patient Characteristics	Treatment and Guideline Rating	Wholesale Acquisition Costs
Genotype 1		
Treatment-naïve	GZR/EBR for 12 weeks (Class I)	$54 600
	LED/SOF for 12 weeks (Class I)	$94 500
	PrO/DAS for 12 weeks (Class I)	$83 319
	SIM+SOF for 12 weeks (Class I)	$150 360
	DAC+SOF for 12 weeks (Class I)	$147 000
	VEL/SOF for 12 weeks (Class I)	$74 760
Genotype 4		
Treatment-naïve	GZR/EBR for 12 weeks (Class IIa)	$54 600
	LED/SOF for 12 weeks (Class IIa)	$94 500
	PrO/DAS for 12 weeks (Class I)	$83 319
	VEL/SOF for 12 weeks (Class I)	$74 760

Abbreviations: HCV, hepatitis C virus; GZR/EBR, grazoprevir/elbasvir; LED/SOF, ledipasvir/sofosbuvir; PrO/DAS, paritaprevir/ritonavir/ombitasvir plus dasabuvir; SIM+SOF, simeprevir + sofosbuvir; DAC+SOF, daclatasvir + sofosbuvir; VEL/SOF, velpatasvir/sofosbuvir.

genotype 4.[1] As the number of strategies to treat chronic HCV has increased, comparative evaluation based on updated guidelines would help aid patients, clinicians, and payers in decision making. Therefore, we conducted a cost-effectiveness analysis to evaluate all recommended treatment strategies for the HCV genotypes where the most options exist.

Methods

Model

We developed a Markov decision model using TreeAge Pro (Williamstown, MA), to simulate the natural history and progression of liver disease among patients infected with chronic HCV genotypes 1 or 4 and compare outcomes of recommended treatment strategies similar to previously published models.[6,51,52] The target population reflects the age and disease severity of patients diagnosed with either genotypes 1 or 4 disease and includes only treatment naïve patients without cirrhosis who are likely to be treated.[53,54] The cycle length for each period was 1 year for a total of 5, 10, and 50 cycles with an annual discount rate of 3% used for all costs and effects.[55]

Treatment strategies for HCV genotypes 1 and 4 are listed in Table 2 based on clinical guidelines developed by the American Association for the Study of Liver Diseases (AASLD) in partnership with the Infectious Diseases Society of America (IDSA).[1] For purposes of this analysis, genotypes 1a and 1b were combined since non-cirrhotic

Table 3. Model Parameters and Assumptions.

	Mean	Distribution	Alpha	Beta	Source
Probability of sustained virologic response (SVR)					
Grazoprevir/elbasvir GT 1	0.95	Beta	299	17	[57]
Grazoprevir/elbasvir GT 4	0.97	Beta	66	2	
Ledipasvir/sofosbuvir GT 1	0.99	Beta	211	3	[58-60]
Ledipasvir/sofosbuvir GT 4	0.95	Beta	21	1	
PrO/dasabuvir GT 1	0.96	Beta	455	18	[61]
PrO/dasabuvir GT 4	0.98	Beta	131	2	
Simeprevir + sofosbuvir GT 1	0.95	Beta	229	11	[62,63]
Daclatasvir + sofosbuvir GT 1	0.98	Beta	124	2	[64]
Velpatasvir/sofosbuvir GT 1	0.98	Beta	383	13	[65]
Velpatasvir/sofosbuvir GT 4	0.99	Beta	120	1	
State transition probabilities					
F0 to F1	0.117	Beta	275.0	2075.3	[6,52]
F1 to F2	0.085	Beta	210.1	2261.2	
F2 to F3	0.12	Beta	288.1	2112.4	
F3 to F4	0.116	Beta	270.6	2062.2	
F4 to decompensated cirrhosis (DC)	0.039	Beta	3.5	86.5	
F4 to hepatocellular carcinoma (HCC)	0.014	Beta	0.2	12.4	
DC to transplant	0.023	Beta	1.3	55.4	
DC to death	0.182	Beta	1626.4	7309.9	
HCC to transplant	0.04	Beta	0.6	14.2	
HCC to death	0.427	Beta	21.4	28.7	
Transplant year 1 to death	0.166	Beta	1.4	6.9	
Posttransplant to death	0.044	Beta	1.6	35.5	
Utility inputs					
Age-specific					
40-49 y	0.87	Uniform	—	—	[66]
50-59 y	0.84	Uniform	—	—	
60-69 y	0.82	Uniform	—	—	
70-79 y	0.79	Uniform	—	—	
≥80 y	0.74	Uniform	—	—	
Disease-specific					
utilityFO	1.00	Uniform	—	—	[6,52]
utilityF1-F2	0.98	Beta	5.9	0.1	
utilityF3	0.85	Beta	38.0	7.0	
utilityF4	0.79	Beta	40.0	11.0	
utilityDC	0.72	Beta	36.0	14.0	
utilityHCC	0.72	Beta	36.0	14.0	
utilityPT	0.83	Beta	8.0	2.0	
	Mean	**Distribution**	**Standard Deviation**		**Source**
State-specific cost inputs					
METAVIR F0-F3	$1,462	Normal	141		[6,52]
METAVIR F4	$4,350	Normal	210		
DC	$11,520	Normal	2780		
HCC	$45,860	Normal	11054		
Transplant	$151,028	Normal	36410		
Posttransplant	$26,371	Normal	6358		

patients are recommended the same 6 strategies for 12 weeks of therapy. Treatment efficacy was based on sustained virologic response (SVR) reported from clinical trials for each of the treatment strategies (Table 3). Only DAAs were compared since older classes and "no treatment" were not appropriate comparators based on the

AASLD-IDSA guidelines. This study did not qualify as Human Research according to the University of Maryland, Baltimore Institutional Review Board.

Disease Progression Probability

Progression of disease was scored using advancing fibrosis stages categorized by METAVIR. The assumptions representing the natural history of liver disease associated with chronic HCV infection in our model are presented in Table 3. Annual probabilities of transitioning among disease stages from previous studies were utilized.[6,52] Patients reaching SVR in year 1 were subject to a conservative estimated probability of background mortality but did not face a probability of reinfection.[6] Patients who failed to reach SVR entered a natural progression process with baseline fibrosis staging severity ranging between METAVIR F0 and F4 from previous estimates of prevalence.[54]

Costs

All patients entering the model were assumed to incur DAA drug costs in the first year of therapy based on wholesale acquisition costs (WAC) prices listed for each treatment regimen for the duration of therapy.[56] Annualized maintenance costs of care were obtained from previous economic analyses of chronic HCV.[6,52] After year 1, patients who reached SVR incurred the same disease state costs as METAVIR F0-F3 disease to account for virologic cure not completely eliminating the damage already done to the liver tissue. Patients who did not reach SVR in year 1 entered the natural progression model of liver disease incurring annual maintenance costs associated with each stage of advanced disease. Patients reaching the transplant stage only stayed in the "transplant" health state for 1 year, immediately progressing to the post-transplant state the following cycle. Patients only incurred DAA treatment costs and transplant costs once and were assumed to not enter a second course of treatment or undergo a second liver transplant.

Health Benefits

Health-related quality of life (HRQoL) was measured by health state utility estimates found in the literature (Table 3). These estimates were used to calculate quality-adjusted life years (QALYs) as the main model outcome. Age-specific adjustments to health state utility after age 40 years were derived from Sullivan and Ghushchyan's study of the Medical Expenditure Panel Survey.[66] Patients reaching SVR after treatment were assumed to have the same quality-of-life as patients with F0 disease with no residual effects from prior HCV disease.

Sensitivity Analysis

One-way sensitivity analyses were conducted by changing input parameters manually across a conservative range for each type.[55] Drug costs were varied from a low value of 50% of WAC price with the base case at 100% of WAC to account for large potential discounting in managed care rebates and pharmaceutical manufacturer price concessions. Probabilities of SVR and utility values were varied by 10% and annual maintenance costs ranged between one standard deviation below and above the mean estimate. A probabilistic sensitivity analysis (PSA) was conducted by assigning distributions for clinical cure, age entering the model at treatment initiation, costs for each health state, and utility adjustments for each health state (Table 3).[55] The PSA used a Monte Carlo simulation of 10 000 repetitions of the model using the parameter distributions in Table 3.

Results

HCV Genotype 1

The results of the base case scenario comparing all 6 approved DAA strategies for genotype 1 are presented in Table 4 in order of ascending effectiveness. The results of the PSA are presented with the median cost-effect pairs with 95% confidence intervals for the cost for all strategies each of 10 000 iterations (Figure 1). The range of effects for all 6 strategies in the lifetime (50-year) model was between 18.08 and 18.40 QALYs, with simeprevir + sofosbuvir as the least effective and daclatasvir/sofosbuvir the most effective. The range of total costs was between $88 107 and $184 636, with grazoprevir/elbasvir the least costly and simeprevir/sofosbuvir the most costly combination. Grazoprevir/elbasvir was the most cost effective option for genotype 1 with velpatasvir/sofosbuvir the next best option with an incremental cost-effectiveness ratio (ICER) of $175 418 when compared with grazoprevir/elbasvir. Ledipasvir/sofosbuvir was cost-effective at $189 040/QALY compared with velpatasvir/sofosbuvir while all other base case strategies were dominated due to being less effective and more costly to the comparator.

HCV Genotype 4

The results of the base case scenario comparing all 4 approved DAA strategies for genotype 4 are presented in Table 4 in order of ascending effectiveness. The results of the PSA are presented with the median cost-effect pairs with 95% confidence intervals for the cost of each strategy in Figure 2. The range of effects for all 4 strategies in the lifetime model was between 18.23 and 18.43 QALYs, with ledipasvir/sofosbuvir as the least effective and velpatasvir/sofosbuvir the most effective. The range of total costs was between $87 063 and $127 637, with grazoprevir/elbasvir

Table 4. Base Case Cost and Effects for Each Regimen in Order of Ascending Effects for 5-, 10-, and 50-Year Cycles: Treatment Regimen.

	5 y		10 y		50 y		Incremental Cost per QALY Gained[a]
	QALYs	Costs ($)	QALYs	Costs ($)	QALYs	Costs ($)	
Genotype 1							
GZR/EBR	4.69	60 169	7.90	66 335	18.19	88 107	—
SIM+SOF	4.70	156 843	7.92	162 772	18.23	183 383	DOMINATED
PrO/DAS	4.70	89 921	7.93	95 797	18.27	116 165	DOMINATED
VEL/SOF	4.71	81 358	7.93	87 198	18.30	107 403	175 418[b]
LED/SOF	4.73	100 979	7.96	106 689	18.40	126 307	189 040[c]
DAC+SOF	4.73	153 346	7.96	159 069	18.40	178 744	DOMINATED
Genotype 4							
LED/SOF	4.70	101 111	7.92	107 038	18.23	127 637	DOMINATED
GZR/EBR	4.71	60 026	7.94	66 029	18.32	87 063	—
PrO/DAS	4.73	89 813	7.96	95 531	18.39	115 180	DOMINATED
VEL/SOF	4.74	81 243	7.97	86 914	18.43	106 352	175 355[b]

Abbreviations: GZR/EBR, grazoprevir/elbasvir; LED/SOF, ledipasvir/sofosbuvir; PrO/DAS, paritaprevir/ritonavir/ombitasvir plus dasabuvir; SIM+SOF, simeprevir + sofosbuvir; DAC+SOF, daclatasvir + sofosbuvir; VEL/SOF, velpatasvir/sofosbuvir.
[a]Incremental cost-effectiveness ratio (ICER) shown for 50-year model.
[b]GZR/EBR comparator for ICER.
[c]VEL/SOF comparator for ICER.

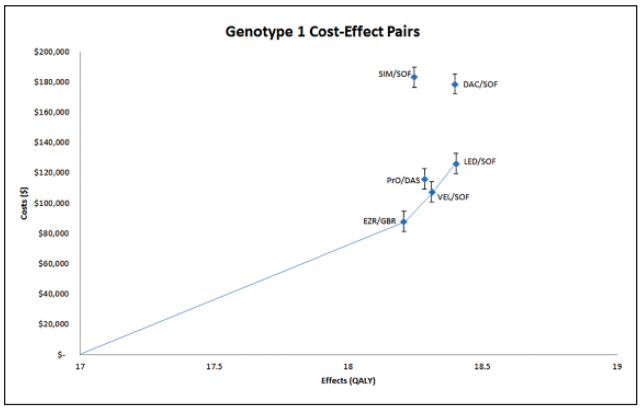

Figure 1. Median cost-effect pairs for Genotype 1 disease with 95% confidence intervals for cost uncertainty.

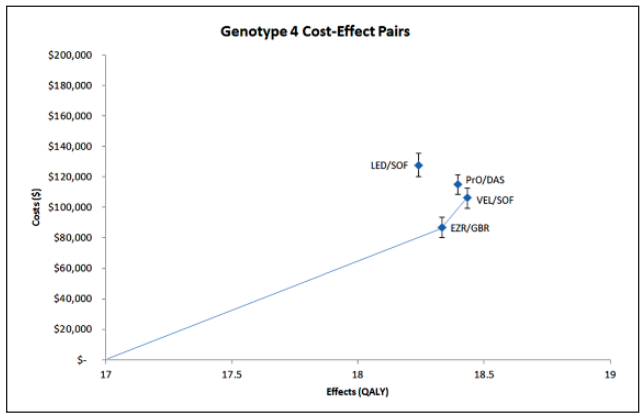

Figure 2. Median cost-effect pairs for Genotype 4 disease with 95% confidence intervals for cost uncertainty.

the least costly and ledipasvir/sofosbuvir the most costly therapy. Grazoprevir/elbasvir was the most cost-effective option for genotype 4 with velpatasvir/sofosbuvir the next best option with an ICER of $175 355 when compared with grazoprevir/elbasvir. Both ledipasvir/sofosbuvir and paritaprevir/ritonavir/ombitasvir plus dasabuvir were dominated treatments in this scenario.

Discussion

DAAs for chronic HCV enables clinical cure, yet medication cost has garnered much debate surrounding treatment affordability for patients, providers, and payers alike.[67-69] Despite the clinical potential, the budget impact of DAAs on private and government entities has given rise to significant restrictions to treatment access that varies across payer source and insurance plan.[70,71]

Since the breakthrough DAA, sofosbuvir, was approved by the Food and Drug Administration (FDA) in December 2013, several competitors have entered the market creating the opportunity for managed care and government agencies to leverage rebates and price discounts in exchange for preferential formulary placement.[72] However, in spite of the additional competition in the market for the pharmacologic treatment of chronic HCV, the increased utilization and expenditure on HCV treatment has significantly contributed to the overall growth in spending on prescription drugs in the United States.[73]

Despite the high costs, DAAs offer an enormous public health benefit. Therefore, one policy question is which DAA provides the greatest value. A comparative cost-effectiveness analysis provides insights for addressing the most value-based approach to DAA coverage and treatment. Our results suggest that grazoprevir/elbasvir is the most cost-effective DAA; however, this result assumes the cost of DAAs reflect listed wholesale acquisition prices without a transparent net price of the product after manufacturer rebates or discounts. As payers are able to secure significant price concessions from manufacturers, the true cost-effectiveness determination may change for the decision-maker. User-friendly models allowing payers to adjust various inputs could be beneficial to decision analysis and transparency.

Our analysis has several other potential limitations. First, we did not consider NS5A resistance-associated variants within the genotype 1a population. While NS5A polymorphisms may reduce the efficacy of grazoprevir/elbasvir in these specific patients, the combined low prevalence and impact on SVR may only have minor influence on the ICER as confirmed by previous analysis of grazoprevir/elbasvir with and without polymorphism testing.[74] This model did not include the additional cost of weight-based ribavirin, which may be added to various regimens depending on the genotype variant and presence of cirrhosis given its low cost relative to DAAs. No preference was given to guideline rating variation across the 6 options in genotype 1 and 4 options in genotype 4 as SVR rate inputs were obtained from clinical trial data, but clinicians may want to consider the level of evidence scored in the guidelines.[1] Patient-level factors, other than age and treatment severity, were not included as all current oral DAAs may reasonably be affected equally by characteristics such as race, gender, substance abuse, or treatment adherence. Disease severity estimates may also be underestimated in the model due to prevalence estimates used, but this bias would impact all regimens equally. Additionally, the benefits of cure in this model were held constant as there is limited long-term effect of cure data available for recently approved DAA regimens. This model also used an average age variable, which may not capture the potentially bimodal prevalence of HCV in the US population that includes younger patients with high-risk behaviors and the "baby boomer" cohort born between 1950 and 1960.[75] Additionally, from the payer perspective, potentially patient-centered outcomes or societal gains were not considered. These variables may affect total costs or efficacy for each agent, but the ICER comparisons should remain relatively constant.

Conclusions

Grazoprevir/elbasvir was the most cost effective DAA for HCV genotype 1 and 4 using publicly available drug pricing sources. Drug costs and rate of clinical cure were the main model drivers for cost-effectiveness in both genotypes.

Declaration of Conflicting Interests

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