Changes in Cost-Effectiveness for Chronic Hepatitis C Virus Pharmacotherapy: The Case for Continuous Cost-Effectiveness Analyses

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ABSTRACT

BACKGROUND: Cost-effectiveness evaluations for hepatitis C virus (HCV) treatments have been published frequently, but new products with significant cost and effectiveness differences make these analyses obsolete. How valuable are economic models for a fixed time period in a dynamic market?

OBJECTIVE: To estimate the cost-effectiveness of the best available HCV treatment at different points in time, using the same comparator to demonstrate how rapid innovation in a disease area influences economic outcomes.

METHODS: A Markov model was used to calculate the cost-effectiveness of treatment in 2010, 2012, 2014, 2016, and 2018 compared with a standard comparator (no treatment) from the payer perspective. Expected drug costs and treatment effectiveness estimates for sustained virologic response (SVR) were calculated using recommended regimens for each of the 6 HCV genotypes at each time point and distribution of genotypes in the United States. Patients entered the model with different stages of fibrosis. Utility estimates for each health state were used to calculate quality-adjusted life-years (QALYs) earned at each cycle. Incremental cost-effectiveness ratios were reported for each year to compare the “treatment versus no treatment” decision at that time.

RESULTS: No HCV treatment resulted in a gain of 11.54 QALYs over a 20-year time horizon at a cost of \$42,938. Costs for treated groups were \$69,075, \$123,267, \$125,431, \$86,782, and \$56,470 for the 2010, 2012, 2014, 2016, and 2018 scenarios, respectively. QALYs gained for treated groups were 12.90, 12.97, 13.34, 13.39, and 13.46 for the 2010, 2012, 2014, 2016, and 2018 scenarios, respectively. The incremental cost-effectiveness ratios in each year compared with no treatment were \$19,218 per QALY, \$56,104 per QALY, \$45,829 per QALY, \$23,699 per QALY, and \$7,048 per QALY.

CONCLUSIONS: Treatment effectiveness for HCV has increased steadily, while treatment costs increased substantially from 2010-2014 before decreasing to its lowest point in 2018. Thus, the dynamic nature of innovation creates the need for iterative cost-effectiveness analyses.

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What this study adds

- Dynamic markets with rapid innovation in a short time period limit the usefulness of any single published CEA.
- In a short period of time, hepatitis C treatment has evolved dramatically with improvements in treatment effectiveness and concurrent declines in treatment costs.

The last decade of advances in the treatment for hepatitis C virus (HCV) has provided an interesting case study of value assessment that pairs significant health gains with headline-grabbing costs. In 2011, the first 2 entities, boceprevir and telaprevir, of a new class of direct-acting antivirals (DAAs) entered the market, offering increased cure rates over the existing treatments of peginterferon/ribavirin-only regimens.¹ In 2013, the announcement of sofosbuvir's approval with even higher cure rates and a “\$1,000 a pill” list price sparked new debate among many stakeholders and provided increased demand for health economic evaluations.^{2,3} Sofosbuvir's approval was a classic example of a substantial investment in pharmaceutical costs today compared with future cost savings expected over a cured patient's lifetime. With the evidence available for liver fibrosis progression, this comparative research question was great for modeling using a health-state approach, and the publication of several economic models ensued.^{3,4} Finally, in 2015 the Institute for Clinical and Economic Review (ICER) published a value assessment of newly approved DAAs and concluded that, despite the new regimens being cost-effective at generally accepted thresholds, 10 out of 12 panelists voted that DAAs represent an overall low value to a state Medicaid program because of the potential budget impact.⁵

Since the development and publication of ICER's DAA value assessment, 3 more DAAs entered the market with significantly lower list prices and additional gains in terms of viral genotype coverage.⁶⁻⁸ Additionally, multiple DAAs have been voluntarily withdrawn from the U.S. market by their manufacturers. The clinical effectiveness of newer products and market dynamics have reshaped the clinical guidelines substantially for HCV.⁹ With lower drug prices and increased effectiveness, the pharmacoeconomics of HCV treatment have rapidly changed in a

What is already known about this subject

- With lower drug prices and increased effectiveness, the pharmacoeconomics of hepatitis C virus (HCV) treatment have rapidly changed in a very short time span, with several new products and multiple products withdrawn.
- Cost-effectiveness analyses (CEAs) for any treatment, including HCV, are typically fixed to answer a single question to compare treatments available at the time the study is conducted.

FIGURE 1 Markov Process Simulating Natural Disease Progression

SVR=sustained virologic response.

very short time span. Thus, the key question is: How valuable are published value assessment reports developed for an intervention during a fixed time period in a dynamic market?

This study aimed to model the cost-effectiveness of DAAs across multiple time points to demonstrate the effect of innovation and competition in a rapidly changing environment. Previous research of cost-effectiveness analyses (CEAs) for chronic HCV have reported common practices in the design of these models and the importance of input parameters, such as rate of sustained virologic response (SVR), cost of DAAs, and comparator selection.^{3,10} This study focuses on these 3 items and discusses the challenges for CEA developers that must be addressed to improve the usefulness of their results.

Methods

Model

A health-state transition (Markov) model was used to calculate the cost-effectiveness of first-line treatment regimens for HCV in 2010, 2012, 2014, 2016, and 2018 compared with no treatment (Figure 1).¹¹ A health sector (payer) perspective was used over a fixed 20-year time horizon. Expected drug costs and treatment effectiveness estimates for SVR were calculated using recommended regimens for each of the 6 HCV genotypes at each time point and the distribution of genotypes in the U.S. population.^{9,12,13} In 2010, the standard of care for all genotypes included peginterferon/ribavirin for a duration of either 24 or 48 weeks.^{14,15} Following the approval of telaprevir and boceprevir in 2011, the 2012

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TABLE 1 Assumptions, Descriptions, and Sources for Treatment Success and Costs over Time

Input	Base Case	Notes	Source
Age at entry	50.00	Fixed age at entry.	30
Discount rate	0.03	Fixed discount for costs and effects.	31
Genotype distribution			
Genotype 1	0.66	Estimated genotype distribution in the United States.	12,13
Genotype 2	0.12		
Genotype 3	0.18		
Genotype 4	0.03		
Genotype 5	0.005		
Genotype 6	0.005		
Treatment success			
2010 regimen SVR rate	0.53	The total SVR rate was a function of effectiveness for each genotype in the given year weighted by the prevalence of each genotype.	14,15
2012 regimen SVR rate	0.58		15
2014 regimen SVR rate	0.86		15,16
2016 regimen SVR rate	0.90		16
2018 regimen SVR rate	0.95		9
Treatment costs			
2010 rebate-adjusted drug costs	28,844	The total treatment cost input was a function of the regimen used for each genotype in the given year weighted by the prevalence of each genotype. Regimen prices were derived from the VA FSS.	19,32
2012 rebate-adjusted drug costs	67,065		
2014 rebate-adjusted drug costs	73,388		
2016 rebate-adjusted drug costs	47,440		
2018 rebate-adjusted drug costs	27,324		
2010 wholesale acquisition costs	41,803	The total treatment cost input was a function of the regimen used for each genotype in the given year weighted by the prevalence of each genotype. Regimen list prices were identified in RED BOOK.	21
2012 wholesale acquisition costs	97,196		
2014 wholesale acquisition costs	106,360		
2016 wholesale acquisition costs	68,753		
2018 wholesale acquisition costs	39,600		
Transition probabilities			
Natural history HCV progression			
F0 to F1	0.077	For comparison with previously published value assessment by ICER, all transition probabilities were derived from this model.	31
F1 to F2	0.074		
F2 to F3	0.089		
F3 to F4	0.088		
F3 to DC	0.012		
F3 to HC	0.00725		
F4 to DC	0.039		
F4 to HC	0.019		
DC to HC	0.014		
DC to transplant	0.017		
HC to transplant	0.017		
Transplant to posttransplant	0.834		
Post-SVR disease progression			
F0 to F1	0.010023	For comparison with previously published value assessment by ICER, all transition probabilities were derived from this model.	31
F1 to F2	0.007282		
F2 to F3	0.01028		
F3 to F4	0.009937		
F3 to DC	0.001028		
F3 to HC	0.004753		
F4 to DC	0.003342		
F4 to HC	0.012449		
DC to HC	0.010		
DC to transplant	0.012		
HC to transplant	0.017		
Transplant to posttransplant	0.834		

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TABLE 1 Assumptions, Descriptions, and Sources for Treatment Success and Costs over Time (continued)

Input	Base Case	Notes	Source
Health-state utilities			
F0	0.98	For comparison with previously published value assessment by ICER, all health-state utilities were derived from this model.	31
F1	0.98		
F2	0.92		
F3	0.79		
F4	0.76		
DC	0.69		
HC	0.67		
Transplant year 1	0.5		
Posttransplant	0.77		
F0, post-SVR	1.0		
F1, post-SVR	1.0		
F2, post-SVR	0.933		
F3, post-SVR	0.96		
F4, post-SVR	0.83		
Death	0		
Annual health-state costs			
F0-F2	912	For comparison with previously published value assessment by ICER, all health-state costs were derived from this model and adjusted to 2018 U.S. dollars.	31
F3	2,420		
F4	2,831		
DC	33,535		
HC	53,490		
Transplant year 1	212,351		
Posttransplant	46,247		
F0-F4, post-SVR	0.5×F0-F4	Annual costs for stages F0-F4 post-SVR were estimated as 50% of natural history, consistent with the 2015 ICER value assessment.	31

DC=decompensated cirrhosis; F=fibrosis stage; HC=hepatocellular carcinoma; HCV=hepatitis C virus; ICER=Institute for Clinical and Economic Review; SVR=sustained virologic response; VA FSS=Veterans Affairs Federal Supply Schedule.

standard of care for genotype 1 patients demonstrated slightly better effectiveness but with additional troublesome adverse effects.¹⁵ Major gains in effectiveness followed with the approval of sofosbuvir in late 2013, which had an effect on the 2014 standard of care for genotypes 1, 2, and 4.^{15,16} All-oral regimens continued to improve the effectiveness of the standard of care for genotypes 1 and 4 in 2016 (elbasvir/grazoprevir), culminating with highly effective pangenotypic agents by 2016-2017 (i.e., sofosbuvir/velpatasvir and glecaprevir/pibrentasvir).^{9,16}

Patients entered the model with different stages of liver fibrosis based on U.S. estimates.^{4,12,17} Natural disease progression, post-SVR progression, and advanced fibrosis progression for reinfecting patients were incorporated into the model.^{11,18} Probability of treatment success for each time point was a function of the reported treatment effectiveness and population distribution for each genotype.^{9,14-16} For example, cure rates ranged from 30%-65% in 2010 based on genotype. The probability of treatment success for each genotype was multiplied by the prevalence of that genotype, and the sum of the resulting product for all 6 genotypes determined the overall probability of treatment success (Equation 1). All model transition probabilities are provided in Table 1.

Equation 1:

$$\text{Total probability of Treatment Success} = \sum_{i=\text{genotype}} (\text{SVR rate})_i \times (\text{Prevalence})_i$$

Costs

For the reference case, net price inputs for the DAA regimens previously listed were estimated using the U.S. Department of Veterans Affairs Federal Supply Schedule (VA FSS) to reflect a lower bound payer cost for each regimen.^{19,20} Since the precise rebate for any specific product was unknown, the net price estimate applied was the average of VA FSS prices as a percentage of the wholesale acquisition cost (WAC) or list price.²⁰ For example, the WAC price for grazoprevir/elbasvir in 2016 was \$54,600, and the rebate-adjusted net price estimate was \$37,674. Since this regimen was only recommended for genotypes 1 and 4, sofosbuvir/velpatasvir WAC and net prices for genotypes 2, 3, 5, and 6 were used, bringing the overall 2016 drug cost estimates to \$68,753 and \$47,440 for WAC and rebate-adjusted net price estimate, respectively (Table 1). The lowest cost treatment option for each HCV genotype was selected for each year scenario. In order to estimate the total expected drug costs for each time point, we used a similar equation to incorporate the costs of different regimens for different genotypes (Equation 2).

TABLE 2 Cost-Effectiveness of Each Treatment Scenario in Order of Ascending Effectiveness, Excluding Dominated Options

Decision Choice	Costs	QALYs	Incremental Costs	Incremental Effects	Incremental Cost-Effectiveness Ratio ^a
No treatment	42,938	11.54	Reference	Reference	Reference
Treatment 2010	56,116	12.50	–	–	Dominated
Treatment 2012	93,036	12.57	–	–	Dominated
Treatment 2014	92,460	12.94	–	–	Dominated
Treatment 2016	65,468	12.99	–	–	Dominated
Treatment 2018	44,194	13.05	1,256	1.51	832/QALY

^aIncremental cost-effectiveness ratio by increasing QALYs.

QALY = quality-adjusted life-year.

Equation 2:

$$\text{Total Cost of Treatment} = \sum_{i=\text{genotype}} (\text{Drug cost})_i \times (\text{Prevalence})_i$$

Health-state cost estimates from the 2015 ICER value assessment were applied for all time points but were adjusted to 2018 U.S. dollars for direct comparison.⁵ These costs only reflect direct medical costs associated with each health state (Table 1).

Utilities

For consistency, the same utility estimates for each health state reported in the 2015 ICER report were used to calculate quality-adjusted life-years (QALYs) earned at each cycle.⁵

Analysis

The primary analysis for this methodology study focused on the changing costs and effectiveness estimates at each time point to estimate incremental cost-effectiveness ratios. A scenario analysis was conducted using only the WAC for each drug referenced in RED BOOK to describe the effect of using list versus net price in the CEA.²¹

Results

Primary Analysis

In the base case, no HCV treatment resulted in a gain of 11.54 QALYs over a 20-year time horizon at a cost of \$42,938. Costs for the treated groups were \$69,075, \$123,267, \$125,431, \$86,782, and \$56,470 for the 2010, 2012, 2014, 2016, and 2018 scenarios, respectively. QALYs gained for the treated groups were 12.90, 12.97, 13.34, 13.39, and 13.46 for the 2010, 2012, 2014, 2016, and 2018 scenarios, respectively. The incremental cost-effectiveness ratios in each year compared with no treatment were \$19,218 per QALY, \$56,104 per QALY, \$45,829 per QALY, \$23,699 per QALY, and \$7,048 per QALY. By comparing incremental costs and effects for each intervention in order of increasing QALYs gained, the HCV treatment in 2018 was dominant (Table 2). In 2016, the 2012 and 2014 treatment options would have been considered dominated by the 2016 agents before the 2018 regimens dominated all 2010-2016 options (Figure 2).

Scenario Analysis

When using WAC as the primary drug price input, the 2018 HCV treatment option was still preferred to other scenarios (Table 3). Depending on the decision maker's willingness-to-pay threshold (\$50,000/QALY, \$100,000/QALY, and \$150,000/QALY), the final determination of cost-effectiveness may have changed. While all treatments would have been cost-effective compared with no treatment at a \$100,000 per QALY threshold, a \$50,000 per QALY threshold would have resulted in 2012 and 2014 treatment options being considered not cost-effective compared with no treatment.

Discussion

Dynamic Cost-Effectiveness in 1 Model

Cost-effectiveness researchers have great influence over the outcome of an economic model through every methodological decision made from the project initiation to completion. The recommendations of expert panels on cost-effectiveness in 1996 and 2016 meant to improve the quality of CEAs and promote comparability across studies have helped guide these methodological decisions but are not capable of solving a major challenge in the implementation of cost-effectiveness research: things change.^{22,23}

The evolution of HCV treatment options over the past decade has generated a valuable case study for those interested in advancing the methods of CEA and organizations conducting value assessments to guide public and private payer decisions. The research and effort required to conduct a thorough CEA that meets best-practice recommendations involves substantial investment and typically ends with a published report or manuscript that has survived the scrutiny of the peer-review process. Once the final CEA has been delivered to the intended audience, the research team moves on to the next project and the cycle continues. The frequency at which these CEAs should be updated with new inputs and assumptions may be limited by resources. However, the case of HCV demonstrates that the value assessment for treatment in rapidly changing clinical scenarios may require revisions every few years.

FIGURE 2 Cost-Effectiveness Plane for Hepatitis C Treatment Options by Year

QALY = quality-adjusted life-year; USD = U.S. dollars.

Similar to a 2016 systematic review of cost-effectiveness studies of DAAs, we found that DAA prices used and SVR rates had an influence over the resulting incremental cost-effectiveness ratio.³ However, a payer cost-effectiveness threshold would be needed to determine whether the final decision recommendation would be to cover or not to cover. For example, a \$100,000 per QALY threshold applied to our model may result in the same coverage determination. Additionally, this CEA example does not address the potential changing population that a payer may have to account for. In the case of a curable infectious disease, a dynamic modeling approach may be necessary to incorporate other benefits of treatment (e.g., role of treatment in preventing new cases) on a covered population.³

Decision Making

Budgeting processes typically follow a fiscal calendar where decisions are made annually, so updated CEA results could influence formulary decisions from year to year. While this could affect many countries with government-supported health technology assessment bodies, the uptake of CEA evidence into formulary decisions in the United States has been less clear.²⁴ While this model demonstrates the variation in CEA results over time, one potential interpretation could be increased value with

innovation. The recent use of subscription-based payment models using a multiyear fixed-price contract for HCV treatments may be an area where more frequent CEA could be needed.²⁵ A multiyear fixed-price contract between a payer and manufacturer initiated in 2012 or 2014 might have been more costly than the proposed state-level subscriptions recently announced.²⁶

The Role of Model Transparency

Published CEAs that are fully transparent with detailed technical appendices could encourage more frequent updates and revisions. The Professional Society for Health Economics and Outcomes Research and Society for Medical Decision Making (ISPOR-SMDM) joint task force guidelines on model transparency and validation define transparency as “clearly describing the model structure, equations, parameter values, and assumptions to enable interested parties to understand the model.”²⁷ While transparency could serve as a step along the path to more frequent updates, transparency should not be confused with accuracy or validity.^{27,28} In order to feel more confident with model results, researchers should consider inclusion of a multistakeholder advisory board to assist with face validity of the model structure and assumptions and compare model results to similar published models for cross validation.^{11,27,29}

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TABLE 3 WAC Drug Price Input Scenario Cost-Effectiveness Results of 20-Year Health-Sector Model

Scenario	No Treatment		Treatment		Incremental Costs	Incremental Effects	Incremental Cost-Effectiveness Ratio ^a
	Costs	QALYs	Costs	QALYs			
2010	42,938	11.54	69,075	12.50	26,137	0.96	27,226/QALY
2012	42,938	11.54	123,167	12.57	80,229	1.03	77,892/QALY
2014	42,938	11.54	125,431	12.94	82,493	1.40	58,924/QALY
2016	42,938	11.54	86,782	12.99	43,844	1.45	30,237/QALY
2018	42,938	11.54	56,470	13.05	13,532	1.51	8,962/QALY

^aIncremental cost-effectiveness ratio by comparing treatment to no treatment.

QALY = quality-adjusted life-year; WAC = wholesale acquisition cost.

Resources Needed

Even if the same model structure and methods are used, significant effort would be required in the evidence synthesis process and in ensuring that all parameter values are updated appropriately. Additionally, the personnel needed to replicate and update current models may require advanced training and could be in short supply. The use of open-source programs and code sharing could reduce costs to some degree, but technical support to ensure that coding errors are not introduced may not be completely eliminated. Having an organization financially supported and charged with this task may help build efficiency, but there may be other unintended consequences of this charge falling on only this one group.

Limitations

This analysis includes limitations that readers should consider while interpreting the results. First, the health-state costs were kept constant for comparison between treatment arms. We justified this decision based on the focus of the analysis, but if hospital, laboratory, clinic visits, or surgical costs also change dramatically then it would be appropriate to adjust. Using a VA drug cost for our reference case also limits the analysis for commercial payers or plans that do not receive the same level of rebates on DAA costs as the VA. While we conducted a scenario analysis using WAC, commercial plans may experience prices that fall somewhere in between the VA and WAC.²⁰ Finally, reinfection rates or other dynamic population considerations were not included in this model, since we determined that these variables would be consistent across the time periods and treatments.

Conclusions

Treatment effectiveness for HCV has increased steadily, while treatment costs increased substantially from 2010-2014 before decreasing to its lowest point in 2018. The dynamic nature of CEAs in a disease state with rapid pharmaceutical innovation may cause some concern for decision makers who rely on a single analysis over time. Model transparency along with resources to update or revise model assumptions would enable

organizations to provide more up-to-date results to inform formulary decisions.

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