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The value of cure associated with treating treatment-naïve chronic hepatitis C genotype 1: Are the new all-oral regimens good value to society?

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Abstract

Background & Aims: All-oral regimens are associated with high cure rates in hepatitis C virus-genotype 1 (HCV-GT1) patients. Our aim was to assess the value of cure to the society for treating HCV infection.

Methods: Markov model for HCV-GT1 projected long-term health outcomes, life years, and quality-adjusted life years (QALYs) gained. The model compared second-generation triple (sofosbuvir+pegylated interferon+ribavirin [PR] and simeprevir+PR) and all-oral (ledipasvir/sofosbuvir and ombitasvir+paritaprevir/ritonavir+dasabuvir± ribavirin) therapies with no treatment. Sustained virological response rates were based on Phase III RCTs. We assumed that 80% and 95% of HCV-GT1 patients were eligible for second-generation triple and all-oral regimens. Transition probabilities, utility and mortality were based on literature review. The value of cure was calculated by the difference in the savings from the economic gains associated with additional QALYs.

Results: Model estimated 1.52 million treatment-naïve HCV-GT1 patients in the US. Treating all eligible HCV-GT1 patients with second-generation triple and all-oral therapies resulted in 3.2 million and 4.8 million additional QALYs gained compared to no treatment respectively. Using $50,000 as value of QALY, these regimens lead to savings of $185 billion and $299 billion; costs of these regimens were $109 billion and $128 billion. The value of cure with second-generation triple and all-oral regimens was $55 billion and $111 billion, when we conservatively assumed only drug costs. Cost savings were greater for HCV-GT1 patient cured with cirrhosis compared to patients without cirrhosis.

Conclusions: The recent evolution of regimens for HCV GT1 has increased efficacy and value of cure.

KEYWORDS

all-oral regimens, economic analysis, HCV treatment, hepatitis C, hepatitis C virus, Markov model, value of cure

Abbreviations: 2GTT, second-generation triple therapy; CC, chronic cirrhosis; CHC, chronic hepatitis C; GT1, genotype 1; HCV, hepatitis C virus; M, million; OBV/PTV/r+DSV, ombitasvir+paritaprevir/ritonavir+dasabuvir; PROs, patient-reported outcomes; PR, peginterferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response; VoC, value of cure; WTP, willingness to pay; W, weeks.

1 | BACKGROUND

Chronic hepatitis C (HCV) remains an important cause of chronic liver disease in the USA and the world. Most of the 3.5-5.3 million Americans living with viral hepatitis C infection are unaware of their infections.[1,2] HCV causes a systemic disease with both hepatic and extrahepatic manifestations.[3] Untreated HCV can lead to liver failure, liver cancer or other life-threatening health problems related to the extrahepatic manifestations of HCV. In fact, about 15 000 individuals die every year from HCV-related liver disease, and as of 2007, the number of HCV-related liver deaths exceeded that of HIV in the US.[4]In addition to causing substantial morbidity and mortality, HCV infection is associated with adverse economic consequences as well as a negative impact on patient-reported outcomes (PROs).[5–8] Total cost for management of HCV is estimated to be between $4.3 and $8.2 billion annually, with the majority of these costs attributable to management of decompensated cirrhosis (46%), compensated cirrhosis (20%) and hepatocellular carcinoma (16%).[9]

More than three-quarters of patients with HCV in the USA are infected with genotype 1 (GT1), most of whom are treatment naïve.[10] Historically, the interferon-based treatment of HCV infection is associated with low efficacy and substantial side effects. In this setting, the new antiviral medications that target hepatitis C virus, cures >95% of patients who are treated.[11,12]Despite substantial gains in treating HCV with these new highly effective antiviral regimens, there are a number of barriers that prevent patients from receiving treatment. Of these, identification of HCV-infected individuals and linking them to care have been the most challenging challenging.[13–15] It is estimated that between 50% and 90% of HCV-infected patients have been undiagnosed in the USA.[2]Another important barrier to treatment has been lack of coverage or suboptimal coverage of HCV treatment.[16] Since the approval of highly effective treatment regimens for HCV, many payers have imposed rigid criteria to restrict treatment.

Unfortunately, many coverage decisions are made based on economic analyses from payers' budgetary perspective. In fact, despite the higher cost-per-pill all per regimen, the cost-per-cure associated with these newer regimens is lower than previous interferon-based regimens.[17] There is strong evidence that the new interferon-free regimens improve PROs[18] and lead to significant savings by improving work productivity.[19] In addition, physicians are asked to make difficult and sometimes ethically challenging choices. In this context, the best economic perspective should be used to assess the long-term economic value of cure to society. The aim of this study was to develop a decision-analytic model to assess the long term value of cure in patients with HCV GT1 in the USA.

Key points

- We performed an economic evaluation of "curing" HCV in GT1 treatment-naïve patients with available regimens.
- The value of cure was defined as the increase in quality-adjusted life years (QALYs) multiplied by the value of a QALY (base case: $50 000) minus the increase in treatment costs.
- At the patient level, the value of cure with second-generation triple and all-oral regimens were $122 580 and $197 574 per patient respectively.
- At the population level, after an initial investment of $129 billion to cover drug costs for all-oral therapy, the society can see an estimated $299 billion savings in the long run.

2 | METHODS

2.1 | Model structure and analyses

We utilized a decision-analytic Markov model, previously described[20] to model a cohort of prevalent US chronic hepatitis C GT1 treatment-naïve patients over a lifetime horizon (Figure 1). The analysis was modelled from the payer perspective, and patients entered the model with a mean age of 52 years. Outcomes and costs were discounted at an annual rate of 3.0%, in accordance with AMCP guidelines.[21]

The objective of the analysis was to evaluate the value of cure to society with a strategy that leads to "curing" all HCV in GT1 treatment-naïve patients with available regimens, taking into account the incremental innovation and improved efficacy and tolerability profile for newer all-oral regimens vs no treatment, previous interferon-based second-generation triple therapy (2GTT) regimens. The value of cure was defined as the increase in quality-adjusted life years (QALYs) multiplied by the value of a QALY (in the model's base case, $50 000)[22] minus the increase in treatment costs. Cost growth with new technology is regarded as justified by the associated value to society when the estimated value of cure is >0 but as not justified when the value of cure is <0. Analyses were performed assuming only the cost of drug treatment, as well as the lifetime total treatment cost.

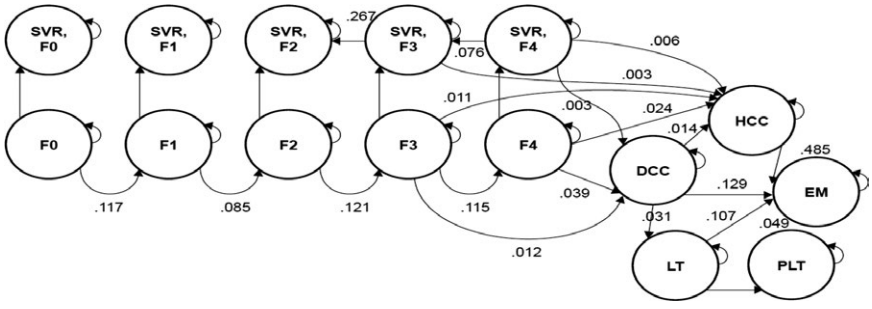

FIGURE 1 Markov mode structure. decompensated cirrhosis (DCC); fibrosis (F)-F4); hepatocellular carcinoma (HCC); liver transplant (LT); post liver transplant (PLT); sustained virological response (SVR)

The model assessed the value of cure of 2GTT and all-oral regimens compared to no treatment. 2GTT included sofosbuvir (SOF)+peginterferon+ribavirin (PR) 12 weeks (W) and simeprevir (SMV)+PR 12W. All-oral therapy included: LDV/SOF 8W (for viral load (VL) <6 million (M) copies); LDV/SOF 12W (for VL>6 M copies); ombitasvir+paritaprevir/ritonavir+dasabuvir (OBV/PTV/r+DSV)±RBV 12W (for GT1a and GT1b patients). In cirrhotic patients, modelled regimens included: LDV/SOF 12W; LDV/SOF 24W; OBV/PTV/r+DSV+RBV 12W (for GT1b patients); OBV/PTV/r+DSV+RBV 24W (for GT1a patients).

2.2 | Model inputs

To estimate the number of HCV GT 1 treatment-naïve patients in the USA, we multiplied the HCV population[2] by the percentage of treatment-naïve patients (74.58%)[5] and the percentage GT1 patients (75.30%)[23] to calculate a prevalent cohort population of 1.52 million patients.

Sustained virological response (SVR), transition probabilities, utilities and mortality were based on literature review and consensus by hepatologists, and have been described previously.[20] Utility values are summarized in Table 1. Drug costs were sourced from Redbook[24] using wholesale acquisition costs. The analysis is presented in 2015 US dollars.

Market shares for each regimen were calculated as follows (Table 2)**:** the relative distribution of GT1a to GT1b patients was 68%-32%,[25,26] and the distribution of noncirrhotic to cirrhosis patients, 83%-17%.[27]Among noncirrhotic patients, the proportion of patients with VL<6M copies was 48%.[28]On the basis of real-world data,[29] we assumed that the distribution of patients receiving LDV/SOF 8W, 12W and 24W regimens was 40%, 52% and 8%**;** based on expert opinion, our assumption for the percentage of patients receiving LDV/SOF vs OBV/PTV/r+DSV-based regimens was 87%-13%. Finally, based on expert opinion, 80% of HCV treatment-naïve GT1patients were assumed to be eligible for 2GTT while 95% were assumed to be eligible for all-oral therapy; all eligible patients were assumed to be treated.

2.3 | Scenario and sensitivity analyses

Since the valuation of a QALY at $50 000 may be outdated,[22] we ran a scenario analysis varying the value of a QALY upto $150 000. One-way deterministic sensitivity analyses explored a range of values for parameters previously determined to be key drivers of the model,[20] Sustained viral response rates were varied by ±10% from the base case and drug acquisition costs were varied by ±20% from the base case to assess the impact of these parameters on the value of cure results. Subgroup analysis was conducted for patients with cirrhosis and without cirrhosis at the initiation of treatment.

3 | RESULTS

3.1 | Patient-level results

Compared to no treatment, 2GTT and all-oral regimens increased HCV drug costs by $90 292 and $89 447 per patient, respectively, and increased per-patient QALYs by 2.18 (+17%) and 3.17 (+25%) respectively (Table 3). Weighted average SVR rates for 2GTT and all-oral regimens were 81.96% and 96.08% (relative to 0% with no treatment), which resulted in costs per SVR of $116 765 and $96 166 respectively (Table 3).

Assuming a QALY value of $50 000, when we conservatively accounted for only drug costs in the analysis without taking downstream cost savings (e.g. decreased number of cases of advanced liver-disease complications) into consideration, the value of cure for 2GTT was $36 579 per patient compared to no treatment whereas the value of cure for all-oral therapy was $73 600, due to the superior SVR rates achieved with these regimens (Table 4). In the subgroup analysis in patients with and without cirrhosis, the value of cure were $43 288 (second-generation triple therapy), and $61 232 (all-oral therapy) higher in patients who initiated treatment at the cirrhotic stage compared with those whose treatment was initiated at the pre-cirrhotic stage.

TABLE 1 Utility values used in the model

Utilities		
Health state	**Utility value**	**Source**
F0	0.790	McLernon, et al.[39]
F1	0.790	McLernon, et al.[39]
F2	0.790	McLernon, et al.[39]
F3	0.790	McLernon, et al.[39]
F4	0.748	McLernon, et al.[39]
F0 SVR	0.840	Wright and Tompkins[40]
F1 SVR	0.840	Wright and Tompkins[40]
F2 SVR	0.840	Wright and Tompkins[40]
F3 SVR	0.840	Wright and Tompkins[40]
F4 SVR	0.799	Wright and Tompkins [40]
DCC	0.672	McLernon, et al.[39]
HCC	0.610	Hsu, et al.[41]
Liver transplant	0.650	Hsu, et al.[41]
Post-liver transplant	0.709	McLernon, et al.[39]
Utility change on treatment	**Value (treatment duration adjusted), %**	**Source**
LDV/SOF 8 weeks	+4.5 (+0.7)	Younossi, et al.[42]
LDV/SOF 12 weeks	+4.5 (+1.0)	Younossi, et al.[42]
LDV/SOF 24 weeks	+4.4 (+1.0)	Younossi, et al.[42]
SOF+PR 12 weeks	−14.6 (−3.3)	Younossi, et al.[42]
SMV 12 weeks+PR	−14.6 (−6.3)	Expert panel consensus
OBV/PTV/r+DSV 12 weeks	+4.5 (1.0%)	Younossi, et al.[42]
OBV/PTV/r+DSV 12 weeks	−6.3 (−1.5)	Younossi, et al.[42]
OBV/PTV/r+DSV 24 weeks	−5.7 (−2.6)	Younossi, et al.[42]

DCC, decompensated cirrhosis; F0-F4, METAVIR liver fibrosis scores F0-F4; HCC, hepatocellular carcinoma; LDV, ledipasvir; OBV/PTV/r+DSV, ombitasvir, paritaprevir, ritonavir, dasabuvir; PR, pegylated interferon+ribavirin; PLT, post-liver transplant; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response.

TABLE 2 HCV treatment strategies

No treatment	Second-generation triple therapy (80% eligible)	All-oral therapy (95% eligible)
No treatment, 100%	SMV 12W+PR, 50%	LDV/SOF, 87%
		8W NC, 40%
		12W NC, 43%
		12W CC, 9%
		24W CC, 8%
	SOF+PR 12W, 50%	OBV/PTV/r+DSV ±RBV, 13%
		12W, NC 1b, 27%
		12W+R, NC 1a, 56%
		12W+R, CC 1b, 5%
		24W+R, CC1a, 12%

CC, compensated cirrhosis; LDV, ledipasvir; NC, noncirrhotic; OBV/PTV/r+DSV, ombitasvir, paritaprevir/ritonavir, dasabuvir; PLT, post-liver transplant; PR, pegylated interferon+ribavirin; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response.

As a drug-cost only analysis does not take into account the full potential economic value of HCV regimens, we also conducted analysis in long-term value of cure over a lifetime horizon. When total lifetime costs of treatment were considered, the value of cure was increased to $122 580 (noncirrhotic: $121 898 vs cirrhosis: $125 908) and $197 574 (noncirrhotic: $191 438 vs cirrhosis: $227 534) for 2GTT and all-oral regimens relative to no treatment respectively.

3.2 | Population-level results

At the population level, assuming a QALY value of $50 000, both 2GTT and all-oral regimens demonstrated positive cure values of $55 billion (noncirrhotic: $44 billion vs cirrhotic:109 billion) and $111 billion (noncirrhotic: 98 billion vs cirrhotic: 177 billion), respectively (drug costs only) and $185 billion (noncirrhotic: 184 billion vs cirrhosis:190 billion) and $299 billion (noncirrhotic: 290 billion vs cirrhosis: 344 billion) (total lifetime costs) relative to no treatment respectively (Figure 2).

TABLE 3 Model results: short-term and long-term economic outcomes

			Short-term outcomes (1 year)				Long-term outcomes (lifetime horizon)	
HCV regimen		Market share	SVR	HCV drug costs	HCV drug+ monitoring+ AE costs	Cost per SVR[a]	Total treatment costs	QALYs
Second-generation triple therapy	Weighted mean	100%	81.96%	$90 292	$95 483	$116 765	$124 648	15.38
	SMV 12W+PR	50%	76.07%	$86 186	$91 607	$120 429	$129 278	15.14
	SOF+PR12W	50%	87.85%	$94 398	$99 358	$113 101	$120 017	15.62
All-oral therapy	Weighted mean	100%	96.08%	$89 447	$92 397	$96 166	$100 805	15.99
	LDV/SOF	87%	96.08%	$88 946	$91 808	$95 553	$100 182	16.00
	NC (1a, 1b), 8W	40%	95.22%	$63 000	$65 481	$68 766	$72 077	16.18
	NC (1a, 1b), 12W	43%	96.55%	$93 987	$96 932	$100 397	$101 635	16.23
	CC (1a, 1b), 12W	9%	96.97%	$93 987	$97 328	$100 368	$119 108	14.98
	CC (1a, 1b), 24W	8%	96.88%	$185 909	$189 682	$195 788	$211 609	14.98
	OBV/PTV/r+DSV±RBV	13%	96.09%	$92 871	$96 346	$100 266	$105 059	15.96
	NC (1b), OBV/PTV/r+DSV 12W	27%	97.83%	$83 118	$85 992	$87 899	$89 732	16.22
	NC (1a), OBV/PTV/r+DSV+RBV 12W	56%	95.19%	$83 799	$87 128	$91 531	$93 943	16.15
	CC (1b), OBV/PTV/r+DSV+RBV 12W	5%	100.00%	$83 799	$87 863	$87 863	$104 690	15.13
	CC (1a), OBV/PTV/r+DSV+RBV 24W	12%	94.64%	$163 843	$169 129	$178 708	$194 718	14.83
No treatment	Weighted mean	N/A	0.00%	$0	$0	$0	$141 856	12.66
	NC	N/A	0.00%	$0	$0	$0	$133 969	13.25
	CC	N/A	0.00%	$0	$0	$0	$180 366	9.76

[a]Cost included HCV drug regimens+monitoring+adverse event (AE) costs; due to rounding, calculated results may differ slightly from the exact results.
AE, adverse event; CC, compensated cirrhosis; HCV, hepatitis C virus; LDV, ledipasvir; NC, noncirrhotic; OBV/PTV/r+DSV, ombitasvir, paritaprevir, ritonavir, dasabuvir; PLT, post-liver transplant; PR, pegylated interferon+ribavirin; QALY, quality-adjusted life year; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virological response; W, week.

TABLE 4 Model results: incremental costs, QALYs and value of cure by fibrosis stage

	Fibrosis stage	Incremental costs	Incremental QALYs (1 QALY=$50 000)	Value of cure
Drug costs only				
Second-generation triple therapy	Noncirrhotic (F0-F3)	$72 234	$101 454	$29 220
	Cirrhosis (F4)	$72 234	$144 742	$72 508
	All patients	$72 234	$108 813	$36 579
All-oral therapy	Noncirrhotic (F0-F3)	$75 650	$140 326	$64 676
	Cirrhosis (F4)	$130 502	$247 674	$125 908
	All patients	$84 975	$158 575	$73 600
Total lifetime costs				
Second-generation triple therapy	Noncirrhotic (F0-F3)	−$20 444	$101 454	$121 898
	Cirrhosis (F4)	$18 834	$144 742	$125 908
	All patients	−$13 767	$108 813	$122 580
All-oral therapy	Noncirrhotic (F0-F3)	−$51 112	$140 326	$191 438
	Cirrhosis (F4)	$20 139	$247 674	$227 534
	All patients	−$38 999	$158 575	$197 574

3.3 | Sensitivity and scenario analyses

Value-of-cure values remained positive when the value of a QALY was varied from $50 000 up to $150 000 (Figure 2), and when both SVRs and drug costs were varied within their sensitivity analysis ranges (Figure 3).

4 | DISCUSSION

This is a comprehensive economic analysis assessing the value of cure for HCV GT1 treatment-naïve patients in the USA. Our results suggest that the long-term value delivered to society by curing HCV GT1 is substantial. In fact, the data show that the value of cure for each HCV-infected individual who is treated with an all-oral regimen is $73 600 per patient. Although the value of cure is also positive with older regimens when we conservatively assumed only drug costs, it is substantially lower ($36 579 per patient). In contrast, if we consider the additional savings associated with reducing the future complications of HCV (lifetime costs), the society will save $197 574 per patient with HCV GT1 who is treated with all-oral regimen. This long-term savings will come at an average cost of $89 447 for the drug cost associated with new all-oral regimens. Overall, treating patients with cirrhosis (vs without cirrhosis) resulted in better value for money to society because of substantially improved outcomes for patients with cirrhosis. If we apply this approach to all HCV GT1 patients in the USA, after an initial investment of $129 billion to cover drug costs, the society can see an estimated $299 billion savings in the long run. In fact, this saving is seen after applying a relatively low willingness-to-pay threshold (WTP) of $50 000/QALY. If WTP threshold were to increase to a more reasonable value of $150 000/QALY, the societal long-term economic benefit of curing all HCV GT1 in the USA will be over $780 billion.

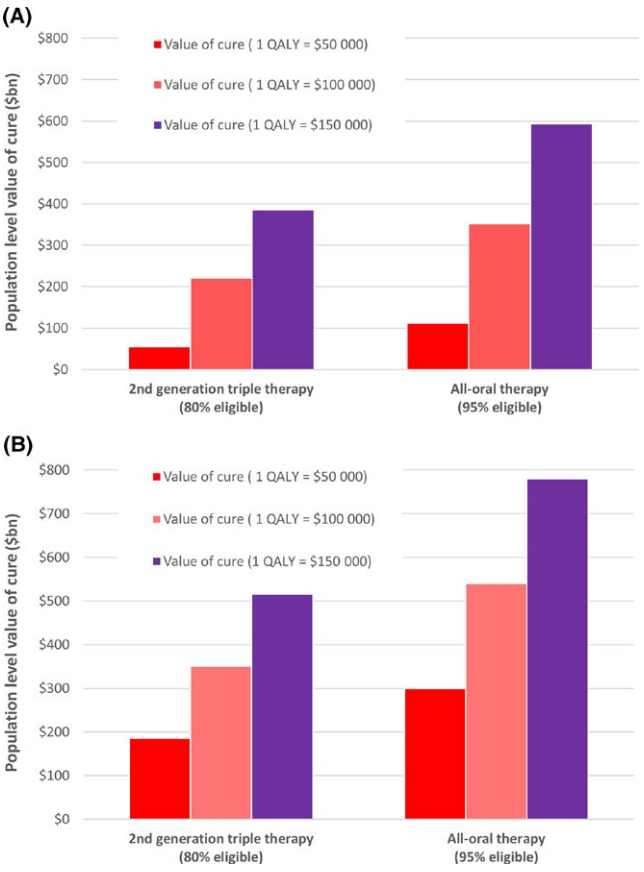

FIGURE 2 Scenario analysis: value of cure compared to no treatment at different QALY thresholds. (A) Drug costs only. (B) Total lifetime costs. QALY, quality-adjusted life year [Colour figure can be viewed at wileyonlinelibrary.com]

Our results were similar to a recent study that examined the association between the stepwise increase in the SVR and HCV drug prices for HCV infection in the Swiss and within the USA.[30] The researchers

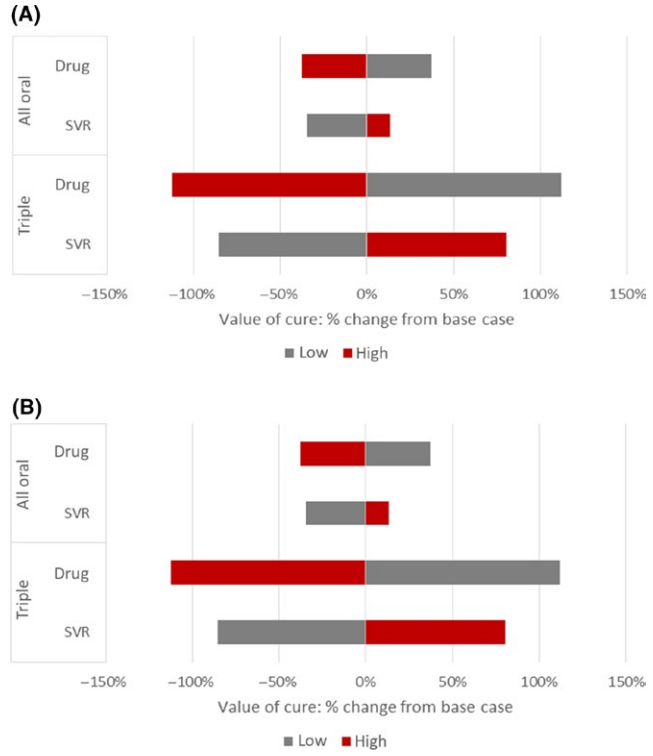

FIGURE 3 Sensitivity analysis results: Value of cure results when varying drug costs and SVR rates. (A) Drug costs. (B) Total lifetime costs. SVR, sustained viral response [Colour figure can be viewed at wileyonlinelibrary.com]

found that the costs of HCV drug regimens increased steadily over time, both in Switzerland and in the USA, in close correlation with the corresponding HCV cure rates but found that the cost per SVR was slightly lower with the second wave direct acting antivirals (DAAs) (SOF, SOF/LDV and OBV/PTV/r+DSV±RBV) compared to the first wave DAAs (telaprevir, boceprevir and SMV).[30] In addition, another recent study found that the costs per SVR with all-oral regimen decreased compared to the previous standards of therapy.[31] Unlike the previous studies, we focused on all-oral and 2GTT regimens to evaluate the long-term value of cure taking downstream cost savings and QALYs into consideration for lifetime horizons as well as short-term outcomes (e.g. cost per SVR and 1-year outcomes).

A number of cost-effectiveness studies have assessed whether the value of a new HCV drug was worth the additional cost using incremental cost-effectiveness ratios with focus on individual drugs.[5,20,32,33] A recent systematic review for 24 cost-effectiveness studies suggest that treatment of HCV GT1 infection with DAAs are cost-effective.[34] However, the cost-effectiveness of a drug that is measured at the patient level does not reflect patients at the population level. In evaluating therapeutic advances, we used the value of cure approach which incorporates value into measurements of cost growth for HCV cure to society at the population level.

The recent availability of all-oral regimes is expected to dramatically impact the landscape of HCV burden. However, affordability and accessibility to these highly effective drugs still remain barriers to the provision of timely treatment because of the high upfront drug costs. Healthcare payers and stakeholders are challenged with the high budget impact of these new HCV drugs despite their long-term economic benefits (cost savings).[30,35] For this reason, healthcare payers in the USA restrict treatment of HCV to patients with advanced liver disease (e.g. Medicaid) and European countries use price negotiation as more HCV drugs are approved and enter the market.[30] Innovative reimbursement and pricing strategies are needed to treat more patients with new drugs that are highly effective and a good value to society.

Several limitations need to be considered in the interpretation of this study. First, we included only treatment-naïve patients infected with HCV GT1. However, patients infected with HCV GT1 represent the majority of the HCV population in USA (75%) and have been the most difficult GT to treat for the last two decades. Although the efficacy of these all-oral regimens and their positive economic benefits of curing HCV can be applied to other HCV GTs that would add more value of cure to the society, further analysis will be needed to see whether the different GTs also have a similar value of cure to the society when treating HCV infection. In addition, we believe the economic benefits seen in this analysis may underestimate the true value of cure because this analysis did not include the economic benefits of curing HCV-related extrahepatic manifestations and the indirect economic benefits of increased work productivity after HCV cure.[36] In this context, recent analyses suggest that the economic burden of the extrahepatic manifestations of HCV is over $2 billion/year and the economic burden of work productivity impairment related to HCV in the USA to be over $7 billion/year. In fact, curing HCV is projected to bring about $2.7 billion savings per year from improved work productivity in the USA.[36] In addition, with significant market competition, most of the new regimens are provided with substantial discounts.[37] Since the prevalence of HCV in Medicaid population is higher than the privately insured patients, there are substantial savings with the cost of drugs used to treat HCV.[38] Last, we focused only on the impact of HCV cure from the USA perspective. Although similar economic benefits are expected in other countries, especially European countries, additional analyses are needed.

In summary, our data suggest that the value of curing HCV GT1 to the society in the USA is substantial. In this context, there is a strong rationale to invest in a strategy that ensures that all infected patients are screened and have access to highly effective and curative regimens. Setting aside the ethics of providing such treatment to those who need it, this analysis clearly shows that there is a large net economic benefit associated with such a strategy.

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CONFLICT OF INTEREST

HP has received a research grant from Gilead Sciences. Except for HP, none of the other authors received any compensation for this study.

COMPETING INTERESTS

ZMY is a consultant to Abbvie, Gilead, BMS and Intercept.

REFERENCES

1. Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. *Hepatology*. 2012;55:1652–1661.
2. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med*. 2014;160:293–300.
3. Cacoub P, Gragnani L, Comarmond C, Zignego AL. Extrahepatic manifestations of chronic hepatitis C virus infection. *Dig Liver Dis*. 2014;46(Suppl 5):S165–S173.
4. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med*. 2012;156:271–278.
5. Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med*. 2015a;162:397–406.
6. Younossi Z, Henry L. Systematic review: patient-reported outcomes in chronic hepatitis C–the impact of liver disease and new treatment regimens. *Aliment Pharmacol Ther*. 2015;41:497–520.
7. Menzin J, White LA, Nichols C, Deniz B. The economic burden of advanced liver disease among patients with hepatitis C virus: a large state Medicaid perspective. *BMC Health Serv Res*. 2012;12:459.
8. Manne V, Sassi K, Allen R, Saab S. Hepatitis C and work impairment: a review of current literature. *J Clin Gastroenterol*. 2014;48:595–599.
9. Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology*. 2013;57:2164–2170.
10. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*. 2015;61:77–87.
11. 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;370:1879–1888.
12. 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;370:1594–1603.
13. Assoumou SA, Huang W, Horsburgh CR Jr, Drainoni ML, Linas BP. Relationship between hepatitis C clinical testing site and linkage to care. *Open Forum Infect Dis*. 2014;1:ofu009.
14. Reau N. HCV testing and linkage to care: expanding access. *Clin Liver Dis*. 2014;4:31–34.
15. Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern Med*. 2002;136:288–292.
16. Stepanova M, Younossi ZM. Interferon-free regimens for chronic hepatitis C: barriers due to treatment candidacy and insurance coverage. *Dig Dis Sci*. 2015;60:3248–3251.
17. 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;162:619–629.
18. Younossi ZM, Stepanova M, Nader F, et al. Patient-reported outcomes in chronic hepatitis C patients with cirrhosis treated with sofosbuvir-containing regimens. *Hepatology*. 2014a;59:2161–2169.
19. Younossi Z, Henry L. The impact of the new antiviral regimens on patient reported outcomes and health economics of patients with chronic hepatitis C. *Dig Liver Dis*. 2014;46(Suppl 5):S186–S196.
20. Younossi ZM, Park H, Saab S, Ahmed A, Dieterich D, Gordon SC. Cost-effectiveness of all-oral ledipasvir/sofosbuvir regimens in patients with chronic hepatitis C virus genotype 1 infection. *Aliment Pharmacol Ther*. 2015a;41:544–563.
21. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
22. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med*. 2014;371:796–797.
23. Nainan OV, Alter MJ, Kruszon-Moran D, et al. Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. *Gastroenterology*. 2006;131:478–484.
24. Red Book Online [Internet]. Micromedex 2.0. http://www.micromedexsolutions.com/home/dispatch. Accessed October 15, 2015.
25. Manos MM, Shvachko VA, Murphy RC, Arduino JM, Shire NJ. Distribution of hepatitis C virus genotypes in a diverse US integrated health care population. *J Med Virol*. 2012;84:1744–1750.
26. Zein NN, Rakela J, Krawitt EL, Reddy KR, Tominaga T, Persing DH. Hepatitis C virus genotypes in the United States: epidemiology, pathogenicity, and response to interferon therapy. Collaborative Study Group. *Ann Intern Med*. 1996;125:634–639.
27. Ipsos Healthcare. US HCV Monitor; 2012.
28. Hajkowicz H, Buggisch P, Petersen J, et al. Ledipasvir/sofosbuvir for 8 weeks—a comparative analysis of clinical trial efficacy versus real world effectiveness. https://www.eiseverywhere.com/file_uploads/c8b381436c7c4414d4838ce778d38098_KrispinHajkowicz-10.pdf. Accessed October 15, 2016.
29. Gilead Sciences Inc. Data on file; 2015.
30. Vernaz N, Girardin F, Goossens N, et al. Drug pricing evolution in hepatitis C. *PLoS ONE*. 2016;11:e0157098–12. doi:10.1371/journal.pone.0157098.
31. Chhatwal J, Chen Q, Kanwal F. Why we should be willing to pay for hepatitis C treatment. *Clin Gastroenterol Hepatol*. 2015b;13:1711–1713.
32. Hagan LM, Yang Z, Ehteshami M, Schinazi RF. All-oral, interferon-free treatment for chronic hepatitis C: cost-effectiveness analyses. *J Viral Hepatitis*. 2013;20:847–857.
33. Zhang S, Bastian ND, Griffin PM. Cost-effectiveness of sofosbuvir-based treatments for chronic hepatitis C in the US. *BMC Gastroenterol*. 2015;15:98–107.
34. Chhatwal J, He T, Hur C, Lopez-Olivo MA. Direct-acting antiviral agents for patients with hepatitis C virus genotype 1 infection are cost saving. *Clin Gastroenterol Hepatol*. 2016; in press. doi:10.1016/j.cgh.2016.09.015.
35. Roy V, King L. Betting on hepatitis C: how financial speculation in drug development influences access to medicines. *BMJ*. 2016; 354–359. doi:10.1136/bmj.i3718.
36. Younossi ZM, Jiang Y, Smith NJ, Stepanova M, Beckerman R. Ledipasvir/sofosbuvir regimens for chronic hepatitis C infection: insights from a work productivity economic model from the United States. *Hepatology*. 2015b;61:1471–1478.
37. Henry J. Kaiser Family Foundation. Summary of the Affordable Care Act. http://files.kff.org/attachment/fact-sheet-summary-of-the-affordable-care-act. Accessed February 29, 2016.
38. Ferro C, Blumen HE, Johnson RL. The burden of hepatitis C virus disease in commercial and managed Medicaid populations. http://us.milliman.com/insight/2015/The-burden-of-hepatitis-C-virus-disease-in-commercial-and-managed-Medicaid-populations/. Accessed January 15, 2016.
39. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. *Med Decis Mak*. 2008;28:582–592.
40. Wright NM, Tompkins CN. A review of the evidence for the effectiveness of primary prevention interventions for hepatitis C among injecting drug users. *Harm Reduct J*. 2006;3:27–36.
41. 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;27:149–157.
42. Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. *J Hepatol*. 2014b;60:530–537.