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Economic Evaluation

A Cost-Effectiveness Analysis of Shortened Direct-Acting Antiviral Treatment in Genotype 1 Noncirrhotic Treatment-Naive Patients With Chronic Hepatitis C Virus

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ABSTRACT

Background: Direct-acting antivirals are successful in curing hepatitis C virus infection in more than 95% of patients treated for 12 weeks, but they are expensive. Shortened treatment durations, which may have lower cure rates, have been proposed to reduce costs.

Objectives: To evaluate the lifetime cost-effectiveness of different shortened treatment durations for genotype 1 noncirrhotic treatment-naive patients.

Methods: Assuming a UK National Health Service perspective, we used a probabilistic decision tree and Markov model to compare 3 unstratified shortened treatment durations (8, 6, and 4 weeks) against a standard 12-week treatment duration. Patients failing shortened first-line treatment were re-treated with a 12-week treatment regimen. Parameter inputs were taken from published studies.

Results: The 8-week treatment duration had an expected incremental net monetary benefit of £7737 (95% confidence interval £3242-£11 819) versus the standard 12-week treatment, per 1000 patients. The 6-week treatment had a positive incremental net monetary benefit, although some uncertainty was observed. The probability that the 8- and 6-week treatments were the most cost-effective was 56% and 25%, respectively, whereas that for the 4-week treatment was 17%. Results were generally robust to sensitivity analyses, including a threshold analysis that showed that the 8-week treatment was the most cost-effective at all drug prices lower than £40 000 per 12-week course.

Conclusions: Shortening treatments licensed for 12 weeks to 8 weeks is cost-effective in genotype 1 noncirrhotic treatment-naive patients. There was considerable uncertainty in the estimates for 6- and 4-week treatments, with some indication that the 6-week treatment may be cost-effective.

Keywords: cost-effectiveness, direct-acting antivirals, hepatitis C virus, shortened treatment duration.

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Introduction

The cost-effectiveness of direct-acting antiviral (DAA) treatment for chronic hepatitis C virus (HCV) has been well documented,[1-4] and a wide array of DAA therapies have been approved for use internationally.[5] The therapies, which are generally administered orally over 12 weeks, are successful in more than 95% of patients with chronic HCV genotype 1 (GT1).[5] The advent of an effective cure has brought the potential to address HCV globally. The World Health Organization recently outlined its commitment toward eliminating HCV by 2030.[6] Nevertheless, the cost of a standard 12-week treatment course is high, and variations in price exist internationally and across DAA regimens. In the United Kingdom, the price set by manufacturers initially ranged from £30 000 to £60 000 per patient,[7-9] whereas in the United States, a 12-week course of treatment can cost more than $90 000 per patient.[10] Although significantly lower prices have been agreed between manufacturers and healthcare payers, these prices have not been made publicly available. Shortened treatment duration is a mechanism that could be used to reduce drug costs, albeit at the expense of potentially curing fewer patients.

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Recent evidence suggests that shortened treatment durations are associated with lower cure rates in GT1 noncirrhotic treatment-naive patients. Kowdley et al[11] reported that the cure rate fell from 96% in patients treated for 12 weeks using a triple-DAA regimen (ombitasvir-paritaprevir-ritonavir with dasabuvir [3D]) to 88% in patients treated for 8 weeks with the same regimen. Sulkowski et al[12] considered shorter treatment durations using a combination of 4 DAAs (daclatasvir, asunaprevir, beclabuvir, and sofosbuvir [DCV-Trio + SOF]) and found that 57% and 29% of patients treated over 6 and 4 weeks, respectively, cleared the virus. Other studies considered the effectiveness of existing DAA therapies over shortened treatment durations, but with the addition of an investigational nonnucleoside or protease inhibitor. For example, Kohli et al[13] found that 40% of patients were cured when treated for 4 weeks using ledipasvir and sofosbuvir (LDV/SOF) plus a nonnucleoside inhibitor (GS9669).

Although cure rates are lower over shortened treatment durations, patients can usually be re-treated with an alternative, or similar, DAA regimen if first-line treatment fails. One concern with first-line treatment failure, however, is that patients can develop resistance to DAA therapies and this can affect the likelihood of future viral eradication.[14] Nevertheless, much evidence suggests that noncirrhotic patients with DAA resistance, or resistance-associated polymorphisms, can clear the virus with further treatment[15-19] even before the advent of combinations with broader antiviral activity. Wilson et al[19] found that 90% of patients with DAA resistance were cured with a 12-week re-treatment using LDV/SOF, whereas 91% of patients overall were cured after shortened first-line treatment failure. Bourliere et al[20] found that 97% of patients who previously failed first-line treatment cleared the virus over 12 weeks using sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX).

Given the burden of high treatment costs, and the potential to cure as many patients using shortened treatment durations (with a re-treatment strategy adopted for all patients who fail first-line treatment), the cost-effectiveness of short-course therapy needs to be considered. In this article, we compared the lifetime cost-effectiveness of different unstratified shortened treatment durations. We modeled outcomes for GT1 noncirrhotic treatment-naive patients with HCV in the United Kingdom, for whom shortened treatment has been reported in the literature, and for whom shortened treatment may be considered in the future.

Methods

We used a decision tree and Markov model to investigate the cost-effectiveness of shortened DAA treatment from the National Health Service perspective in the United Kingdom. We applied monthly cycles during the first year in the decision tree to simulate treatment outcomes and annual cycles in the Markov model to simulate the natural history of HCV. We adopted a lifetime time horizon (60 years, from an initial age of 40 years) and discounted costs and utilities at 3.5% per annum, as per the National Institute for Health and Care Excellence (NICE) guidelines.[21]

Target Population

The model simulated outcomes for GT1 noncirrhotic treatment-naive patients infected with HCV, combining data from subtypes 1a and 1b. We modeled outcomes for a representative population with noncirrhotic HCV in the United Kingdom, on the basis of Hartwell et al.[22] At baseline, 51.1% and 48.9% of patients had mild (F0-F1) and moderate (F2-F3) liver fibrosis, respectively. At model entry, patients were aged 40 years and 70% were men (Table 1).

Treatment Comparators and Regimens

We compared 3 unstratified shortened treatment durations (8, 6, and 4 weeks) against the standard 12-week treatment duration. We considered treatment regimens currently used in the United Kingdom in our analysis. In the base-case analysis, we used a triple-DAA regimen (3D) for first-line treatment because of the availability of data on the effectiveness of shortened treatment.[11] 3D contains 2 fixed-dose tablets with 12.5 mg ombitasvir, 75 mg paritaprevir, and 50 mg ritonavir, which are taken daily along with 1 dose of 250 mg dasabuvir.[8]

We assumed that patients who failed first-line treatment were re-treated for 12 weeks, as per recent UK guidelines.[30,31] We used SOF/VEL/VOX as the salvage regimen. SOF/VEL/VOX is a nonstructural protein 5A (NS5A) inhibitor-containing regimen that is administered once daily using a fixed-dose tablet; each tablet contains 400 mg sofosbuvir, 100 mg velpatasvir (NS5A inhibitor), and 100 mg voxilaprevir (protease inhibitor).[28] SOF/VEL/VOX is the currently recommended treatment regimen for patients who previously failed first-line treatment in the United Kingdom.[30,31]

Model Structure

The decision tree was designed to capture treatment outcomes in the first year using monthly cycles (Figure 1A). Patients were assessed for sustained virological response at 12 weeks posttreatment (SVR12, effective cure), which was defined as having HCV ribonucleic acid less than 25 IU per milliliter. Patients who failed first-line treatment were re-treated at 24 weeks. All patients entered the Markov model on the basis of their response to treatment.

The Markov model was adapted from previously validated models that characterize the natural disease history of HCV.[3,22,32,33] Patients entered the model on the basis of their initial distribution of liver fibrosis (mild or moderate), and whether treatment had been successful (Figure 1B). In HCV-cleared patients, we modeled potential reinfection. Patients without SVR12 could progress from mild (F0-F1) to moderate (F2-F3) to severe liver fibrosis, or compensated cirrhosis (F4). Once in this health state, patients could develop more advanced liver disease, including hepatocellular carcinoma and decompensated cirrhosis. Patients with decompensated cirrhosis were also at risk of hepatocellular carcinoma, with both groups of patients at risk of requiring a liver transplant. We modeled liver-related deaths for each of these advanced health states with 2 health states captured in the hepatocellular carcinoma and liver transplant health states to reflect the initial and subsequent risk of liver-related mortality. At any stage in the Markov model, patients could die of non–liver-related deaths.

Model Assumptions

We assumed there was no progression to more severe health states during treatment, such as compensated cirrhosis (F4), or once treatment had been successful. Only if patients became reinfected could disease progression occur. There are no clinical guidelines on the appropriate length of time patients should wait before a salvage treatment is administered. In our model, we assumed that the wait time did not affect the success of re-treatment.

Table 1. Summary of treatment, epidemiological, cost, and quality-of-life inputs for probabilistic sensitivity analyses.

Variable	Base case	Distribution	α	β	Source
Patient characteristics					
Initial distribution of liver fibrosis					
Mild (F0-F1)	51.1%	–	–	–	Hartwell et al[22]
Moderate (F2-F3)	48.9%	–	–	–	Hartwell et al[22]
Age (y)	40	–	–	–	Hartwell et al[22]
Sex, male	70%	–	–	–	Hartwell et al[22]
Efficacy (SVR12)					
First-line treatment					
12 wk	0.96	Beta	76	3	Kowdley et al[11]
8 wk	0.87	Beta	69	10	Kowdley et al[11]
6 wk	0.64	Beta	6	3	Sulkowski et al[12,*]
4 wk	0.38	Beta	1	2	Sulkowski et al[12,*]
Re-treatment					
12 wk	0.973	Beta	142	4	Bourliere et al[20]
Annual transition probabilities					
Fibrosis progression					
Mild-to-moderate	0.025	Beta	38	1 484	Grieve et al,[23] Wright et al[24]
Moderate-to-CC	0.037	Beta	27	699	Grieve et al,[23] Wright et al[24]
Nonfibrosis progression					
CC-to-DCC	0.039	Beta	15	359	Fattovich et al[25]
CC-to-HCC	0.014	Beta	2	135	Cardoso et al[26]
DCC-to-HCC	0.014	Beta	2	135	Cardoso et al[26]
HCC-to-liver transplant	0.020	Beta	98	4 801	Hartwell et al[22]
DCC-to-liver transplant	0.020	Beta	98	4 801	Grieve et al[23]
Liver-related mortality					
DCC-to-liver death	0.130	Beta	147	983	Fattovich et al[25]
HCC-to-liver death (first year)	0.430	Beta	117	155	Fattovich et al[25]
HCC-to-liver death (subsequent year)	0.430	Beta	117	155	Fattovich et al[25]
Liver transplant-to-liver death (first year)	0.150	Beta	85	481	Grieve et al[23]
Liver transplant-to-liver death (subsequent year)	0.057	Beta	85	1 407	Bennett et al[27]
Reinfection	0.010	Beta	4	391	Johnson et al[3]
Costs					
Treatment-related costs					
3D (monthly)	£12 140.56	Fixed	–	–	National Institute for Health and Care Excellence[8]
SOF/VEL/VOX (monthly)	£14 942.33	Fixed	–	–	National Institute for Health and Care Excellence[28]
Monitoring costs (monthly)	£162.34	Fixed	–	–	National Institute for Health and Care Excellence[8]
Health state costs					
SVR mild (F0-F1)	£60.36	Gamma	34	2	Backx et al[29]
SVR moderate (F2-F3)	£60.36	Gamma	34	2	Backx et al[29]
Mild (F0-F1)	£166.50	Gamma	13	13	Hartwell et al[22]
Moderate (F2-F3)	£612.50	Gamma	35	17	Backx et al[29]
CC (F4)	£951.13	Gamma	17	54	Backx et al[29]
DCC	£12 833.96	Gamma	15	849	Hartwell et al[22]
HCC (first year)	£11 436.41	Gamma	13	894	Hartwell et al[22]
HCC (subsequent year)	£11 436.41	Gamma	13	894	Hartwell et al[22]
Liver transplant (first year)	£51 769.79	Gamma	15	3 473	Hartwell et al[22]
Liver transplant (subsequent year)	£1 949.08	Gamma	14	136	Hartwell et al[22]
Adverse event costs					
Anemia	£501.58	Gamma	10	48	Johnson et al[3]
Rash	£166.50	Gamma	16	10	Johnson et al[3]
Depression	£414.17	Gamma	16	26	Johnson et al[3]
Neutropenia	£980.26	Gamma	10	98	Johnson et al[3]
Thrombocytopenia	£875.16	Gamma	14	62	Johnson et al[3]
Utilities					
Treatment-related utilities (penalties)					
Mild (F0-F1)—3D (monthly)	−0.001	Fixed	–	–	Johnson et al[3]
Moderate (F2-F3)—3D (monthly)	−0.001	Fixed	–	–	Johnson et al[3]
Health state utilities					
SVR mild (F0-F1)	0.820	Fixed	–	–	Wright et al[24]
SVR moderate (F2-F3)	0.710	Fixed	–	–	Wright et al[24]
Mild (F0-F1)	0.770	Beta	141	42	Wright et al[24]
Moderate (F2-F3)	0.660	Log-normal	–	–	Wright et al[24]
CC (F4)	0.550	Log-normal	–	–	Wright et al[24]

continued on next page

Table 1. Continued

Variable	Base case	Distribution	α	β	Source
DCC	0.450	Beta	55	67	Wright et al[24]
HCC (first year)	0.450	Beta	55	67	Wright et al[24]
HCC (subsequent year)	0.450	Beta	55	67	Wright et al[24]
Liver transplant (first year)	0.450	Beta	55	67	Hartwell et al[22]
Liver transplant (subsequent year)	0.670	Beta	32	16	Wright et al[24]

CC indicates compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR12, sustained virological response at 12 wk; 3D, ombitasvir, paritaprevir, ritonavir with dasabuvir.
*Synthesized from Kowdley et al[11] and Sulkowski et al[12] (for further details, see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.12.011).

Parameter Inputs

We informed the model using a synthesis of evidence, as presented in Table 1 and described herein.

Treatment-related inputs

We synthesized evidence from 2 sources to inform the efficacy of first-line 3D treatment. Kowdley et al[11] reported SVR12 for 3D after 12 and 8 weeks of treatment, on the basis of a large phase 2b clinical trial with 571 patients, and found that 96% and 88% of patients, respectively, cleared the virus. Evidence on shorter treatment durations for 3D was not available; nevertheless, SVR12 for an alternative DAA regimen using DCV-Trio + SOF was reported by Sulkowski et al[12] for a similar population after 6 and 4 weeks of treatment. The small phase 2 clinical trial with 28 patients reported that 57% and 29% of patients achieved SVR12 after 6 and 4 weeks of treatment, respectively. For our analysis, we assumed that the odds ratio of SVR12 after 6 and 4 weeks of treatment using DCV-Trio + SOF could be applied to 3D. We calculated the odds ratio of available data (ie, 8 vs 12 weeks and 4 vs 6 weeks), averaged these to estimate 8 versus 6 weeks, and applied these to our baseline 3D estimates to obtain predicted estimates for 6 and 4 weeks for 3D therapy. We used a Bayesian Markov chain Monte-Carlo simulation framework to pool the evidence to propagate and reflect the uncertainties in these estimates for use in probabilistic sensitivity analysis (for further details, see Appendix 1 in Supplemental Materials found at 10.1016/j.jval.2018.12.011). The estimated SVR12 was 96%, 87%, 64%, and 38% after 12, 8, 6, and 4 weeks of treatment, respectively, with uncertainty around these estimates presented in Table 1.

Bourliere et al[20] provided evidence on the efficacy of re-treatment using SOF/VEL/VOX from 2 phase 3 clinical trials (POLARIS-1 and POLARIS-4). Overall, 97.3% of patients achieved SVR12; we used this parameter to inform the expected SVR12 in patients who failed any of the treatment strategies. We assessed uncertainty in this parameter using data obtained from Bourliere et al[20] and beta distributions.

Treatment-related adverse events associated with DAA treatment were modeled to reflect the potential impact of these clinical events over different treatment durations. We obtained the probability of adverse events occurring from a clinical trial of 3D treatment, as reported by Johnson et al.[3] To estimate the probability of these events occurring over different treatment durations, we converted the probabilities to rates and calculated the time-dependent probability for each strategy (see Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.12.011). We assumed that the probability of adverse events occurring was the same for re-treatment as for first-line treatment. The adverse events included anemia, rash, depression, grade 3 or 4 neutropenia, and grade 3 or 4 thrombocytopenia.

Epidemiological inputs

The Markov model simulated the natural disease history of HCV using annual transition probabilities, which are presented in Table 1. We derived estimates from published studies on the probability of reinfection (1% per annum),[3] fibrosis[23,24] and nonfibrosis[25,26] progression, liver-related mortality,[23,25,27] and all-cause mortality, stratified by age and sex.[34]

Costs

The model considered both treatment-related and health state costs from the perspective of the National Health Service in the United Kingdom (Table 1). All unit costs were expressed in sterling (£) and valued at 2016/2017 prices.

The costs for the drug regimens were taken from the respective NICE technology appraisals for 3D[8] and SOF/VEL/VOX (Table 1). These costs were applied on a pay-per-tablet basis, rather than a pay-per-treatment success basis. We also considered monitoring costs, and derived these from a previous technology appraisal for a similar DAA.[7] We assumed that monitoring costs were the same for first-line treatment and re-treatment because these costs were not expected to vary by DAA treatment. Treatment-related costs (drug and monitoring costs) were assumed to be fixed in the model because these prices were not expected to vary in the United Kingdom. The costs associated with adverse events were taken from the study by Johnson et al.[3] We assessed uncertainty in these estimates using gamma distributions.

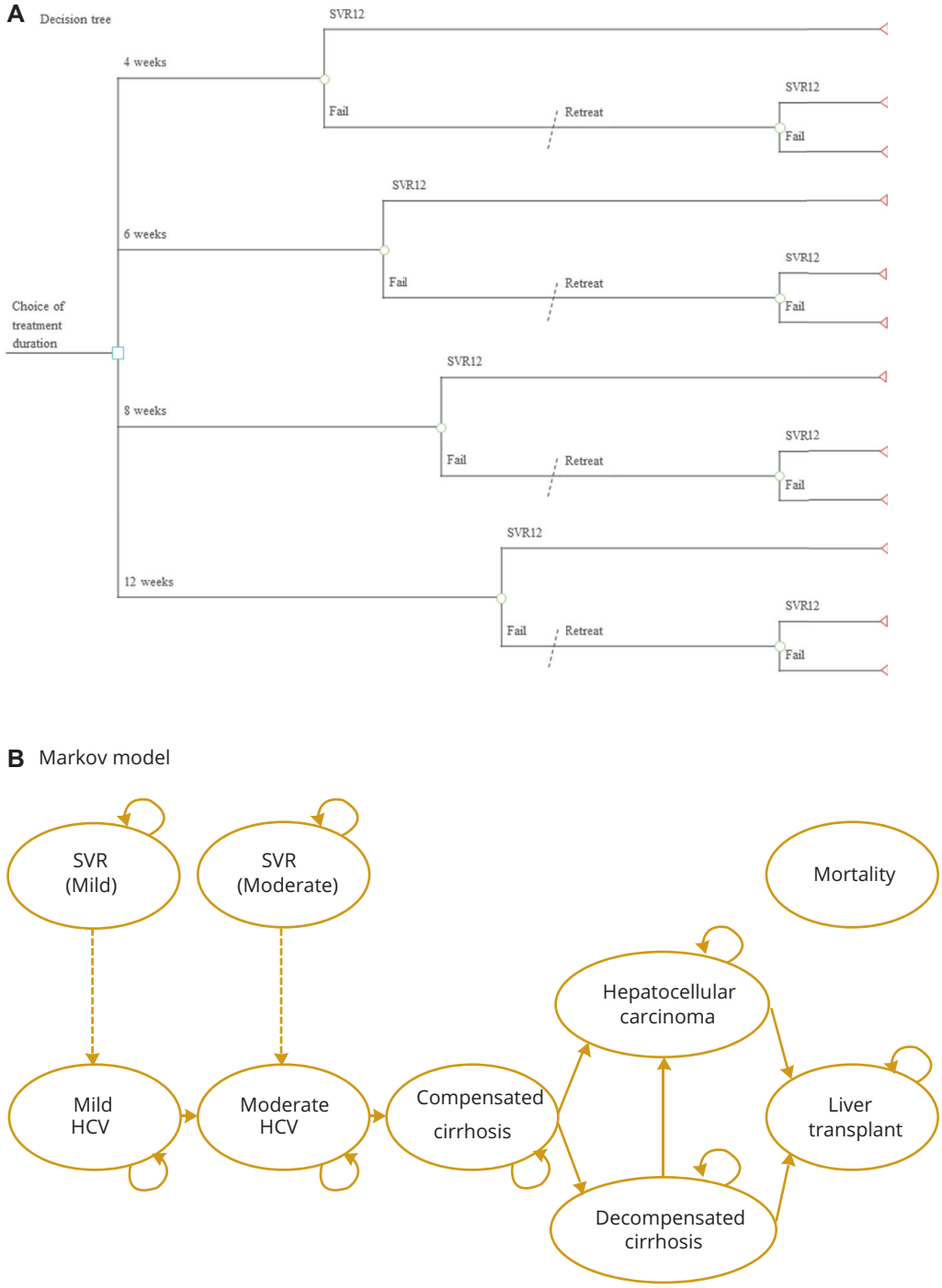
Health state costs were derived from a previous UK evaluation of HCV by Hartwell et al[22] and a cost analysis of resource use incurred by both HCV-infected and HCV-cleared patients, undertaken by Backx et al.[29] Gamma distributions were assumed for all cost inputs. We updated costs to 2016/2017 prices using the Hospital and Community Health Services index[35] (Table 1).

Utility weights

We derived treatment-related and health state utility estimates from published studies (Table 1). Johnson et al[3] provided treatment-related utilities for 3D treatment. The quality-of-life estimates were obtained from the 5-level EuroQol 5-dimensional questionnaire, which was administered to patients participating in clinical trials for 3D treatment. For our analysis of shortened treatment, we converted the 12-week treatment estimates to reflect the monthly deterioration in quality of life because of adverse events associated with treatment. We assumed the same treatment-related utilities for SOF/VEL/VOX because these have not yet been published.

Health state utilities for HCV infection were derived from Wright et al[24] and reflected the expected annual health-related quality of life associated with each HCV health state. As in the study by Wright et al,[24] and other analyses,[3,22] we assumed that

Figure 1. Economic model structure: (A) Decision tree simulating treatment outcomes; (B) Markov model simulating natural disease history.



Patients entered the model depending on their response to treatment and liver firbrosis
--Dotted line reflects reinfection
[a] Captures all-cause mortality and live-related mortality
[b] Models first and subsequent years to reflect different liver-related mortality rates
SVR, sustained virologic response at 12 weeks

HCV indicates hepatitis C virus; SVR, sustained virological response.

the health utility associated with treatment success (SVR12) was greater than the baseline utility level by a score of 0.05 for both mild and moderate liver fibrosis. We assumed that the health utility in successfully treated patients was fixed in the model. We investigated uncertainty in infected patients using beta distributions (Table 1).

Table 2. Cost-effectiveness findings.

Analysis	Costs (£) (95% CI)	QALYs (95% CI)	Cost per cure (£) (95% CI)	INMB (£) (95% CI)*,†	*P*(CE)†
Base-case analysis					
12 wk	40 911 (38 742 to 44 007)	15.51 (15.00 to 16.16)	41 051 (38 788 to 44 313)	–	.029
8 wk	32 821 (29 513 to 36 971)	15.49 (14.98 to 16.14)	33 194 (29 701 to 37 669)	7 737 (3 242 to 11 819)	.558
6 wk	37 668 (25 511 to 52 476)	15.44 (14.92 to 16.11)	39 048 (25 746 to 56 050)	1 860 (−14 517 to 15 153)	.245
4 wk	43 126 (20 506 to 59 551)	15.38 (14.83 to 16.07)	46 021 (20 762 to 67 835)	−4 735 (−24 197 to 20 141)	.168
Sensitivity analysis (80% reduction in drug prices)					
12 wk	11 455 (9 951 to 13 657)	15.51 (14.99 to 16.16)	11 495 (9 972 to 13 721)	–	.220
8 wk	9 738 (8 083 to 12 016)	15.49 (14.97 to 16.14)	9 848 (8 136 to 12 217)	1 370 (−344 to 2 685)	.470
6 wk	10 892 (7 617 to 14 835)	15.44 (14.90 to 16.11)	11290 (7 709 to 15 949)	−815 (−6 868 to 3 170)	.203
4 wk	12 203 (6 634 to 17 020)	15.38 (14.82 to 16.07)	13 008 (6 706 to 19 512)	−3 197 (−12 090 to 4 291)	.107

CI indicates confidence interval; INMB, incremental net monetary benefit; *P*(CE), probability most cost-effective; QALY, quality-adjusted life-year.
*Versus 12 wk.
†At £20 000 willingness to pay.

Cost-Effectiveness Analyses

Base-case analysis

The base-case analysis compared the lifetime cost-effectiveness of different shortened treatment durations against the standard 12-week treatment duration for GT1 noncirrhotic treatment-naive patients in the United Kingdom. We calculated expected costs and quality-adjusted life-years (QALYs) per 1000 patients using a probabilistic analysis, with parameters sampled from predefined distributions over 10 000 simulations in Microsoft Excel software.[36] The expected costs and QALYs were computed as an average over the 10 000 simulations. We calculated the expected incremental net monetary benefit (INMB) of each shortened treatment strategy relative to 12 weeks of treatment, assuming a willingness-to-pay (WTP) threshold of £20 000:

$$\text{Expected INMB} = (\text{Expected QALYs}) * £20\,000 - (\text{Expected costs}).$$

We also calculated the expected cost per cure:

$$\text{Cost per cure} = \frac{\text{cCost[duration]}}{\text{pCured[duration]}},$$

where pCured is the proportion of patients cured over the treatment duration. We reported the probability that any strategy was the most cost-effective treatment strategy at different WTP thresholds using cost-effectiveness acceptability curves.

Sensitivity analyses

We considered alternative DAA regimens currently used in the United Kingdom as first-line treatment to assess the impact of different drug prices and utility scores on cost-effectiveness. These included LDV/SOF, daclatasvir plus sofosbuvir (DCV/SOF), and elbasvir/grazoprevir (ELB/GZR). (The cost and utility estimates used in these analyses are detailed in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.12.011.)

We assessed the impact on cost-effectiveness of lower drug prices. The base-case analysis used prices reported in the NICE technology appraisals; nevertheless, reduced drug prices were agreed by the drug manufacturers and NICE, which have not been made publicly available. In a sensitivity analysis, we reduced drug prices by 80% (to £7284.34 and £8965.40 per 12-week course for first-line treatment and re-treatment, respectively). We considered alternative discount rates in sensitivity analyses to assess the impact of lower (1.5%) and higher (5%) discount rates on cost-effectiveness findings. This was useful to assess the generalizability of our findings to other healthcare settings where different discount rates are applied. Here, we assumed the same 80% reduction in drug prices.

Scenario analyses

Because of uncertainty in the cost of treatment in the United Kingdom and elsewhere, we used a threshold analysis to investigate cost-effectiveness under different drug prices. Here, we ranged the cost from £0 to £40 000 per 12-week course for both first-line treatment and re-treatment simultaneously.

We also used threshold analyses to investigate the impact of different first-line cure rates on cost-effectiveness for each shortened treatment strategy separately, assuming the same 80% reduction in drug prices. First, we considered higher SVR rates for the 8-week treatment, holding all else constant, because the base-case rate of 87% was somewhat conservative; higher success rates over 8 weeks have been reported for other regimens,[37] as well as newer DAAs.[38] In this scenario, we ranged SVR12 between 86% and 96%. After the 6-week treatment, we varied the first-line cure rate between 40% and 85% (ie, between the SVR12 after 4 [38%] and 8 [87%] weeks of treatment), holding all else constant. Finally, we investigated the cost-effectiveness of the 4-week treatment at higher cure rate thresholds, constrained at 65% (ie, constrained at the SVR12 after 6 weeks of treatment).

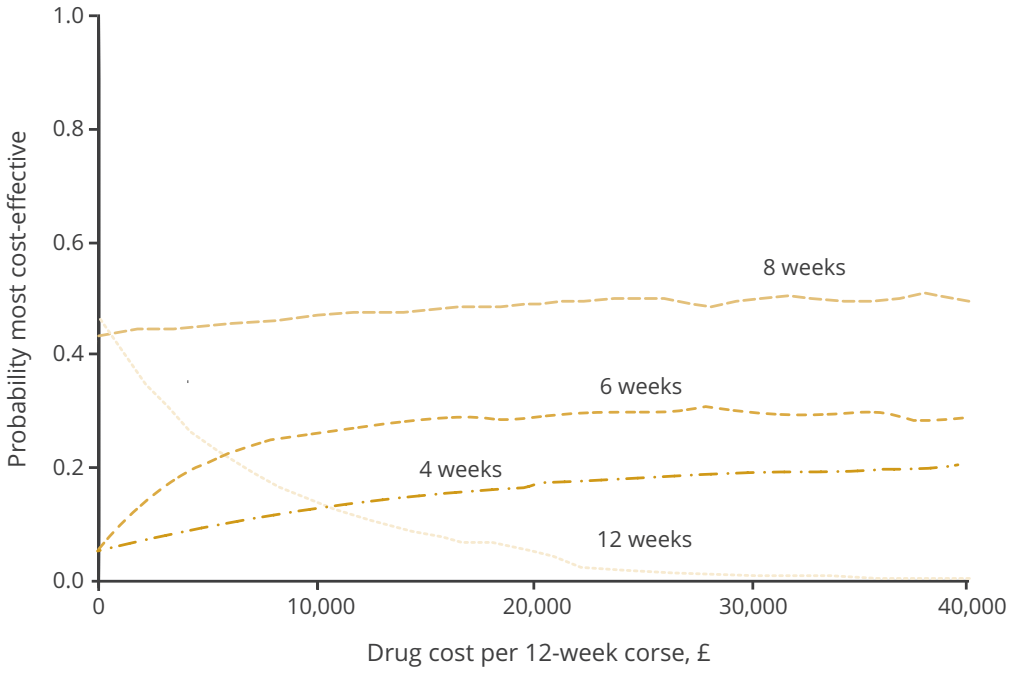
Because of some uncertainty in the cure rate after re-treatment, we conducted a threshold analysis on this parameter also. Here, we varied the cure rate between 0% and 100% and assumed the same thresholds for each shortened treatment strategy. We assumed the same 80% reduction in drug prices in this scenario also.

Results

Base-Case Findings

The 8-week treatment generated lower expected lifetime costs and fewer QALY gains compared with the 12-week treatment. The strategy had the lowest expected lifetime cost per cure at £32 607 (95% confidence interval [CI] £29 288-£36 699). At a WTP threshold of £20 000, despite the smaller QALY gains, the strategy had the highest INMB per 1000 patients at £7737 (95% CI £3242-£11 819) because of the considerable cost savings associated with the shortened treatment strategy (Table 2). At 56%, the strategy had the highest probability of being the most cost-effective

Figure 2. Probability of cost-effectiveness at £20 000 willingness to pay and different drug costs.



option. The 6-week treatment produced a positive expected INMB, although some uncertainty was observed because of imprecise estimates on the effectiveness of shortened treatment (INMB £1860 [95% CI −£14 517 to £15 153]). The strategy had a lower probability of being the most cost-effective at 25%. Similar uncertainty was observed in the 4-week treatment strategy, which produced a negative expected INMB (−£4735 [95% CI −£24 197 to £20 141]) because of higher overall lifetime costs and lower QALY gains. The strategy had 17% probability of being the most cost-effective.

Sensitivity Analyses Findings

Changing the drug regimen for first-line treatment did not affect the base-case findings, except in the case of the 4-week treatment strategy that produced a positive INMB using DCV/SOF as first-line treatment. The main driver for this change was the increased cost of first-line treatment, which increased the overall cost of the 12-week treatment. In all cases, the 8- and 6-week treatment strategies produced a positive expected INMB (see Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.12.011). Greater uncertainty was observed when DCV/SOF was used as first-line treatment; nevertheless, the shortened treatment strategies had comparably higher probabilities of being the most cost-effective treatment strategies compared with the 12-week treatment (see Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.12.011).

Reducing drug costs by 80% introduced some uncertainty in the results. Because of the reduced cost savings, the 8-week treatment strategy returned a considerably smaller INMB with some uncertainty observed (£1370 [95% CI −£344 to £2685]). Nevertheless, the strategy still had the highest probability (47%) of being the most cost-effective because of lower expected lifetime costs (Table 2; cost-effectiveness acceptability curves are presented in Appendix 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.12.011).

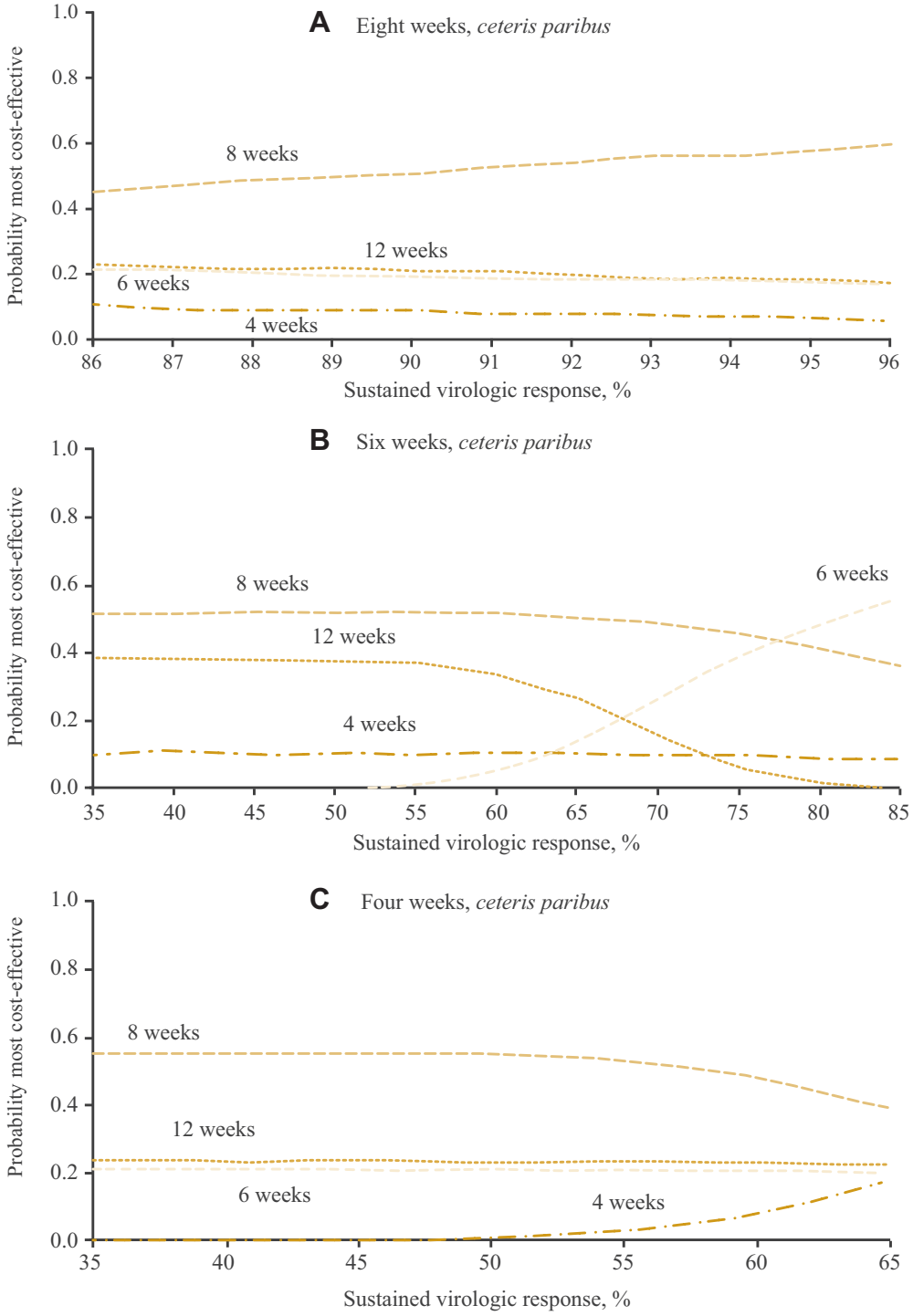
The results were robust to changes in the discount rate (see Appendix 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.12.011). At the lower rate of 1.5%, the same uncertainty was observed, and the 8-week treatment strategy still had the highest probability of being the most cost-effective, at 46%. At the higher rate of 5.0%, the probability that the 8-week treatment was the most cost-effective increased to 50% and no uncertainty in the expected INMB was observed.

Scenario Analyses Findings

Figure 2 presents the findings from the drug-cost threshold analysis. The results are plotted using information on the probability of cost-effectiveness at £20 000 WTP. The horizontal axis presents the different drug costs. At 0 drug costs, the 12-week treatment was the most cost-effective option because of the obvious QALY advantage over the shortened treatment strategies. Nevertheless, the 8-week treatment had the highest probability of being the most cost-effective at all drug costs above 0 because of the available cost savings. At all prices higher than £6000 per 12-week course, the 6-week treatment had a consistently higher probability (>20%) than the 12-week treatment of being the most cost-effective. The 4-week treatment had a consistently low probability (<20%) of being the most cost-effective strategy at all drug prices.

Figure 3 presents the findings from the first-line cure rate threshold analysis after 8, 6, and 4 weeks of treatment, respectively. The results are similarly plotted using information on the probability of cost-effectiveness. The probability that the 8-week treatment duration is cost-effective increases with each percentage increase in SVR12 (Figure 3A). At 96% SVR12, *ceteris paribus*, the probability that the strategy is the most cost-effective is 60%. If

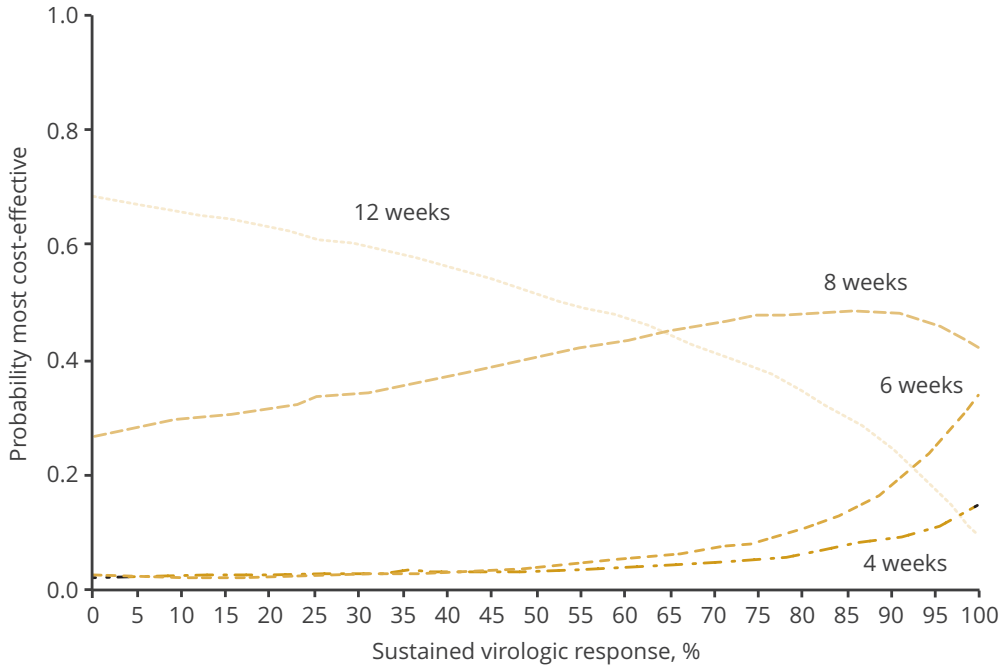
Figure 3. Probability of cost-effectiveness at £20 000 willingness to pay and different first-line cure rate thresholds: (A) 8-wk treatment; (B) 6-wk treatment; (C) 4-wk treatment.



SVR12 after the 6-week treatment was 77% or higher, *ceteris paribus*, the strategy had the highest probability of being the most cost-effective strategy (Figure 3B). The 4-week treatment had the lowest probability of being the most cost-effective, even when SVR12 was as high as 65% (Figure 3C).

The results from the re-treatment cure rate threshold analysis are presented in Figure 4. At re-treatment cure rates higher than 65%, the 8-week treatment had the highest probability of being the most cost-effective strategy. The 6- and 4-week treatments had a higher probability of being cost-effective compared with the

Figure 4. Probability of cost-effectiveness at £20 000 willingness to pay and different re-treatment cure rate thresholds.



12-week treatment if SVR12 after re-treatment was 92.5% and 97.5% or higher, respectively.

Discussion

Strengths and Limitations

To our knowledge, this is the first study to consider the cost-effectiveness of short-course therapy for chronic HCV. We compared 3 different shortened treatment durations using data reported in the literature for a noncirrhotic treatment-naive population. We developed a decision tree to capture treatment outcomes and adapted a previously validated Markov model to reflect the disease history of HCV. We assessed a number of DAA regimens currently used in the United Kingdom and conducted various sensitivity and scenario analyses. Our results were generally robust to these analyses.

There are limitations to this work. The evidence on the effectiveness of shortened treatment duration is limited, and often limited to DAAs not currently approved. With the exception of Kowdley et al[11] who reported the effectiveness of 3D treatment, which is currently recommended for use internationally, most studies considered the effectiveness of a combination of DAA regimens,[12] or explored the effectiveness of existing DAA regimens but with the addition of an investigational nonnucleoside or protease inhibitor, for example.[13,39,40] As a consequence, these analyses have had little impact on policy. For instance, in the United Kingdom, the recommended standard treatment duration for all DAA regimens in GT1 is 12 to 16 weeks, with the exception of LDV/SOF, which is recommended for use over 8 weeks in patients with low baseline viral load, and glecaprevir/pibrentasvir, which is a new regimen that is licensed for use over 8 weeks.[41] Although the evidence is limited, we used the data from Kowdley et al[11] as our baseline source for efficacy data on 12 and 8 weeks of treatment and predicted the expected cure rate for this regimen over 6- and 4-week durations using data from Sulkowski et al.[12]

The evidence for the effectiveness of re-treatment is also limited, although most studies report considerably high success rates in GT1 noncirrhotic patients.[15,17-20,42] For our analysis, we used recent evidence from Bourliere et al[20] who investigated the effectiveness of re-treatment using the now currently recommended re-treatment regimen (SOF/VEL/VOX) over 12 weeks for a similar noncirrhotic population that failed first-line therapy. In scenario analysis, we assessed lower re-treatment cure rates and found that the shortened treatment strategies were more cost-effective than the 12-week treatment, provided SVR12 after re-treatment was 65% or higher after the 8-week treatment, and 92.5% and 97.5% after the 6- and 4-week treatment, respectively.

Although the cost of DAA treatment is high, we do not know the actual price healthcare payers pay for these drugs. In our base-case analysis, we assumed the prices reported in the technology appraisals,[7-9,43] which are an exaggeration of the actual prices paid. In a threshold analysis, we varied these prices and found that the base-case findings remained generally robust at prices lower than £40 000 per 12-week course.

Finally, we took a UK perspective in this article. Although some variations in monitoring costs might exist internationally, there is little to differentiate in terms of treatment costs, patient outcomes, and disease progression. Discount rates differ across some settings; for instance, in Australia, Estonia, Latvia, Lithuania, and Ireland, the applied discount rate is 5%, whereas in Canada it is 1.5%.[44] We applied these rates in sensitivity analyses and found that the results remained generally unchanged, suggesting that our findings may be generalizable to other healthcare settings that assume the same, or either lower or higher, discount rates. The findings are also likely generalizable across DAA regimens, which are generally homogeneous; DAAs have similar cure rates,

comparably high treatment costs, and uniform impact on patients' quality of life. We did not explore strategies that might stratify patients as suitable for shortened therapy at 4 and 6 weeks, although such approaches are likely to improve the cost-effectiveness of treatment.

Implications for Practice

Our findings that the 8-week (or even 6-week) shortened treatment duration is likely to be cost-effective are important in the context of clinical practice. Treating patients over shortened durations in resource-constrained settings, for example, allows scarce resources, such as staff, to be better allocated and distributed although such approaches need to be balanced against the complexity of delivering care. The decision to treat patients, particularly those with high loss to follow-up, such as chaotic drug users, is also less problematic. Treating these patients over shortened treatment durations is effective and cost-effective if a salvage treatment can be administered. This may be useful in settings in which there is a limited time available for treatment (eg, prisons); nevertheless, the decision to treat patients serving short sentences remains problematic because of loss to follow-up. Future research should identify the potential cost-effectiveness of shortened treatment durations in this context.

Although short-course therapy is not currently recommended, the cost-effectiveness of this approach is clear. Shortening treatment to 8 or 6 weeks using existing DAA therapies, such as 3D, LDV/SOF, DCV/SOF, and ELB/GZR, appears cost-effective, although some uncertainty in the 6-week treatment strategy exists. We highlight the need for further evidence on the efficacy of 6 and 4 weeks of treatment using licensed regimens, along with evidence on the success of re-treatment. Future research should also identify patients for whom shortened treatment is likely to be effective, with treatment duration optimized on the basis of baseline viral load or resistance to DAA therapies, for example, which has been shown to limit patients' chance of viral eradication,[45,46] particularly in those with prolonged exposure to treatment previously.[15]

Conclusions

We compared the lifetime cost-effectiveness of 3 unstratified shortened treatment durations (8, 6, and 4 weeks) against the standard 12-week treatment, with a re-treatment strategy adopted for all patients who failed first-line treatment, for GT1 noncirrhotic treatment-naive patients in the United Kingdom. The 8-week treatment generates marginally fewer expected lifetime QALYs than the 12-week treatment duration, but is the most cost-effective option because of considerably lower expected lifetime costs arising from lower first-line treatment costs. There is considerable uncertainty surrounding the cost-effectiveness of 6 and 4 weeks of treatment because of limited evidence on efficacy, although there is some indication that the 6-week treatment may be cost-effective, whereas the 4-week treatment is likely not cost-effective.

Provided drug costs are above 0, the 8-week treatment has the highest probability of being the most cost-effective because of the available cost savings versus the standard 12-week treatment. The 6-week treatment had a higher probability than the 12-week treatment of being the most cost-effective at all drug prices higher than £6000 per 12-week course; nevertheless, the probability was generally low at approximately 30%. The 8-week treatment is highly cost-effective at higher first-line cure rates; at 96% SVR12, the strategy has 60% probability of being the most cost-effective. The 6-week treatment would be the most cost-effective option if the first-line cure rate was 77% or higher, whereas the 4-week treatment always had a low probability of being the most cost-effective, even when the first-line cure rate was as high as 65%. Shortening treatment duration is cost-effective if the re-treatment cure rate is 65% or higher after the 8-week treatment, or 92.5% and 97.5% after the 6- and 4-week treatment, respectively.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.12.011.

REFERENCES

1. Chahal HS, Marseille EA, Tice JA, et al. Cost-effectiveness of early treatment of hepatitis C virus genotype 1 by stage of liver fibrosis in a US treatment-naive population. *JAMA Intern Med*. 2016;176(1):65–73.
2. 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*. 2015;162(6):397–406.
3. Johnson SJ, Parise H, Virabhak S, Filipovic I, Samp JC, Misurski D. Economic evaluation of ombitasvir/paritaprevir/ritonavir and dasabuvir for the treatment of chronic genotype 1 hepatitis C virus infection. *J Med Econ*. 2016;19(10):983–994.
4. 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(6):407–419.
5. World Health Organization. *Guidelines for the Screening, Care and Treatment of Persons With Chronic Hepatitis C Infection*. Geneva, Switzerland: World Health Organization; 2016.
6. World Health Organization. *Global Health Sector Strategy on Viral Hepatitis 2016-2021*. Geneva, Switzerland: World Health Organization; 2016.
7. National Institute for Health and Care Excellence. *Technology Appraisal Guidance [TA363]: Ledipasvir–Sofosbuvir for Treating Chronic Hepatitis C*. London: National Institute for Health and Care Excellence; 2015.
8. National Institute for Health and Care Excellence. *Technology Appraisal Guidance [TA365]: Ombitasvir–Paritaprevir–Ritonavir With or Without Dasabuvir for Treating Chronic Hepatitis C*. London: National Institute for Health and Care Excellence; 2015.
9. National Institute for Health and Care Excellence. *Technology Appraisal Guidance [TA364]: Daclatasvir for Treating Chronic Hepatitis C*. London: National Institute for Health and Care Excellence; 2015.
10. Corman S, Elbasha EH, Michalopoulos SN, Nwankwo C. Cost-utility of elbasvir/grazoprevir in patients with chronic hepatitis C genotype 1 infection. *Value Health*. 2017;20(8):1110–1120.
11. Kowdley KV, Lawitz E, Poordad F, et al. Phase 2b trial of interferon-free therapy for hepatitis C virus genotype 1. *N Engl J Med*. 2014;370(3):222–232.
12. Sulkowski MS, Flamm S, Kayali Z, et al. Short-duration treatment for chronic hepatitis C virus with daclatasvir, asunaprevir, beclabuvir and sofosbuvir (FOURward study). *Liver Int*. 2017;37(6):836–842.
13. Kohli A, Kattakuzhy S, Sidharthan S, et al. Four-week direct-acting antiviral regimens in noncirrhotic patients with hepatitis C virus genotype 1 infection: an open-label, nonrandomized trial. *Ann Intern Med*. 2015;163(12):899–907.
14. Pawlotsky JM. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. *Gastroenterology*. 2016;151(1):70–86.
15. Lawitz E, Flamm S, Yang JC, et al. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks. Paper presented at: Meeting of the European Association for the Study of the Liver; April 22-26, 2015; Vienna, Austria.

16. Lawitz E, Poordad F, Gutierrez J, et al. C-swift retreatment final results: highly successful retreatment of GT1-infected patients with 12 weeks of elbasvir/grazoprevir plus sofosbuvir and ribavirin after failure of short-duration all-oral therapy. Paper presented at: European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain.
17. Lawitz E, Poordad F, Wells J, et al. Sofosbuvir-velpatasvir-voxilaprevir with or without ribavirin in direct-acting antiviral-experienced patients with genotype 1 hepatitis C virus. *Hepatology*. 2017;65(6):1803–1809.
18. Poordad F, Bennett M, Sepe TE, et al. Ombitasvir/paritaprevir/r, dasabuvir, and sofosbuvir treatment of patients with HCV genotype 1-infection who failed a prior course of DAA therapy: the quartz-i study … 95-100% SVR. Paper presented at: European Association for the Study of the Liver; April 13-17, 2016; Barcelona, Spain.
19. Wilson EM, Kattakuzhy S, Sidharthan S, et al. Successful retreatment of chronic HCV genotype-1 infection with ledipasvir and sofosbuvir after initial short course therapy with direct-acting antiviral regimens. *Clin Infect Dis*. 2016;62(3):280–288.
20. Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. *N Engl J Med*. 2017;376(22):2134–2146.
21. National Institute for Health and Care Excellence. *Guide to the Methods of Technology Appraisal 2013*. London: National Institute for Health and Care Excellence; 2013.
22. Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess*. 2011;15(17):i-xii, 1-210.
23. Grieve R, Roberts J, Wright M, et al. Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. *Gut*. 2006;55(9):1332–1338.
24. Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess*. 2006;10(21):1–113, iii.
25. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology*. 1997;112(2):463–472.
26. Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol*. 2010;52(5):652–657.
27. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med*. 1997;127(10):855–865.
28. National Institute for Health and Care Excellence. *Technology Appraisal Guidance [TA507]: Sofosbuvir–Velpatasvir–Voxilaprevir for Treating Chronic Hepatitis C*. London: National Institute for Health and Care Excellence; 2018.
29. Backx M, Lewszuk A, White JR, et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. *J Viral Hepat*. 2014;21(3):208–215.
30. National Health Service. *National Clinical Guidelines for the Treatment of HCV in Adults*. Scotland: National Health Service; 2018.
31. National Health Service. *Specialised Commissioning Drugs Briefing: Spring 2018*. London: National Health Service; 2018.
32. Grishchenko M, Grieve RD, Sweeting MJ, et al. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. *Int J Technol Assess Health Care*. 2009;25(2):171–180.
33. Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11(11):1–205, iii.
34. National life tables, 2013-2015. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Accessed June 10, 2017.
35. Curtis L, Burns A. *Unit Costs of Health and Social Care 2017*. Canterbury, Kent: Personal Social Services Research Unit, University of Kent; 2017.
36. Microsoft. *Microsoft Excel (2016)*. Redmond, WA: Microsoft Corp; 2016.
37. Sarrazin C. The importance of resistance to direct antiviral drugs in HCV infection in clinical practice. *J Hepatol*. 2016;64(2):486–504.
38. Zeuzem S, Foster GR, Wang S, et al. Glecaprevir–pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. *N Engl J Med*. 2018;378(4):354–369.
39. Kattakuzhy S, Wilson E, Sidharthan S, et al. Moderate sustained virologic response rates with 6-week combination directly acting anti-hepatitis C virus therapy in patients with advanced liver disease. *Clin Infect Dis*. 2016;62(4):440–447.
40. Kohli A, Osinusi A, Sims Z, et al. Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study. *Lancet*. 2015;385(9973):1107–1113.
41. National Institute for Health and Care Excellence. *Technology Appraisal Guidance [TA499]: Glecaprevir–Pibrentasvir for Treating Chronic Hepatitis C*. London: National Institute for Health and Care Excellence; 2018.
42. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med*. 2013;368(20):1878–1887.
43. National Institute for Health and Care Excellence. *Technology Appraisal Guidance [TA413]: Elbasvir–Grazoprevir for Treating Chronic Hepatitis C*. London: National Institute for Health and Care Excellence; 2016.
44. Attema AE, Brouwer WBF, Claxton K. Discounting in economic evaluations. *Pharmacoeconomics*. 2018;36(7):745–758.
45. Cloherty G, Talal A, Coller K, et al. Role of serologic and molecular diagnostic assays in identification and management of hepatitis C virus infection. *J Clin Microbiol*. 2016;54(2):265–273.
46. Itakura J, Kurosaki M, Higuchi M, et al. Resistance-associated NS5A variants of hepatitis C virus are susceptible to interferon-based therapy. *PLoS One*. 2015;10(9):e0138060.