The Cost-Effectiveness of Sofosbuvir-Based Regimens for Treatment of Hepatitis C Virus Genotype 2 or 3 Infection

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Abstract

Background—Chronic infection with hepatitis C virus (HCV) genotype 2 or 3 can be treated with sofosbuvir without interferon. Because sofosbuvir is costly, its benefits should be compared with the additional resources used.

Objective—To estimate the cost-effectiveness of sofosbuvir-based treatments for HCV genotype 2 or 3 infection in the United States.

Design—Monte Carlo simulation, including deterministic and probabilistic sensitivity analyses.

Data Sources—Randomized trials, observational cohorts, and national health care spending surveys.

Target Population—8 patient types defined by HCV genotype (2 vs. 3), treatment history (naive vs. experienced), and cirrhosis status (noncirrhotic vs. cirrhotic).

Time Horizon—Lifetime.

Perspective—Payer.

Intervention—Sofosbuvir-based therapies, pegylated interferon–ribavirin, and no therapy.

Outcome Measures—Discounted quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratios (ICERs).

Results of Base-Case Analysis—The ICER of sofosbuvir-based treatment was less than $100 000 per QALY in cirrhotic patients (genotype 2 or 3 and treatment-naive or treatment-experienced) and in treatment-experienced noncirrhotic patients but was greater than $200 000 per QALY in treatment-naive noncirrhotic patients.

Results of Sensitivity Analysis—The ICER of sofosbuvir-based therapy for treatment-naive noncirrhotic patients with genotype 2 or 3 infection was less than $100 000 per QALY when the cost of sofosbuvir was reduced by approximately 40% and 60%, respectively. In probabilistic sensitivity analyses, cost-effectiveness conclusions were robust to uncertainty in treatment efficacy.

Limitation—The analysis did not consider possible benefits of preventing HCV transmission.

Conclusion—Sofosbuvir provides good value for money for treatment-experienced patients with HCV genotype 2 or 3 infection and those with cirrhosis. At their current cost, sofosbuvir-based regimens for treatment-naive noncirrhotic patients exceed willingness-to-pay thresholds commonly cited in the United States.

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In December 2013, the U.S. Food and Drug Administration approved sofosbuvir, a nucleotide analogue inhibitor of hepatitis C virus (HCV) NS5B polymerase with activity against all HCV genotypes (1). In combination with ribavirin, sofosbuvir can be used to treat patients with chronic HCV genotype 2 or 3 infection without interferon, yielding cure rates greater than with the previous standard of care (2, 3). Cure, also known as sustained virologic response (SVR), is associated with a greatly reduced lifetime risk for liver-related morbidity and mortality and short-term survival improvements for patients with advanced liver disease (4).

Sofosbuvir changed the landscape of HCV therapy given that concerns about interferon-related toxicity historically limited provider and patient enthusiasm for HCV treatment (5). However, sofosbuvir currently costs approximately $1000 per tablet, or $28 000 for 4 weeks (6). Many HCV-infected persons rely on publicly funded health insurance, and these programs do not guarantee access to such costly drugs (7). Several state Medicaid programs recently announced that sofosbuvir will be available only to patients with advanced liver disease (8).

Treatment strategies that do not use limited resources where they are likely to have the greatest impact may result in unequal access to interferon-free regimens, thereby limiting the population-level benefits of new HCV treatments. Our goal was to evaluate the cost-effectiveness of sofosbuvir-based treatment strategies for patients with HCV genotype 2 or 3 infection to identify approaches that would maximize the number of patients who achieve HCV cure given competing demands on resources.

Methods

Analytic Overview

We used the Hepatitis C Cost-Effectiveness model, a Monte Carlo simulation of screening and treatment for HCV, to estimate the effectiveness and cost-effectiveness of strategies for treating chronic HCV genotype 2 or 3 infection. The model is summarized in this section, and details are available in the Supplement (available at www.annals.org) and elsewhere (9, 10). We considered 8 patient types defined by HCV genotype (2 vs. 3), treatment history (naive vs. experienced), and fibrosis stage (noncirrhotic vs. cirrhotic) (Table 1). We did not consider treatment of decompensated cirrhosis because management of end-stage liver disease is beyond the scope of this article.

For each patient type and treatment strategy, we used the model to simulate clinical outcomes and costs. Outcomes included quality-adjusted life expectancy (QALE) (measured in quality-adjusted life-years [QALYs]) and lifetime medical costs, both discounted at 3% annually (11). We calculated the incremental cost-effectiveness ratio (ICER) of each treatment strategy as the additional cost divided by the additional QALYs gained compared with the next less expensive strategy (11, 12). Strategies that resulted in higher costs but fewer QALYs gained and those with a higher ICER compared with a more effective strategy were considered inefficient ("dominated") and were excluded from the final incremental comparisons (11, 13).

We used reports from published clinical trials and observational cohorts to inform base-case parameters for treatment efficacy, disease progression, toxicity, quality of life (QoL), and cost (2–4, 6, 14–34). We conducted 1-way deterministic sensitivity analyses for plausible ranges (Table 2) and also modeled 2 specific scenarios. In the first scenario, we modeled a cohort of patients with fibrosis (METAVIR score F3) to determine the cost-effectiveness of treating patients with advanced fibrosis but not cirrhosis. In the second scenario, which would favor HCV treatment, costs attributable to all stages of HCV infection were doubled and were then assumed to return to zero after attainment of SVR.

We also performed probabilistic sensitivity analyses on treatment efficacy parameters. We defined distributions for each parameter based on outcomes from clinical trials. We conducted multiple iterations of the analyses by drawing parameter values from the distributions, and we displayed results by using cost-effectiveness acceptability curves (36).

We constructed the model and performed analyses using TreeAge Pro 2012 software (TreeAge Software).

Model Structure

The model functioned on 2 levels: disease progression and clinical decision making.

Disease Progression–Level Simulation—The disease progression–level simulation modeled 3 stages of liver disease: mild to moderate fibrosis, cirrhosis, and decompensated cirrhosis. Each of 1 million hypothetical persons in the patient-level simulation was assigned a unique time from HCV infection to development of cirrhosis such that some progressed

rapidly while others did not develop cirrhosis before they died of non–HCV-related causes (32, 33). Consistent with previous studies, all disease stages of HCV infection were associated with increased resource use and decreased QoL compared with no infection, with progressively higher resource use and lower QoL for each successive stage of disease (Table 2) (18, 19, 37–41). When persons became cirrhotic, they were subject to increased mortality attributable to liver disease, which further increased with decompensated cirrhosis (31, 42, 43).

Clinical Decision-Making–Level Simulation: HCV Therapy—Although the model included 3 stages of HCV disease progression for the disease progression–level simulation, for the purpose of HCV treatment, all patients were categorized as either "cirrhotic" or "noncirrhotic."

Pegylated Interferon–Ribavirin (Treatment-Naive Patients Only): Patients initiated a planned 24-week course of weekly pegylated interferon-α2a (180 mcg subcutaneously) in combination with twice-daily oral ribavirin (400 mg). Patients in the simulation had routine HCV RNA testing at the end of treatment week 4. To maximize the benefit while minimizing exposure to interferon, those with detectable viremia stopped therapy, whereas those with suppressed HCV RNA (rapid virologic response) continued a planned 24-week treatment course (2). In sensitivity analyses, we also modeled a scenario with no response-guided therapy using pegylated interferon–ribavirin.

In each treatment month, patients were at risk for premature treatment discontinuation due to nonadherence or major toxicity (Table 1 of the Supplement) (2, 30). Major toxicity resulted in immediate cessation of therapy and was associated with additional costs and a QoL decrement (14, 23–26, 44), whereas nonadherence resulted in withdrawal without additional costs or QoL decrements (Table 2 and Table 2 of the Supplement). Patients who withdrew from therapy were not eligible to attain SVR and continued to progress according to their assigned disease progression parameters.

All patients receiving HCV medications experienced a monthly QoL decrement related to adverse symptoms (14, 15). A proportion of patients experienced non–treatment-ending toxicity, including moderate anemia managed by ribavirin dose reduction and moderate neutropenia managed by pegylated interferon dose reduction and twice-weekly filgrastim (35). Because toxicity management varies, sensitivity analyses considered management of anemia without colony-stimulating factors. Patients with non–treatment-ending toxicity accrued cost adjustments related to dosing changes and additional therapies, but they continued to receive HCV treatment and were eligible to attain SVR.

Sofosbuvir–Ribavirin for 12, 16, or 24 Weeks: Patients initiated a 12-, 16-, or 24-week course of once-daily oral sofosbuvir (400 mg) and twice-daily oral ribavirin (600 mg). Similar to pegylated interferon–ribavirin, all patients had decreased QoL while taking medications, some experienced non–treatment-ending toxicity, and some withdrew from therapy due to nonadherence or toxicity (2, 3). Compared with pegylated interferon–ribavirin, however, patients receiving sofosbuvir–ribavirin had higher QoL during therapy,

less toxicity, and a lower probability of treatment withdrawal (Table 2 and Table 1 of the Supplement).

Pegylated Interferon–Ribavirin–Sofosbuvir (Patients With Genotype 3 Infection Only): Patients initiated a 12-week course of weekly pegylated interferon (180 mcg subcutaneously) in combination with twice-daily ribavirin (600 mg) and once-daily sofosbuvir (400 mg) (29). The approach to modeling adherence, toxicity, and QoL during therapy was the same as for pegylated interferon–ribavirin.

HCV Therapy Efficacy

The model had 3 treatment-related parameters that affected SVR: probability of withdrawal due to nonadherence or treatment-ending toxicity, probability of virologic failure (for response-guided pegylated interferon–ribavirin therapy only), and probability of achieving SVR conditional on treatment completion.

We used a Bayesian approach and the mathematical properties of the β distribution to develop probability density functions for each parameter based on data from clinical trials (Supplement) (2, 3, 29, 30).

Costs

We assessed costs from the payer perspective in 2013 U.S. dollars. During each simulation month, persons accrued age- and sex-stratified "background costs" attributable to non–HCV-related health care (20). They also accrued monthly HCV-specific costs, which varied by disease stage, with increasing resource use for each stage of advancing disease (Table 2) (27, 37). Costs of HCV therapy included drugs, clinic visits, laboratory tests, and toxicity management (Table 2 and Tables 3 and 4 of the Supplement). Monthly costs related to liver disease (including physician visits, emergency department visits, and hospitalizations) were estimated using γ distributions, from which each simulated person was assigned a randomly drawn value.

Quality of Life

Quality of life reflected the combination of 3 independent utility functions, which we combined multiplicatively. First, we considered utility related to non-HCV comorbid conditions; all simulated persons had a "background" QoL that was a function of age and sex. Second, we considered HCV-specific utility; HCV-related QoL was a function of fibrosis stage, with progressively lower utility with advancing disease. Third, we considered treatment-related utility. All patients had decreased QoL while receiving HCV therapy, which reflected the disutility of treatment adverse effects. Quality of life during interferon-free treatment was higher (multiplier, 0.99) than during therapy involving interferon (multiplier, 0.88) (15). Moreover, when patients had a treatment-ending major toxicity event, they experienced a temporary disutility related to the event (14).

Benefits of SVR

With successful treatment (SVR), fibrosis progression halted; HCV-attributable costs were reduced to 50% of the person's disease stage–specific cost before initiation of therapy (27,

45); QoL reverted to that of HCV-uninfected persons of the same age and sex (35); and, in patients who were cirrhotic before attaining SVR, liver-related mortality decreased by 94% (4).

Role of the Funding Source

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Results

Genotype 2

Noncirrhotic Patients—Without therapy, discounted QALE among treatment-naive noncirrhotic patients with HCV genotype 2 infection was 13.9 QALYs, with a mean discounted lifetime medical cost of $169 000 (Table 3). Treatment with 24 weeks of pegylated interferon–ribavirin resulted in SVR in 82% of patients, leading to an incremental QALE gain of 1.5 QALYs, an incremental cost of $4300, and an ICER of $3000 per QALY gained compared with no treatment. Compared with pegylated interferon–ribavirin, 12 weeks of sofosbuvir–ribavirin resulted in SVR in 98% of patients, an incremental QALE gain of 0.4 QALY, and an incremental cost of $87 900, corresponding to an ICER of $238 000 per QALY gained.

In treatment-experienced patients, sofosbuvir–ribavirin was compared with no treatment because pegylated interferon–ribavirin was not a treatment option. Twelve weeks of sofosbuvir–ribavirin resulted in SVR in 96% of patients, with an ICER of $63 700 per QALY gained. Extending therapy to 16 weeks resulted in SVR in 99% of patients and an ICER of $468 000 per QALY compared with 12 weeks of therapy (Table 3).

Cirrhotic Patients—Treatment with 24 weeks of pegylated interferon–ribavirin resulted in SVR in 62% of treatment-naive cirrhotic patients. Compared with no treatment, the incremental QALE gain was 6.2 QALYs and the incremental cost was $54 000, resulting in an ICER of $8700 per QALY gained. Treatment with sofosbuvir–ribavirin for 12 weeks resulted in 90% attaining SVR, with an ICER of $35 500 per QALY compared with 24 weeks of pegylated interferon–ribavirin (Table 3).

In treatment-experienced cirrhotic patients, 16 weeks of sofosbuvir–ribavirin resulted in longer QALE than 12 weeks of the same therapy at a lower cost per QALY gained. Consequently, the latter regimen was dominated by the former. Sixteen weeks of sofosbuvir–ribavirin resulted in SVR in 77% of patients, with an additional 6.7 QALYs, an incremental cost of $183 000, and an ICER of $27 300 per QALY gained compared with no treatment (Table 3).

Genotype 3

Noncirrhotic Patients—In treatment-naive noncirrhotic patients with genotype 3 infection, pegylated interferon–ribavirin resulted in SVR in 71%, a QALE gain of 1.9

QALYs compared with no treatment, and an incremental cost of $9300, resulting in an ICER of $4800 per QALY (Table 4). Only 61% achieved SVR with 12 weeks of sofosbuvir–ribavirin, resulting in lower QALE than for pegylated interferon–ribavirin at a higher cost, thus making it dominated. Treatment with 12 weeks of pegylated interferon–ribavirin–sofosbuvir resulted in SVR in 82% of patients, a QALE gain of 0.4 QALY compared with pegylated interferon–ribavirin, an incremental cost of $95 400, and an ICER of $263 000 per QALY. Treatment with 24 weeks of sofosbuvir–ribavirin resulted in SVR in 93% of patients and extended QALE by 0.3 QALY compared with 12 weeks of pegylated interferon–ribavirin–sofosbuvir at an incremental cost of $80 200, resulting in an ICER of $266 000 per QALY.

In treatment-experienced noncirrhotic patients, pegylated interferon–ribavirin–sofosbuvir resulted in a higher percentage attaining SVR, longer QALE, and lower incremental lifetime medical costs compared with both 12 and 16 weeks of sofosbuvir–ribavirin, making both strategies dominated. Compared with no treatment, pegylated interferon–ribavirin–sofosbuvir resulted in an additional 1.3 QALYs at an incremental cost of $105 000, resulting in an ICER of $82 000 per QALY. Extending therapy to 24 weeks of sofosbuvir–ribavirin resulted in 86% achieving SVR, a QALE gain of 0.1 QALY compared with pegylated interferon–ribavirin–sofosbuvir, an incremental cost of $81 500, and an ICER of $1 100 000 per QALY (Table 4).

Cirrhotic Patients—Among treatment-naive cirrhotic patients with genotype 3 infection, treatment with 24 weeks of pegylated interferon–ribavirin resulted in 30% achieving SVR, an incremental QALE gain of 2.9 QALYs, an incremental cost of $39 600, and an ICER of $13 600 per QALY compared with no treatment. Twelve weeks of sofosbuvir–ribavirin was dominated by pegylated interferon–ribavirin–sofosbuvir. Treatment with 12 weeks of pegylated interferon–ribavirin–sofosbuvir had an ICER of $22 600 per QALY compared with pegylated interferon–ribavirin. Twenty-four weeks of sofosbuvir–ribavirin resulted in SVR in 90% of patients, with an ICER of $107 000 per QALY compared with pegylated interferon–ribavirin–sofosbuvir (Table 4).

Among treatment-experienced patients, pegylated interferon–ribavirin–sofosbuvir resulted in a higher percentage attaining SVR, longer QALE, and lower lifetime medical costs than 12, 16, or 24 weeks of sofosbuvir–ribavirin, making these 3 strategies dominated. Compared with no treatment, pegylated interferon–ribavirin–sofosbuvir led to an additional 7.2 QALYs at an incremental cost of $162 000, corresponding to an ICER of $22 300 per QALY (Table 4).

Deterministic Sensitivity Analysis

The cost-effectiveness of sofosbuvir-based therapy was most sensitive to the cost of sofosbuvir. In treatment-naive noncirrhotic patients with genotype 2 infection, the ICER of 12 weeks of sofosbuvir–ribavirin compared with 24 weeks of pegylated interferon–ribavirin was less than $100 000 per QALY gained when the cost of 4 weeks of sofosbuvir was less than $16 000, and sofosbuvir became cost-saving when it cost less than $7000 for 4 weeks (Figure 1). In treatment-naive noncirrhotic patients with genotype 3 infection, the ICER for

12 weeks of pegylated interferon–ribavirin–sofosbuvir compared with 24 weeks of pegylated interferon–ribavirin was less than $100 000 per QALY when 4 weeks of sofosbuvir cost less than $12 000. The higher ICERs for genotype 3 infection compared with genotype 2 infection reflect the smaller incremental benefit of sofosbuvir-based regimens for genotype 3 infection. The ICER for 24 weeks of sofosbuvir–ribavirin compared with 12 weeks of pegylated interferon–ribavirin–sofosbuvir was less than $100 000 per QALY only when the cost of 4 weeks of sofosbuvir was less than $7000 (Figure 2). If pegylated interferon–ribavirin–sofosbuvir was not considered as a treatment option, the ICER of 24 weeks of sofosbuvir–ribavirin compared with 24 weeks of pegylated interferon–ribavirin was less than $100 000 per QALY when 4 weeks of sofosbuvir cost less than $11 000. Among treatment-naive noncirrhotic patients, we also investigated cost-effectiveness by disease stage and found that in those with METAVIR stage F3 disease, the ICERs of 12 weeks of sofosbuvir–ribavirin for genotype 2 treatment and 12 weeks of pegylated interferon–ribavirin–sofosbuvir for genotype 3 treatment were less than $100 000 per QALY gained compared with pegylated interferon–ribavirin (Table 5 of the Supplement). However, in patients with stage F0 to F2 disease, the ICER of sofosbuvir-based regimens was more than $100 000 per QALY gained compared with pegylated interferon–ribavirin. Similarly, when we decreased the median time from infection to development of cirrhosis (consequently increasing the fibrosis stage of patients who were not yet cirrhotic), the ICERs of sofosbuvir-based therapy for treatment-naive noncirrhotic patients were less than $100 000 per QALY gained compared with pegylated interferon–ribavirin (Table 6 of the Supplement).

Other than treatment costs, uncertainty in base-case parameter estimates had no effect on the conclusions from the base-case analysis. When we changed base-case model parameters to reflect higher HCV-related mortality, successful treatment was associated with greater QALE gains and lower ICERs for sofosbuvir-based therapy. However, none of the ICERs crossed the $100 000-per-QALY threshold (Table 7 of the Supplement). Likewise, when we assumed both younger and older mean age, cost-effectiveness conclusions did not change (Tables 8 and 9 of the Supplement), and when we assumed a lower utility with HCV infection or varied the utility during interferon-based therapy, none of the base-case conclusions changed (Tables 10 to 12 of the Supplement). Among noncirrhotic patients with genotype 2 infection, we found no utility loss value during interferon therapy that resulted in an ICER less than $100 000 per QALY for sofosbuvir–ribavirin compared with pegylated interferon–ribavirin. Similarly, costs of toxicity management, including use of colony-stimulating factors, did not affect cost-effectiveness conclusions (Tables 13 and 14 of the Supplement). In a scenario with high costs in all stages of chronic infection and no HCV-related costs after attainment of SVR, the ICERs of sofosbuvir-based therapy in treatment-naive noncirrhotic patients remained above $200 000 per QALY (Table 15 of the Supplement). A scenario considering the effect of removing rules for discontinuation of therapy based on rapid virologic response (thus exposing viremic patients to the full treatment course) yielded no overall changes (Table 16 of the Supplement).

Probabilistic Sensitivity Analysis

For all patient types, the base-case findings were robust to uncertainty in treatment efficacy parameters. Among treatment-naive noncirrhotic patients with genotype 2 or 3 infection, the probability that sofosbuvir-based therapy would be preferred to pegylated interferon–ribavirin was greater than 50% only when the societal willingness-to-pay threshold was greater than $250 000 per QALY (Figures 3 and 4 of the Supplement). In contrast, among treatment-experienced patients and those with cirrhosis, sofosbuvir-based therapy was cost-effective in more than 90% of simulations when the societal willingness-to-pay threshold was less than $100 000 per QALY.

Discussion

We used evidence-based simulation modeling to investigate the cost-effectiveness of treating patients with HCV genotype 2 or 3 infection with interferon-free therapy. We found that at its current cost, sofosbuvir-based HCV therapy improves outcomes and provides good economic value in patients with cirrhosis and genotype 2 or 3 infection and in those who were previously treated with interferon. However, in treatment-naive noncirrhotic patients, for whom pegylated interferon–ribavirin remains a treatment option, the ICER of sofosbuvir-based therapy for genotype 2 or 3 infection is well over $100 000 per QALY. These conclusions were robust to sensitivity analyses that incorporated uncertainty around treatment efficacy, mortality, QoL, and costs.

There are 2 reasons that sofosbuvir-based therapy is not a cost-effective option for treatment-naive noncirrhotic patients with genotype 2 or 3 infection. First, the relative benefits of interferon-free treatment are reduced because pegylated interferon–ribavirin remains an effective treatment option in treatment-naive patients (approximately 80% efficacy). In contrast, pegylated interferon–ribavirin is not an effective option for treatment-experienced patients, and the incremental benefits of sofosbuvir are larger than for no treatment, resulting in ICERs of less than $100 000 per QALY.

Second, HCV-infected patients are at low risk for death from HCV until they develop cirrhosis, and not all develop cirrhosis. As a result, the SVR benefits of interferon-free therapy do not translate directly into substantial increases in life expectancy or QALE in noncirrhotic patients. This finding was consistent even when we increased mortality in cirrhotic patients, assumed lower QoL with early-stage HCV infection, and assumed higher costs attributable to HCV infection.

Translating these results into clinical practice raises 2 key questions about affordability. First, from the societal perspective, what is a reasonable price for sofosbuvir (or any new HCV medication)? In our analyses, the price of sofosbuvir was the primary driver of cost-effectiveness. At a current U.S. cost of $28 000 for 4 weeks of therapy, no reasonable estimates of HCV mortality or QoL effects led to sofosbuvir having an ICER less than $100 000 per QALY gained in treatment-naive noncirrhotic patients.

Second, should providers avoid administering interferon, regardless of the cost? Recent HCV guidelines identified pegylated interferon–ribavirin as a regimen "to avoid" for

treating HCV (24). Patients with insurance have little motivation to initiate older therapies associated with longer treatment and substantial toxicity. From a societal perspective, however, is it acceptable to limit the total number of people treated for HCV to avoid using interferon at all costs? If not, the best approach would be for payers to negotiate price discounts for sofosbuvir consistent with its value because such negotiations could play a major role in improving access to HCV therapy.

If such negotiations are unsuccessful, however, our analysis supports an approach where providers offer pegylated interferon–ribavirin to treatment-naive noncirrhotic patients and reserve sofosbuvir for cirrhotic patients and those who cannot tolerate or have previously not benefitted from interferon-based therapy. Such a strategy would prioritize the sickest patients for costly new therapies while offering a less costly alternative to patients with early disease. However, this may raise provider concerns because before sofosbuvir was approved, many providers deferred treatment for patients with early-stage HCV in anticipation of interferon-free regimens (46). Now that such therapy is available, can providers feasibly defer therapy until these patients have more advanced disease?

Our approach has several limitations. First, our analysis did not consider costs and benefits of preventing HCV transmission. Epidemiologic modeling suggests that aggressive screening and treatment for HCV could decrease its incidence in injection drug users (47). Treating HCV genotype 2 and 3 infection may be particularly important for prevention given that up to 45% of injection drug–using youths in some cohorts are infected (48). Including the benefits of prevention in a cost-effectiveness analysis of HCV therapy would be premature, however, because the concept is unproven.

Second, our efficacy inputs were based on results from clinical trials. To the extent that real-world effectiveness of sofosbuvir-based regimens is lower than the efficacy observed in clinical trials, the ICERs of sofosbuvir-based therapy may be higher than those reported.

Third, we included 12 weeks of pegylated interferon–ribavirin–sofosbuvir as a treatment option for patients with genotype 3 infection and found that it was cost-effective for certain subgroups (29). However, 24 weeks of sofosbuvir–ribavirin is the only sofosbuvir-based regimen that is approved by the U.S. Food and Drug Administration for genotype 3 infection (1). Assuming that pegylated interferon–ribavirin–sofosbuvir is not a feasible treatment strategy, we calculated ICERs comparing 24 weeks of sofosbuvir–ribavirin with 12 weeks of pegylated interferon–ribavirin and found that sofosbuvir was more economically attractive but still had a cost-effectiveness ratio greater than $100 000 in treatment-naive noncirrhotic patients (Table 17 of the Supplement).

Fourth, we did not consider sofosbuvir–ledipasvir–ribavirin for treatment of patients with genotype 3 infection. Findings from the ELECTRON-2 study suggest that this regimen may be effective for such patients (49). However, the generalizability of those results is not certain, and the most recent treatment guidelines, which are based on ELECTRON-2 data, do not recommend this regimen for genotype 3 infection (24).

Finally, we performed an analysis of sofosbuvir for HCV genotypes 2 and 3, but most HCV infection in the United States is genotype 1 (50). Because approval of regimens treating

genotypes 2 and 3 is not imminent, we expect therapeutic options to be more static in the near future compared with those for genotype 1. The cost-effectiveness and budgetary impact of recently approved agents for genotype 1 are important questions that will be best answered when those regimens are approved and it becomes clearer how they will be used in practice. The conclusions of this analysis of treatment of genotype 2 or 3 infection should not be used to infer the likely cost-effectiveness of new regimens for HCV genotype 1.

In summary, this analysis shows that at its current U.S. cost of $28 000 for 4 weeks of therapy, sofosbuvir-based treatment for HCV genotype 2 or 3 infection extends QALE and provides good value for money in cirrhotic patients and in treatment-experienced patients. Among treatment-naive noncirrhotic patients, however, the ICER of sofosbuvir-based treatments exceeds the commonly cited U.S. willingness-to-pay threshold of $100 000 per QALY gained. One option for using sofosbuvir is to treat only cirrhotic patients and those who have previously not benefitted from interferon. However, this approach would mean requiring persons with early-stage HCV infection, who have been waiting for the availability of interferon-free regimens before initiating treatment, to continue waiting until they develop more advanced liver disease or, alternatively, treating patients with early-stage infection with interferon followed by a sofosbuvir-based regimen if interferon is not effective. Options that would expand access to curative therapy include negotiating a reduced cost of sofosbuvir or waiting for approval of new medications with the expectation that market forces could decrease costs. At its current cost, access to sofosbuvir will likely be unequal and restricted and will limit the number of people ultimately cured of HCV infection in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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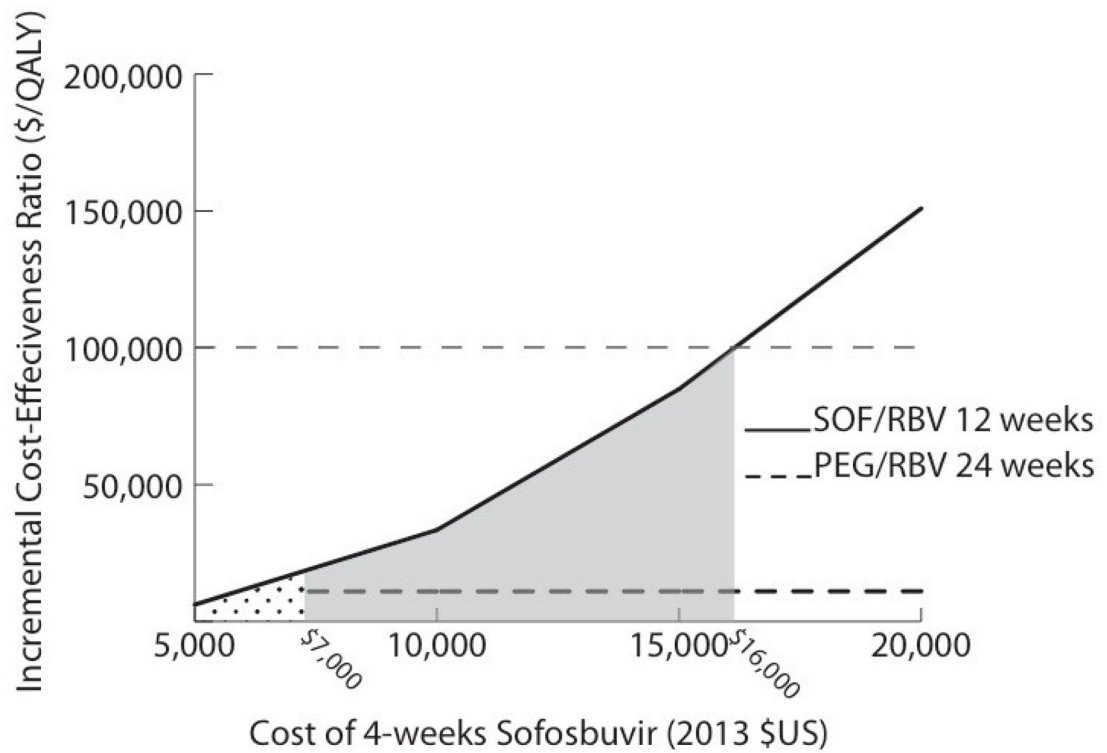
Figure 1. Results of 1-way sensitivity analyses of the effect of the cost of SOF on the ICER of SOF-based therapy for treatment of HCV genotype 2 infection in treatment-naive non-cirrhotic patients

The dotted area illustrates the range of costs at which SOF–RBV is cost-saving compared with PEG–RBV. The gray shaded area depicts the range of costs at which the ICER of SOF–RBV is <$100 000 per QALY gained compared with PEG–RBV. HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir.
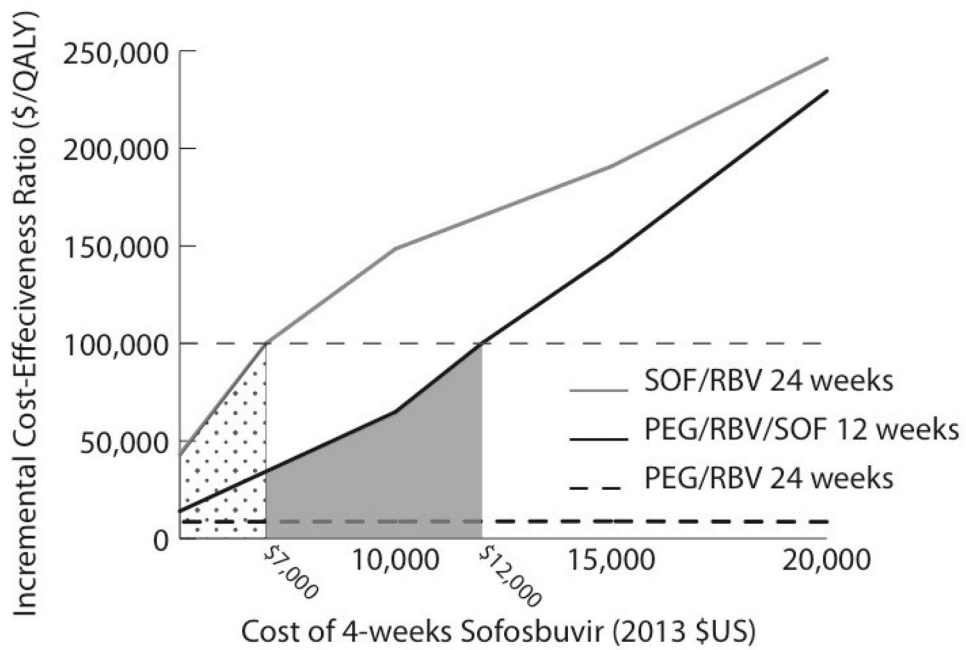
Figure 2. Results of 1-way sensitivity analyses of the effect of the cost of SOF on the ICER of SOF-based therapy for treatment of HCV genotype 3 infection in treatment-naive non-cirrhotic patients

The dotted area illustrates the range of costs at which the ICER of SOF–RBV is <$100 000 per QALY gained compared with PEG–RBV–SOF. The gray shaded area depicts the range of costs at which the ICER of PEG–RBV–SOF is <$100 000 per QALY compared with PEG–RBV. HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir.

Table 1

Treatment Strategies Considered in Cost-Effectiveness Analysis of Therapies for HCV Genotype 2 or 3 Infection

Treatment History	Strategies
Genotype 2	
Naive	No treatment
	24 wk of PEG–RBV
	12 wk of SOF–RBV[*]
Experienced	No treatment
	12 wk of SOF–RBV[*]
	16 wk of SOF–RBV
Genotype 3	
Naive	No treatment
	24 wk of PEG–RBV
	12 wk of SOF–RBV
	24 wk of SOF–RBV[*]
	12 wk of PEG–RBV–SOF
Experienced	No treatment
	12 wk of SOF–RBV
	16 wk of SOF–RBV
	24 wk of SOF–RBV[*]
	12 wk of PEG–RBV–SOF

HCV = hepatitis C virus; PEG = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir.

[*] Recommended by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.

Table 2

Model Inputs for Analysis of Cost-Effectiveness of SOF-Based Therapy for Treatment of HCV Genotype 2 or 3 Infection

Variable	Base-Case Value	Range Evaluated in Sensitivity Analyses[*]	Reference
Cohort characteristics			
Mean age of treatment-naive patients (SD), *y*	48 (7)	38 (7)–58 (7)	2
Mean age of treatment-experienced patients (SD), *y*	54 (7)	44 (7)–64 (7)	3
Proportion of treatment-naive men	0.66	0–1	2
Proportion of treatment-experienced men	0.71	0–1	3
Mean age at HCV infection, *y*	26	16–36	34
HCV disease progression			
Median time to cirrhosis from age of infection (10th, 90th percentiles) *y*	25 (23–27)	10–40	32, 33
Median time to first liver-related event after development of cirrhosis (10th, 90th percentiles), *y*	11 (9–14)	6–19	31
Liver-related mortality with compensated cirrhosis, *deaths per 100 person-years*	1.39	0.96–1.82	31
Liver-related mortality with decompensated cirrhosis, *deaths per 100 person-years*	12.00	8.28–15.72	31
Reduction in liver-related mortality after SVR, *%*[†]	94	81–98	4
HCV therapy efficacy (SVR probabilities) in treatment-naive patients[‡]			
24 wk of PEG–RBV			2
Genotype 2 without cirrhosis	0.82	0.82 (0.06)	
Genotype 2 with cirrhosis	0.62	0.62 (0.13)	
Genotype 3 without cirrhosis	0.71	0.71 (0.04)	
Genotype 3 with cirrhosis	0.29	0.29 (0.08)	
12 wk of SOF–RBV			2
Genotype 2 without cirrhosis	0.98	0.98 (0.02)	
Genotype 2 with cirrhosis	0.90	0.90 (0.09)	
Genotype 3 without cirrhosis	0.61	0.61 (0.04)	
Genotype 3 with cirrhosis	0.34	0.34 (0.08)	
24 wk of SOF–RBV			30

Variable	Base-Case Value	Range Evaluated in Sensitivity Analyses[*]	Reference
Genotype 3 without cirrhosis	0.93	0.93 (0.03)	
Genotype 3 with cirrhosis	0.90	0.90 (0.08)	
12 wk of PEG–RBV–SOF			29
Genotype 3 without cirrhosis	0.82	0.82 (0.12)	
Genotype 3 with cirrhosis	0.82	0.82 (0.12)	
HCV therapy efficacy (SVR probabilities) in treatment-experienced patients[‡]			
12 wk of SOF–RBV			3
Genotype 2 without cirrhosis	0.96	0.96 (0.04)	
Genotype 2 with cirrhosis	0.58	0.58 (0.15)	
Genotype 3 without cirrhosis	0.37	0.37 (0.08)	
Genotype 3 with cirrhosis	0.19	0.19 (0.01)	
16 wk of SOF–RBV			3
Genotype 2 without cirrhosis	0.99	0.99 (0.002)	
Genotype 2 with cirrhosis	0.77	0.77 (0.13)	
Genotype 3 without cirrhosis	0.59	0.59 (0.08)	
Genotype 3 with cirrhosis	0.57	0.57 (0.02)	
24 wk of SOF–RBV			30
Genotype 3 without cirrhosis	0.86	0.86 (0.04)	
Genotype 3 with cirrhosis	0.59	0.59 (0.02)	
12 wk of PEG–RBV–SOF			29
Genotype 3 without cirrhosis	0.83	0.83 (0.11)	
Genotype 3 with cirrhosis	0.82	0.82 (0.01)	
Costs[§]			
Non–HCV-related medical costs, *$ per mo*			
Background medical costs (without HCV infection)[//]	135–1035	70–1550	28
HCV-related medical costs, *$ per mo*			
No cirrhosis (SD)	240 (60)	180 (45)–300 (75)	27
Mild to moderate cirrhosis (SD)	430 (120)	310 (87)–540 (146)	27
Decompensated cirrhosis (SD)	820 (210)	610 (156)–1030 (258)	27

Variable	Base-Case Value	Range Evaluated in Sensitivity Analyses[*]	Reference
Cost multiplier after achievement of SVR	0.50	0.00–0.70	27
HCV therapy costs, *$ per 4 wk*			
Provider visits[¶]	120	60–180	25, 26
PEG[**]	2500	1300–3800	6
RBV[††]			
1200 mg/d	2500	1300–3800	6
800 mg/d	1700	900–2600	6
SOF	28 000	5000–30 000	6
Filgrastim[‡‡]	2000	1000–3000	6
Total HCV therapy costs, *$*			6, 25, 26
24 wk of PEG–RBV	25 300	12 800–37 800	
12 wk of SOF–RBV	91 500	22 000–97 500	
16 wk of SOF–RBV	121 900	30 000–129 900	
24 wk of SOF–RBV	182 900	44 900–194 900	
12 wk of PEG–RBV–SOF	99 000	30 000–105 000	
1-time costs, *$*			
Managing treatment-ending toxicity during interferon-containing therapy	750	380–1100	2, 6, 23–26
Managing treatment-ending toxicity during interferon-free therapy	600	300–900	2, 6, 23–26
Quality of life			
After achievement of SVR[§§]	0.74–0.90	0.60–1.00	20–22
With HCV infection			
No to moderate fibrosis	0.89	0.75–1.00	16, 18, 19
Cirrhosis	0.62	0.55–0.75	16, 18, 19
Decompensated cirrhosis	0.48	0.40–0.60	16, 18, 19
Receiving interferon-containing therapy[////]	0.88	0.50–0.96	15, 17, 20
Receiving interferon-free therapy[////]	0.99	0.95–1.00	15
Major toxicity decrement[¶¶]	0.16	0.09–0.25	14

HCV = hepatitis C virus; PEG = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response.

Table 3

Cost-Effectiveness of Treatment of Patients With HCV Infection: Genotype 2[*]

Treatment Strategy	SVR, %	Cost, $	Incremental Cost, $	QALYs	Incremental QALYs	ICER, $/QALY
No cirrhosis						
Naive						
No treatment	–	169 000	–	13.9	–	–
24 wk of PEG–RBV	82	173 000	4300	15.5	1.5	3000
12 wk of SOF–RBV	98	261 000	87 900	15.8	0.4	238 000
Experienced						
No treatment	–	163 000	–	12.3	–	–
12 wk of SOF–RBV	96	258 000	95 700	13.8	1.5	63 700
16 wk of SOF–RBV	99	288 000	29 500	13.9	0.1	468 000
Cirrhosis						
Naive						
No treatment	–	94 000	–	5.1	–	–
24 wk of PEG–RBV	62	150 000	54 000	11.3	6.2	8700
12 wk of SOF–RBV	90	253 000	103 000	14.2	2.9	35 500
Experienced						
No treatment	–	85 000	–	4.1	–	–
12 wk of SOF–RBV	58	230 000	145 000	9.3	5.2	Dominated[†]
16 wk of SOF–RBV	77	268 000	183 000	10.8	6.7	27 300

HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response.

[*] All costs are in 2013 U.S. dollars.

[†] More costly and less effective than a competing strategy or had an ICER greater than that of a more effective strategy.

Table 4

Cost-Effectiveness of Treatment of Patients With HCV Infection: Genotype 3[*]

Treatment Strategy	SVR, %	Cost, $	Incremental Cost, $	QALYs	Incremental QALYs	ICER, $/QALY
No cirrhosis						
Naive						
No treatment	–	165 000	–	13.0	–	–
24 wk of PEG–RBV	71	175 000	9300	15.0	1.9	4800
12 wk of SOF–RBV	61	269 000	94 000	14.8	–0.2	Dominated[†]
12 wk of PEG–RBV–SOF	82	270 000	95 400	15.4	0.4	263 000
24 wk of SOF–RBV	93	350 000	80 200	15.7	0.3	266 000
Experienced						
No treatment	–	163 000	–	12.3	–	–
12 wk of PEG–RBV–SOF	83	267 000	105 000	13.6	1.3	82 000
12 wk of SOF–RBV	36	273 000	5700	12.9	–0.7	Dominated[†]
16 wk of SOF–RBV	59	294 000	26 900	13.2	–0.3	Dominated[†]
24 wk of SOF–RBV	86	349 000	81 500	13.7	0.1	1 100 000
Cirrhosis						
Naive						
No treatment	–	95 000	–	5.1	–	–
24 wk of PEG–RBV	30	135 000	39 600	8.0	2.9	13 600
12 wk of SOF–RBV	34	228 000	92 500	8.5	0.5	Dominated[†]
12 wk of PEG–RBV–SOF	81	256 000	120 700	13.3	5.3	22 600
24 wk of SOF–RBV	90	341 000	85 600	14.1	0.8	107 000

Treatment Strategy	SVR, %	Cost, $	Incremental Cost, $	QALYs	Incremental QALYs	ICER, $/QALY
Experienced						
No treatment	–	85 000	–	4.1	–	–
12 wk of SOF–RBV	19	211 000	126 000	5.8	1.7	Dominated[†]
12 wk of PEG–RBV–SOF	80	247 000	162 000	11.4	7.2	22 300
16 wk of SOF–RBV	57	256 000	8700	9.1	–2.2	Dominated[†]
24 wk of SOF–RBV	59	314 000	67 100	9.2	–2.2	Dominated[†]

HCV = hepatitis C virus; ICER = incremental cost-effectiveness ratio; PEG = pegylated interferon; QALY = quality-adjusted life-year; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response.

* All costs are in 2013 U.S. dollars.

[†] More costly and less effective than a competing strategy or had an ICER greater than that of a more effective strategy.