A Decision-Analytic Markov Model to Evaluate the Health Outcomes of Sofosbuvir for Previously Untreated Patients With Chronic Hepatitis C Virus Genotype 1 Infection

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Background

- Hepatitis C virus (HCV) is a serious disease that can lead to liver scarring (e.g., compensated cirrhosis). If left untreated, HCV can progress to liver failure, including decompensated cirrhosis and/or hepatocellular carcinoma. The only cure for advanced liver disease is a liver transplant.
- Approximately 3.2 million people in the United States (US) are currently living with HCV, and 17,000 new HCV cases are estimated each year.[1] HCV is the leading indication of liver transplantation in the US.[1]
- Treatment of HCV aims for sustained virologic response (SVR), or viral cure. SVR is achieved when HCV RNA is undetectable 12 or 24 weeks after the conclusion of treatment, depending on the treatment regimen.
- Sofosbuvir (SOF) is a nucleotide polymerase inhibitor that has shown excellent clinical efficacy in previously untreated patients with HCV genotype 1 when used in combination with pegylated interferon alfa and ribavirin (PR) for 12 weeks.[2]
- Other HCV treatments are available, including telaprevir (TVR)+PR for 24-48 weeks, boceprevir (BOC)+PR for 28-48 weeks, and PR for 48 weeks.

Objective

- To evaluate the potential long-term health outcomes associated with SOF+PR compared with other available treatment options.

Methods

Decision-Analytical Model and Assumptions

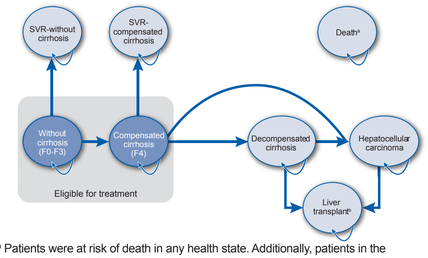
- A decision-analytic model was developed to project long-term health outcomes for previously untreated mono-infected chronic HCV genotype 1 patients.
- The model consists of an initial decision tree, in which patients are eligible to receive treatment, and a state-transition model to project patients' outcomes.
  - The initial decision tree has four antiviral treatment options:
    - SOF+PR for 12 weeks
    - TVR+PR for 24-48 weeks
    - BOC+PR for 28-48 weeks
    - PR for 48 weeks
  - The state-transition model has six health states with annual transitions (Figure 1):
    - Without cirrhosis
    - Compensated cirrhosis
    - Decompensated cirrhosis
    - Hepatocellular carcinoma
    - Liver transplant
    - Death

Methods (cont'd)

Input Parameters

- The treatment-naïve, mono-infected HCV genotype 1 patient cohort had an average age of 52 years and an average weight of 79 kg; 17% had cirrhosis before treatment.
- SVR, discontinuation, and adverse event rates were taken from clinical trials for each treatment comparator.[2-6] SVR rates by treatment regimen and cirrhosis status are shown in Figure 2.
- Health-state transition probabilities (i.e., progression to compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, and death) were obtained from published literature and publicly available sources (Table 1).
- Utility scores for each health state were taken from clinical trial results and published literature (Table 2). On-treatment utility scores accounted for a quality-of-life decrement attributable to adverse events related to each treatment regimen. SVR health-state utility scores accounted for a utility increment related to achieving SVR.[2,7,8]

Figure 1. Overview of State-Transition Model Structure



[a] Patients were at risk of death in any health state. Additionally, patients in the decompensated cirrhosis, hepatocellular carcinoma, and liver transplant health states were additionally at risk for disease-specific mortality.

[b] Following the year of liver transplantation, patients were assumed to remain in a post-transplant health state until their deaths.

Figure 2. Treatment Efficacy (SVR Rates by Treatment Regimen and Cirrhosis Status)

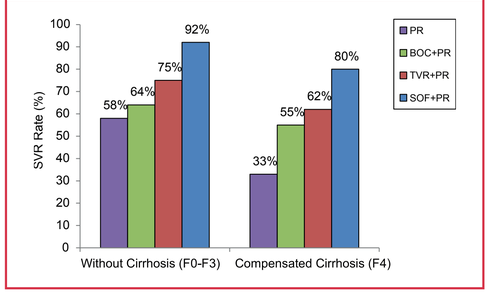


Table 1. Transition Probabilities for Patients Without SVR[9]

From	To	Annual Transition Probabilities
Without cirrhosis	Compensated cirrhosis[10]	
	30-39 years	0.058
	40-49 years	0.046
	50+ years	0.046
Compensated cirrhosis	Decompensated cirrhosis[11]	0.030
	Hepatocellular carcinoma[12]	0.015
Decompensated cirrhosis	Hepatocellular carcinoma[12]	0.015
	Liver transplant[12]	0.017
	Death[7]	0.260
Hepatocellular carcinoma	Death[7]	0.485
Liver transplant	Death, year 1[12]	0.107
Post–liver transplant	Death, year 2[12]	0.049

[9] Patients were at risk of death in any health state, stratified by age (Murphy et al., 2013).
[10] Thein et al., 2008; [11] Davis et al., 2010; [12] Razavi et al., 2012; [7] Liu et al., 2012.

Table 2. Utility Values

Health State	Utility Value
Without cirrhosis[13,14]	0.79
Compensated cirrhosis[15]	0.75
Decompensated cirrhosis[15]	0.67
Hepatocellular carcinom[16]	0.61
Liver transplant[16]	0.65
Post–liver transplant[15]	0.71
Increments/Decrements for Treatment and SVR	**Value**
Decrement for treatment with SOF+PR[17]	–14.50%
Decrement for treatment with TLV+PR[7]	–16.50%
Decrement for treatment with BOC+PR[7]	–16.50%
Decrement for treatment with PR[17]	–12.43%
Increment for achieving SVR[8]	+0.05

[13] Thein et al., 2005; [14] Chong et al., 2003; [15] McLernon et al., 2008; [16] Hsu et al., 2012; [17] Date on file; [7] Liu et al., 2012; [8] Wright et al., 2006.

Results

- The SOF+PR regimen was associated with the fewest liver-related complications and the fewest HCV-related deaths (Figure 3).
- Patients receiving SOF+PR had the longest life-expectancy and experienced the most quality-adjusted life-years (QALYs) (Table 3).
- Number needed to treat (NNT) outcomes were favorable for SOF+PR. NNT represents the number of patients who would need to be treated with SOF+PR rather than a comparator to achieve one positive outcome or avoid one negative outcome (Table 3).

Figure 3. Discounted Health Outcomes for Cohorts of 10,000 Treated Patients

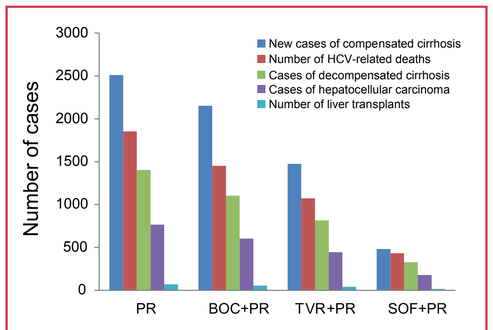


Table 3. Health Outcomes

Discounted Health Outcomes[a]	PR	BOC+PR	TVR+PR	SOF+PR
Life-years	17.2	17.5	17.8	18.2
QALYs	14.6	14.9	15.2	15.7
NNT[b] (SOF+PR vs. Comparator)	**PR**	**BOC+PR**	**TVR+PR**	**SOF+PR**
NNT to achieve an additional SVR	3	4	6	--
NNT to avoid a case of compensated cirrhosis	5	6	11	--
NNT to avoid a case of decompensated cirrhosis	10	13	21	--
NNT to avoid a case of hepatocellular carcinoma	17	24	38	--

a Health outcomes are presented on a per-patient basis and discounted at an annual rate of 3.0%.
b NNT represents the number of patients who would need to be treated with SOF+PR rather than a comparator to achieve one positive outcome or avoid a negative outcome.

Limitations

- This analysis involved the typical limitations of pharmacoeconomic analyses. To estimate the long-term impact of clinical trial outcomes, the model predicted the course of liver disease for each individual over his or her remaining lifetime based on the best natural disease progression data available.
- The model used clinical inputs from the clinical trials for SOF+PR and its comparators, which represent efficacy in a controlled environment rather than a real-world setting.
- SVR rates for each comparator were obtained from individual clinical trial arms, as no meta-analysis including SOF+PR and its comparators is currently available.

Discussion & Conclusions

- **The SOF-based regimen was projected to yield better health outcomes than the other available treatment options.**
  - **Number of cases of advanced liver disease were 77-81% lower for SOF+PR vs. PR, 70-78% lower for SOF+PR vs. BOC+PR, and 60-67% lower for SOF+PR vs. TVR+PR**
- **Large discrepancies in efficacy, side effect, and adherence rates have been reported for currently available regimens in real-world versus clinical trial settings. Additional analyses are necessary to determine the potential impact of the greater expected real-world differences between the SOF-based regimen and other therapies.**

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