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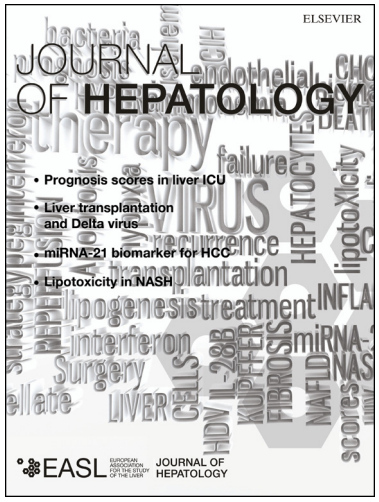

Impact of Interferon Free Regimens on Clinical and Cost Outcomes for Chronic Hepatitis C Genotype 1 Patients

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Abbreviations

HCV-hepatitis C

IFN-pegylated-interferon alpha

RBV-ribavirin

DAA-direct-acting antiviral agent

SVR-sustained virologic response

IFN, BV, DAA-Triple therapy

ICER-incremental cost-effectiveness analysis

QALYs- quality-adjusted life years- a standard metric that incorporates both length and quality of life

CHC-chronic hepatitis C

HIV-immunodeficiency virus

TVR- telaprevir

BOC-boceprevir

GT-genotype

F2-F4-moderate or advanced fibrosis

F0-F1-mild fibrosis

WAC-wholesale acquisition cost

NADAC National Average Drug Acquisition Cost (NADAC

CMS-Centers for Medicare and Medicaid Services

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Abstract

Hepatitis C (HCV) is a common cause of chronic liver disease worldwide. Current standard treatment for genotype-1 patients uses a triple combination of pegylated-interferon alpha (IFN), ribavirin (RBV) and a direct-acting antiviral agent (DAA) with 75-80% sustained virologic response (SVR) rates. **Aim**: Determine cost-effectiveness of staging-guided versus treat all HCV genotype-1 patients with interferon-based versus interferon-free regimens. **Methods**: A decision analytic Markov model simulating patients until death compared four strategies for treating HCV genotype-1: Triple therapy (IFN, RBV, DAA) with staging-guidance or treat all and oral IFN-free regimen with staging-guidance or treat all. Strategies with staging initiated treatment at fibrosis stages F2-F4, with staging repeated every 5 years until age 70. The reference case was a treatment-naïve 50-year-old. Analysis was repeated for 50% increase in cost of oral therapy. Effectiveness was measured in quality-adjusted life years (QALYs). **Results**: Treat all patients with oral IFN-free regimen was the most cost-effective strategy, with an ICER of $15,709/QALY at baseline cost of oral therapy. The ICER remained below $50,000/QALY in sensitivity analyses for baseline and +50% cost of oral therapy scenarios. The treat all strategy was also the most effective strategy; associated with the lowest risk of developing advanced liver disease. **Conclusions**: Treating all HCV patients with oral IFN-free regimen reduced the number of patients developing advanced liver disease and increased life expectancy. Additionally, IFN-free regimen without staging may be the most cost-effective approach for treating HCV genotype-1 patients. The efficacy and safety of these regimens must be confirmed using randomized clinical trials.

Introduction

There are approximately 130 – 200 million people infected with the hepatitis C virus (HCV) worldwide [1, 2]. In comparison to human immunodeficiency virus (HIV), HCV is a more prevalent and yet a less diagnosed viral infection [3]. One of the important reasons for this discrepancy is the gap in knowledge amongst health care workers, social service providers, and other stakeholders about the extent, seriousness and total disease burden associated with HCV [4].

Progression of HCV-related liver disease is variable and associated with factors including duration of infection, age, male gender, obesity and type 2 diabetes, consumption of alcohol, and HIV co-infection [5, 6]. If left untreated, the median expected time to cirrhosis is 30 years. It is estimated that approximately a third of those infected are expected to develop cirrhosis within 20 years [1-6]. Assuming there are no changes in the standard of care for CH-C, the total number of patients who will develop advanced liver disease in 20 years is projected to increase 4-fold [7]; while the proportion of patients progressing to cirrhosis may increase from 25% as of 2010 to 37% by 2020 [8]. Finally, a recently validated forecasting model for HCV related morbidity and mortality in the U.S. has estimated that over the next 50 years, out of the population of the untreated CH-C without cirrhosis, 1.76 million people will develop cirrhosis, 418,000 will develop liver cancer, and 1,071,000 will die from cirrhosis related complications [9]. Similarly, another study estimated that from the year 2010 through 2019, 165,900 deaths from chronic liver disease, 27,200 deaths from hepatocellular carcinoma, and $10.7 billion in direct medical expenditures for HCV will occur. During this same period, HCV may lead to 720,700 years of decompensated cirrhosis and hepatocellular carcinoma and to the loss of 1.83 million years of life in those younger than 65 at a societal cost of $21.3 and $54.2 billion, respectively [10].

Although the burden of CH-C is astounding, effective treatment (sustained virologic response) does lead to cure and is shown to improve outcomes, specifically by decreasing morbidities and mortality in patients with advanced liver disease. In fact, sustained virologic response (SVR) has now been shown to be

durable and reduce all- cause mortality and cirrhosis-related complications among patients infected with HCV [11,12, 13].

Historically, treatment of CH-C genotype 1 with pegylated interferon and ribavirin was associated with an SVR rate of approximately 45% in previously untreated patients. In 2011, the FDA approved two inhibitors of the non-structural protein 3/4A protease– telaprevir (TVR) and boceprevir (BOC). These drugs are used in combination with pegylated-interferon (IFN) and ribavirin (RBV) with a SVR rate of 75% in treatment-naïve HCV genotype (GT)-1 patients [14,15]. Despite these gains, challenges of these regimens related to side effects limit their widespread use [14,15]. Additionally, a complex dosing schedule (DAA taken three times daily and RBV taken two times daily) with a heavy daily pill burden (17-18 pills on BOC regimen, 11-12 pills on TVR regimen) make patient adherence difficult. Finally, drugs with the potential to interact with TVR and BOC are frequently prescribed for patients with HCV [14,15]. In fact, a recent report from a large community trial suggested significant side effects associated with these regimens in patients with HCV related cirrhosis [16]. On the other hand, patients with HCV and advanced fibrosis are precisely those patients who are at the most urgent need for treatment. In order to establish stage of hepatic fibrosis prior to treatment of chronic hepatitis C patients with genotype 1, historically, clinicians have required staging of liver disease through a liver biopsy. This treatment decision guided by the stage of liver disease for HCV genotype 1 has been recommended to target only those who could potentially benefit the most as well as to minimize the side effects. One of the reasons for this recommendation was related to the relatively low efficacy of anti-HCV treatment and/or the substantial side effects associated with interferon-based therapy. In fact, given the high efficacy and relatively short duration of treatment for HCV genotypes 2 and 3, biopsy-guided treatment for CH-C patients with G2 and G3 has not been used. In the era of highly effective antiviral regimens for HCV genotype 1 with higher efficacy and better side effect profile, the value of biopsy-guided treatment becomes questionable. In contrast, the issue of staging for all HCV patients, regardless of the treatment decision, remains important for other management needs such as screening for hepatocellular carcinoma (HCC) and varices.

In the recent years, a number of interferon-free regimens have been developed and the end for IFN containing regimens for patients with CH-C is rapidly approaching. In fact, several combinations of all-oral regimens for treatment-naïve patients with HCV GT 1 have been shown to have high response rates with very low discontinuations due to adverse events [17-21]. As the efficacy, safety, and tolerability data for these regimens emerge, research comparing the differences between IFN-containing and IFN-free regimens becomes increasingly important. Through Markov modeling simulation, this analysis' aim was to determine the cost-effectiveness of IFN-containing versus IFN-free regimens for patients infected with HCV genotype 1. We assessed the impact of treatment decision based on stage of liver disease (staging-guided) versus treat all on the cost-effectiveness of these regimens.

Methods

To simulate HCV-G1 patients, a decision analytic Markov model was created using TreeAge Pro software. The model followed patients from the time of initial treatment decision until death. Four treatment strategies were considered, consisting of two different treatment regimens and two options for selecting when to treat based on the stage of liver disease. One strategy used the current standard triple therapy, consisting of IFN, RBV and a protease inhibitor (TVR or BOC). In this strategy, treatment was guided based on a Metavir score. Patients with moderate or advanced fibrosis (F2-F4) were started on treatment, while patients with mild fibrosis (F0-F1) were followed up with subsequent assessment every 5 years until age 70 and were treated when their fibrosis had progressed. A second strategy was to use all-oral IFN-free regimen for 12 weeks, with the treatment decision based on the stage of liver disease similar to the steps described for triple therapy. Two additional strategies were considered whereby each treatment regimen (Triple or Oral IFN-Free regimens) was given to all patients regardless of the stage of liver disease.

The reference case was a 50 year-old G1-HCV patient who had not been previously treated and had no contraindications for an IFN-based therapy. Strategies were compared on the basis of cost, effectiveness and the incremental cost-effectiveness ratio. We employed multiple measures of effectiveness. For the purpose of the incremental cost-effectiveness analysis, we used quality-adjusted life years (QALYs), a

standard metric that incorporates both length and quality of life. However, in order to make maximum use of the information generated from this model, strategies were also compared on the basis of the progression of disease and clinical outcomes. Specifically, strategies were compared on the basis of what proportion progressed to compensated cirrhosis, decompensated cirrhosis, HCC and transplant. Developing compensated cirrhosis was only counted if the patient did not have cirrhosis at baseline, and reached compensated cirrhosis without having achieved SVR. Cost and QALYs were discounted at the standard 3% per year. Undiscounted life expectancy was also calculated.

Treatment Protocols

Triple therapy was a combination of IFN, RBV and a DAA. In the main analysis, TVR was the DAA considered (Table 1) [22]. Treatment was response-guided and began with 12 weeks of therapy with all 3 agents, followed by an additional 12 or 36 weeks of double-therapy (IFN+RBV), depending on response. Usual stopping rules at weeks 4 and 12 were applied. In sensitivity analysis, all the data related to BOC was considered instead of TVR [21, 23].

Oral therapy consisted of a combination of oral agents, all IFN-free, for 12 weeks. Model parameter values were based on pooled results of 12 week regimens from data presented to international meetings [17-20].

For both treatment regimens (IFN containing and IFN-Free), we considered two different strategies based on the stage of liver disease. One strategy was to treat all patients without staging. The other strategy was to first establish the stage, and then treat only those patients with fibrosis stages F2-F4. Patients with mild fibrosis (F0-F1) were followed every 5 years until age 70, and were treated if they had progressed to stages F2-F4.

Natural History

Parameters capturing the natural history of CH-C are found in Table 2. Baseline fibrosis stage at presentation was based on the distribution from a study in an urban clinical setting. Stage-specific

progression rates for all fibrosis stages were taken from the data for clinical settings in the meta-analysis by Thein et al [24]. Progression to decompensated cirrhosis, HCC, liver transplantation and death were taken from various sources in the literature, with rates from advanced fibrosis with SVR based on relative risks [9-10, 25-34]. We created a Markov model with these parameters and calibrated to determine the annual progression from F3 to HCC [35,36].

Costs

Costs are listed in Table 1 of the Supplementary Document. Costs of laboratory tests and office visits were taken from the 2012 Medicare fee schedule. Protocol-based testing was based on a protocol in the outpatient clinic setting. This protocol included an annual level 3 office visit with complete blood count, liver profile test and an HCV RNA by polymerase chain reaction test [37]. Additionally, routine follow-up of patients with compensated HCV-cirrhosis consisted of: semi-annual office visit with liver ultrasound and alpha-fetoprotein; annual complete blood count, liver profile and HCV-RNA testing as well as esophagogastroduodenoscopy (EGD) performed every 3 years.

While liver biopsy has often been used for staging of liver disease, the introduction of Fibroscan promises a reliable, non-invaisive and potentially less expensive method. For this study, we chose to use the cost of Fibroscan for the baseline cost of staging, and the cost of liver biopsy was included in the sensitivity analysis. Reimbursement for Fibroscan has not been fully established in the United States at the time of this study. We chose to conservatively estimate the cost of Fibroscan as the cost of liver ultrasound, which most likely is a slight underestimate, creating a small bias in favor of staging.

Annual cost of decompensated cirrhosis, hepatocellular carcinoma, first year following transplant and subsequent years following transplant were taken from the study by McAdam-Marx [35]. These costs were originally stated in 2009 US dollars and were inflated to 2012 US dollars based on the medical care component of the consumer price index [38,39].

For drug costs, we tried to represent the actual price paid by pharmacies. Two sources of drug cost data were consulted. The 2012 wholesale acquisition cost (WAC) was one source [38]. The other was the 2012 National Average Drug Acquisition Cost (NADAC), a survey of retail pharmacies conducted by the Centers for Medicare and Medicaid Services (CMS) [39]. We used the lower price of the two sources for each drug.

Cost of oral therapy was unavailable since these treatments are currently unapproved. The baseline cost of oral therapy was calibrated such that the average total treatment cost of oral therapy was equal to the average total treatment cost of triple therapy, despite the shorter duration of oral therapy. This resulted in a baseline cost of oral therapy of $5,800 per week. We also considered the scenario where this baseline cost was increased by 50% to $8,700 per week. All costs were expressed in 2012 US dollars.

Quality of Life

Quality of life was incorporated through the use of health state utility scores, with length of time in a health state being weighted by the utility score. Utility scores were taken from the literature (Supplementary Table 2) [40-47]. For many values there were multiple published results using similar methods, and the median score was used. Utility scores for transplantation were based longitudinal data from Ratcliffe et al [45].

The disutility for treatment with oral agents is unknown. It appears to be better tolerated than interferon-based therapy, and so the disutility should be less than for triple therapy. This is supported by recent data which found the disutility of oral therapy to be .03 (Unpublished data, Younossi 2013).

Sensitivity Analysis

Univariate sensitivity analysis was conducted for each model parameter. Probabilistic sensitivity analysis was run for both models: baseline and 50% higher cost of oral therapy. Details of ranges and distributions used for these sensitivity analyses can be found in supplementary document 1.

Results

Simulation of Clinical Outcomes with Different Strategies:

While the treat-all strategies would treat 100% of the patients, staging-driven treatment initially treated only 58% of the patients. However, staging-driven strategies would eventually treat another 25% of the patients who originally had little or no fibrosis, but later progressed to fibrosis stage F2 or beyond. This would leave only 17% of the patients untreated. Thus, the difference in the number of patients treated between the two strategies is not as large as it initially appears.

In terms of clinical outcomes, results favored oral therapy over triple IFN-based combination therapy, and treating all patients over staging-guided treatment (Table 3). Rates of progression from baseline staging pre-cirrhosis to compensated cirrhosis (without having achieved SVR) were just 6.5% and 10.6% for oral therapy for all and for oral therapy for those after staging, respectively. In comparison, triple therapy treating all patients and treating with triple therapy only after staging had 11.8% and 13.4% reaching compensated cirrhosis without SVR. Rates of decompensated cirrhosis and HCC were far lower for oral therapy, with small advantages for treating all. Only 12.7% (treat with triple therapy after staging strategy) and 10.9% (treat all with triple therapy strategy) of patients reached advanced liver disease under oral therapy, as opposed to 24.2% (triple therapy after staging) and 21.3% (triple therapy for all). Approximately 5% of patients eventually received a liver transplant under triple therapy, compared to about 3% for oral therapy. Life expectancy was highest for the regimen using oral therapy for all at 29.978 years, compared to 29.827 for oral therapy after staging, 28.520 for triple therapy for all and 28.324 for triple therapy after staging. It is important to note that for reference, life expectancy for a 50 year-old in U.S. population is an additional 31.428 years.

Baseline Analysis:

In the baseline analysis, the cost of oral therapy was calibrated so that the average cost of oral therapy was the same as the average cost of triple therapy. Due to superior outcomes reducing the downstream costs, both oral therapy strategies led to lower lifetime cost compared to the two triple therapy options (Table 4A). Based on the simulation model of 50,000 patients, the regimen with oral therapy after staging

had the lowest mean total cost at $77,133 followed by the regimen of oral therapy for all at $90,681, triple IFN-containing therapy after staging at $93,981 and triple IFN containing therapy for all at $106,554. Effectiveness, as measured in QALYs, also favored the oral therapies with oral all having a mean effectiveness of 18.391 QALYs, followed by oral after staging at 17.529, triple therapy for all at 17.201 and triple therapy after staging at 16.386.

Incremental Cost Effectiveness Analysis:

The incremental cost-effectiveness analysis showed that at the baseline cost of oral therapy, both triple therapy strategies were dominated by oral all and oral after staging, having both higher cost and lower effectiveness (Table 4A). Compared to oral regimen after staging, oral regimen for all patients had an incremental cost-effectiveness ratio (ICER) of $15,709/QALY. Increasing the cost of oral therapy by 50% of the baseline led to triple therapy after staging being the least costly option, while triple therapy for all remained dominated by oral regimen (Table 4B). However, because of superior outcomes, oral therapies remained cost-effective. Compared to the current standard treatment (triple therapy after staging for G1), oral regimen after staging had an ICER of just $8,611/QALY. However, oral regimen for all HCV-G1 was still the most cost-effective strategy with an ICER of $25,109/QALY, which is still well below all commonly used thresholds of cost-effectiveness ($50,000/QALY).

Results of Sensitivity Analysis:

Sensitivity analysis on the disutility of oral therapy had minimal impact on the ICER. One-way sensitivity analysis failed to find any variables impacting the cost-effectiveness of oral therapy using a threshold of $50,000/QALY. This treatment strategy remained cost-effective even using a higher cost for oral therapy. In fact, even with this higher cost of oral therapy and a conservative ICER threshold of $50,000/QALY, oral therapy remained cost-effective as long as the end-of-treatment response was at least 0.85 (baseline=0.99), a value well below the range used for sensitivity analysis.

We further explored the potential impact of a large reduction in the cost of Telaprevir and Borceprevir. Using the baseline cost of oral therapy, oral therapy remained cost-effective using a threshold of $50,000/QALY.

Finally, the sensitivity analysis showed that the cost of staging had no impact on the results. Using the $50,000/QALY threshold of cost-effectiveness, treating all was still cost-effective even if there was no cost for staging.

Results were very similar when boceprevir was used in place of telaprevir. Boceprevir strategies had slightly lower cost and effectiveness compared to telaprevir. Staging-guided treatment with boceprevir had a mean total cost of $86,953 and mean effectiveness of 16.176, compared to $93,746 and 16.770 QALYs, respectively, for treating all.

Probabilistic sensitivity analysis was run for both scenarios for the cost of oral therapy with results nearly uniformly supporting oral therapy for all patients. Using the baseline cost of oral therapy, treating all with oral therapy was cost-effective in 100% of samples using a threshold for cost-effectiveness of $50,000/QALY (Supplementary Document 1, Figure 1). When the cost of oral therapy was increased, the probabilistic sensitivity analysis was rerun, treating all with oral therapy remained cost-effective in 99.6% of the samples at the same $50,000/QALY threshold (Supplementary Document 1, Figure 2).

Discussion

This is the first study to investigate cost effectiveness of an IFN-free regimen for the treatment of patients with genotype 1 CH-C. Using a decision analytic Markov model, the results of this study demonstrated that an IFN-free oral regimen for 12 weeks was the most cost effective treatment choice for this cohort of patients. Further, oral therapy for all G1-HCV patients without staging seems to be superior over the current standard of IFN-based triple therapy after staging for G1-HCV patients. Furthermore, IFN-free without staging was more cost effective than oral IFN-free regimen after staging. In fact, our sensitivity analyses showed that the cost of staging itself has no impact on cost-effectiveness of this regimen. This

study suggests that with the development of highly effective IFN-free regimens with high SVR rates, low side effects and shorter duration, decision to treat or not to treat should not be based on the stage of liver disease. Nevertheless, the issue of staging remains important for other management issues in patients with liver disease such as screening for HCC or varices.

In this study, effectiveness, as measured in QALYs, also favored the oral IFN-free regimen for all with a mean effectiveness of 18.360 QALYs, followed by oral interferon free after staging at 17.505, triple therapy for all at 17.189, followed by treating with triple therapy after staging at 16.376.

For this study, cost-effectiveness of a regimen was measured by ICER. Our analysis showed that "treat all with oral therapy" strategy without staging was the most cost-effective strategy, with an ICER of $15,709/QALY. This regimen remained cost-effective (below $50,000/QALY) even after large departures from the baseline cost and utility of oral therapy. This data suggest by treating all patients regardless of the stage of their liver disease, morbidity and mortality will be potentially be reduced. As depicted in table 3, this strategy leads to fewer cases of cirrhosis, decompensated liver disease, HCC and liver transplantation. These data indicate that the improvement in outcomes may be related to less delay in treatment of the cohort of patients with CH-C. This is an important point as noted by McEwan at al. that the timing and initiation of treatment is significant in slowing down or halting the liver disease progression [46]. They found that by initiating immediate treatment, especially for those with more advanced disease, costs and complications would be minimized and health related quality of life would be maximized [46]. Our current analyses suggest that liver disease stage-guided treatment protocols for G1-HCV should be revisited. Especially in the era of IFN-free regimen with efficacy rates and better safety profile, treating all G1-HCV patients with IFN-free oral therapy appears to be improve outcomes and be more cost-effective.

This issue becomes even more important in the context of recent recommendation regarding HCV screening by the United States Centers for Disease Control (CDC) which was also supported by European and international bodies as well as different medical societies and U.S. Preventive Services Task Force (USPTF) [48-50]. In fact, two models assessing cost-effectiveness of screening for the Baby

boomers found that screening individuals born between 1945-1965 is cost effective. Both analyses assumed treatment with current standard treatment after liver biopsy [9, 29]. These strategies for birth-cohort screening are likely to provide important health benefits by reducing lifetime cases of advanced liver disease and HCV-related deaths and are cost-effective at conventional willingness-to-pay thresholds. One could argue that strategies to identify patients through recently recommended screening strategy followed by all oral IFN-free treatment may be even more cost effective. Nevertheless, this strategy will require additional economic analysis.

There are several limitations to this study which have also been noted by other investigators when working with model simulation [30,44,46]. While Fibroscan has been approved in the United States to assess stage of fibrosis, the reimbursement for it was not established at the time of this study. We chose to conservatively estimate the cost of this ultrasound-based procedure as the cost of liver ultrasound. This underestimate created a small bias in favor of staging strategies, yet treating all G1-HCV patients without staging proved superior to those strategy that required staging. In fact, our conclusion that treating all is more cost-effective than staging remained true even if staging was performed for free. Also, the model did not account for logistical issues of a large, sudden spike in demand for treatment that could lead to substantial delays in initiation of therapy. Telaprevir was only used as a comparison even though boceprevir was also included but this event should not impact overall outcome since they are equivalent in response or if anything there is a slightly but not clinically significant lower response rate with boceprevir. We also did not include the recent data reported from CUPIC suggesting lower efficacy and higher side effects for triple combination in the community setting [16]. We believe this data would further support all oral regimen. Nevertheless, similar effectiveness data for oral regimens is not available and this comparison cannot be currently justified. Finally, we did not account for any increase or decrease in clinical services that may be required for a treatment plan advocated by large scale implementation of the findings of this study.

In summary, our data shows that oral IFN free therapy for all HCV-G1 patients reduced the number of patients developing advanced liver disease and increased life expectancy. Additionally, this therapeutic

choice may be the most cost-effective approach for treating HCV GT 1 patients. Further, these findings, combined with prior studies addressing the cohort of patients that should be screened, helps to establish a potential guideline for working with the general population in the identification of patients with HCV. Nevertheless, the efficacy and safety of these IFN-free regimens must be fully confirmed using phase III randomized controlled trials.

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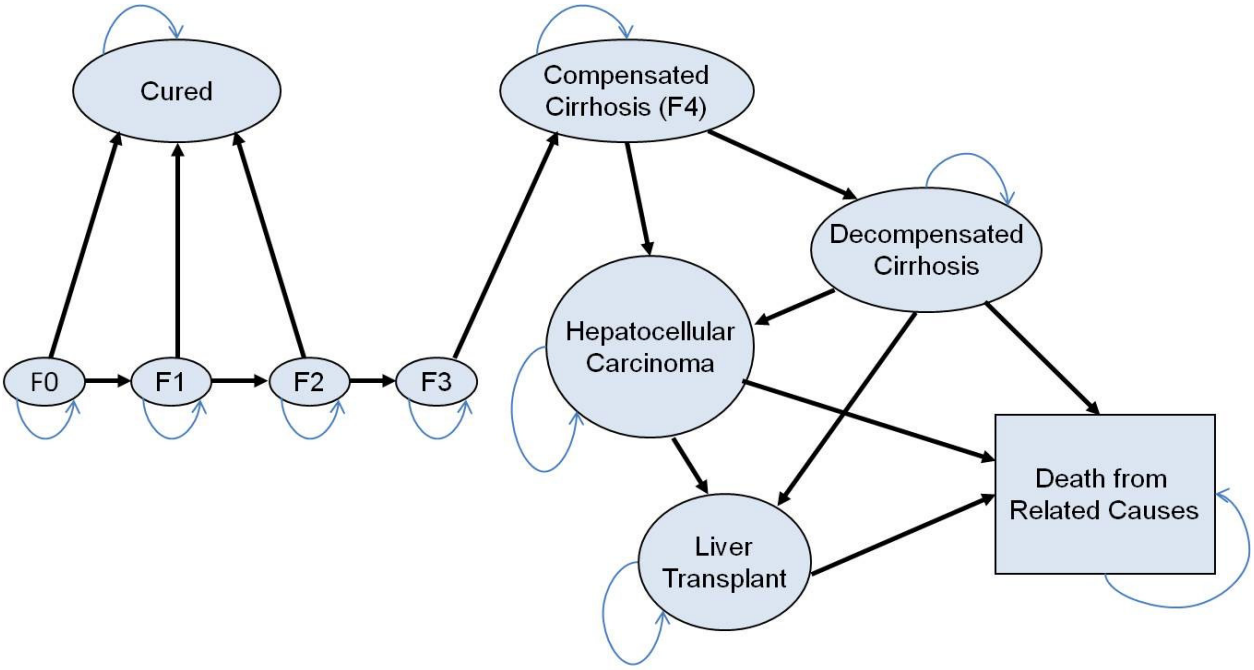
Figure 1. Markov State Transition Diagram



Notes:

1. Death from other causes not depicted.
2. Following successful treatment in F0-F2, the patient is considered cured.
3. Following successful treatment in F3 or Compensated Cirrhosis (F4), the patient remains in that state with greatly reduced probability of progression.

Figure 2. Probabilistic Sensitivity Analysis – Cost of Therapy Equal to Baseline

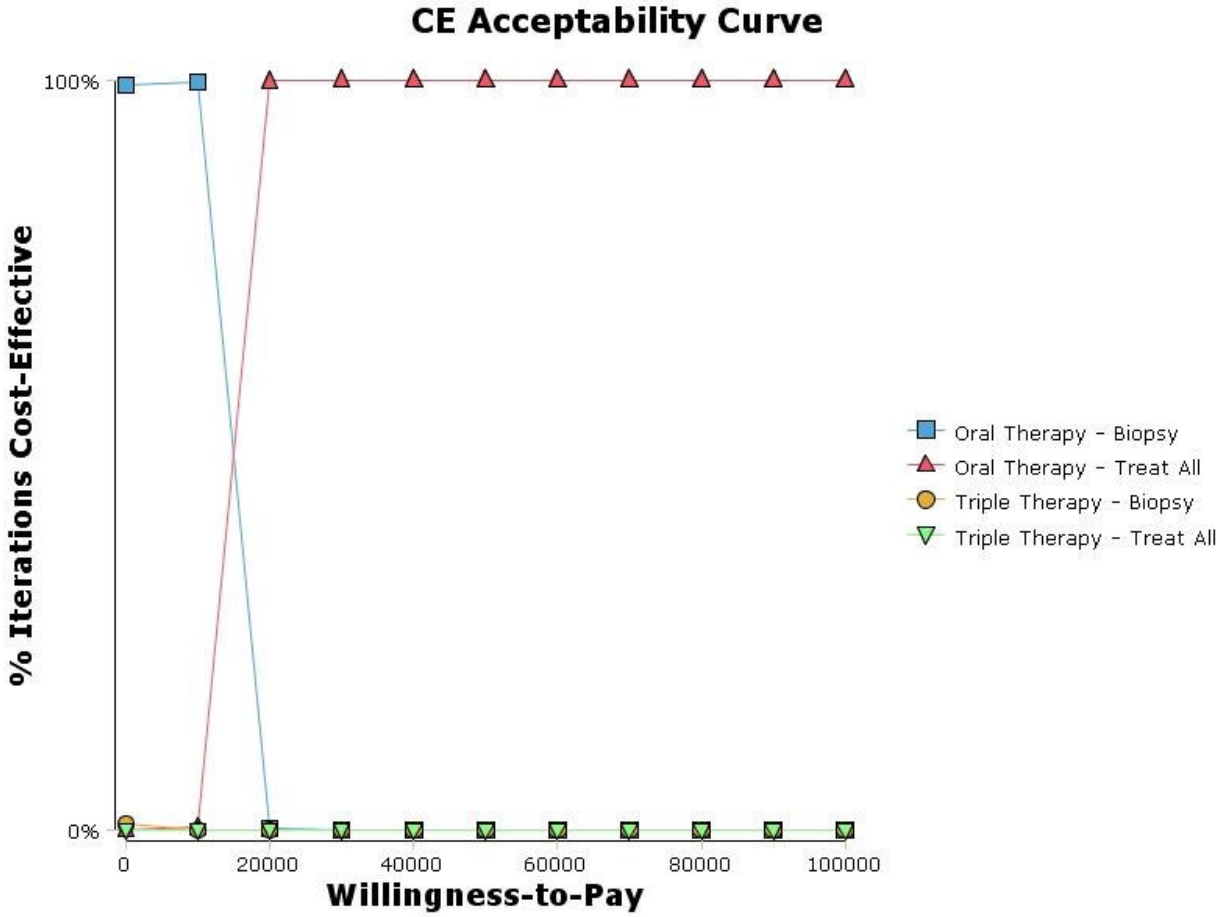


Figure 3. Probabilistic Sensitivity Analysis – Cost of Therapy 50% Above Baseline

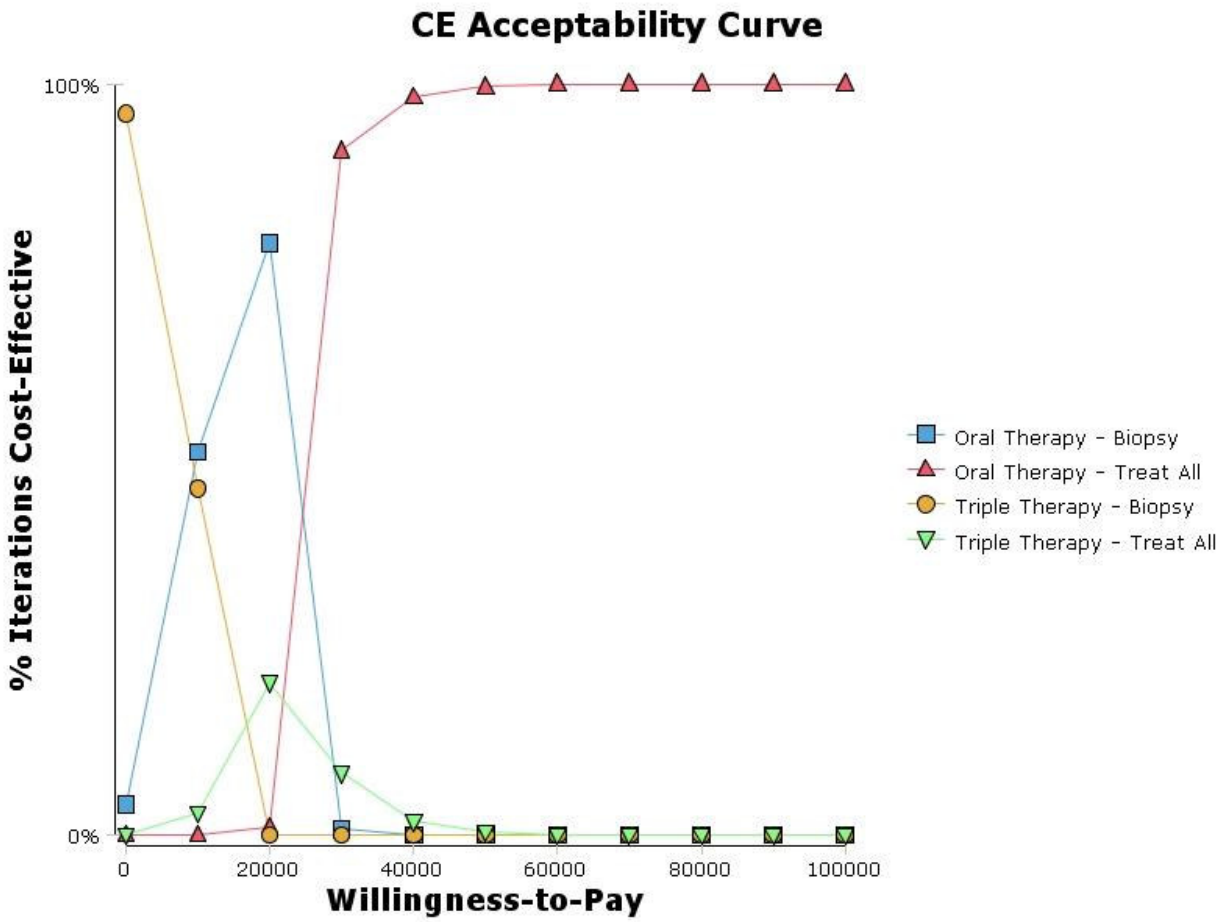


Table 1. Treatment Probabilities

	Baseline	Source(s)
Telaprevir		
Treatment Failure		
End of Triple Therapy	0.03	22
End of Double Therapy	0.05	22
EOT Response	0.82	22
24 weeks therapy	0.58	22
48 weeks therapy	0.24	22
Relapse	0.09	22
SVR		
Overall	0.73	22
F0 - F1	0.81	22
F2	0.75	22
F3 - F4	0.62	22
Discontinuation		
Overall	0.10	22
During Triple Therapy	0.07	22
During Double Therapy	0.03	22
Oral Therapy		
EOT Response	0.99	17-20
Relapse	0.08	17-20
Discontinuation	0.00	17-20
Boceprevir (sensitivity analysis)		
Fail Lead-In		
Overall	0.05	23
F0-F2	0.04	Estimated
F3-F4	0.12	Estimated
Discontinuation	0.13	23
Futility	0.08	23
EOT Response		
Overall	0.74	23
F0-F2	0.77	23
F3-F4	0.55	23
Duration of Therapy		
28 Weeks	0.68	23
48 Weeks	0.32	23
% Receiving Epogen	0.38	21
Duration of Epogen (wks)	12.00	21

Table 2. Transition Probabilities

Parameter	Baseline	Source(s)
Initial Fibrosis Distribution		
F0	.18	47
F1	.24	47
F2	.17	47
F3	.13	47
F4	.28	47
F0 to F1	.124	24
F1 to F2	.088	24
F2 to F3	.123	24
F3 to F4	.119	24
SVR F3 to SVR F4	.0046	25
F3 to HCC	.008	34
F4 to Decompensated Cirrhosis	.039	9, 29
F4 to HCC	.025	9
Relative Risk with SVR, F4 to Decompensated Cirrhosis	.0857	12, 26
F3 or F4 to HCC	.24	48, 49
Decompensated Cirrhosis to HCC	0.025	9
Decompensated Cirrhosis to Transplant	.031	10, 27
Decompensated cirrhosis to Death	.135	9, 28
HCC to Transplant	.1033	29
HCC to Death	.427	30, 31
Transplant to Death Year 1	0.14	32
Years 2-4	0.0384	32
Years 5-15	0.0252	33
Years 16+	0.0136	33

Table 3 - Outcomes

	Triple Therapy		Oral Interferon-Free Therapy	
	Staging	**Treat All**	**Staging**	**Treat All**
Life Expectancy (yrs)	28.324	28.520	29.827	29.978
Progression to:				
Cirrhosis (%)	29.4	23.6	10.6	6.5
Decompensated (%)	13.4	11.8	5.9	4.9
HCC (%)	12.0	10.5	7.3	6.4
Decompensated or HCC(%)	24.2	21.3	12.7	10.9
Transplant (%)	5.2	4.6	3.1	2.7

Table 4 – Cost and Effectiveness

A. Baseline

Strategy	Cost ($)	Incr. Cost ($)	Effectiveness (QALYs)	Incr. Eff. (QALYs)	ICER ($/QALY)
Oral - Staging	77,133		17.529		
Oral - Treat All	90,681	13,548	18.391	.862	15,709
Triple Therapy - Staging	93,981		16.386		Dominated
Triple Therapy – Treat All	106,554		17.201		Dominated

B. Cost of Oral Therapy 50% Higher than Baseline

Strategy	Cost ($)	Incr. Cost ($)	Effectiveness (QALYs)	Incr. Eff. (QALYs)	ICER ($/QALY)
Triple Therapy - Staging	93,981		16.386		
Oral - Staging	103,826	9,845	17.529	1.143	8,611
Triple Therapy – Treat All	106,554		17.201		Dominated
Oral - Treat All	125,481	21,655	18.391	.862	25,109