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Hepatitis C, disease and its management: a cost-effectiveness analysis of the new generation oral protease inhibitors

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Abstract

Background—Hepatitis C, caused by a single stranded RNA virus, has become a global health problem. Infecting millions of individuals in the United States alone, chronic Hepatitis C viral infection can lead to devastating medical problems including cirrhosis and hepatocellular carcinoma. These problems create millions of dollars in health care costs for treatment and management. This study determines the cost effectiveness of Hepatitis C treatment with the new generation of oral protease inhibitors.

Methods—A Markov Model was constructed to simulate the progression of genotype 1 chronic hepatitis C disease in a cohort of 50-year-old patients. A decision tree, along with the Markov Model, was then used to determine duration of disease, treatment success, progression of disease, and mortality. At the end of each stage in the model, the cost and quality-adjusted life years (QALY) were summed for each individual. These were then used to calculate the overall cost effectiveness ratio (CER) using QALY as the unit of effectiveness. Four treatment options were modeled: Sofosbuvir with Pegylated interferon-alfa & Ribavirin (SOF/pegIFN&RBV), Sofosbuvir with Ribavirin (SOF/RBV), Simeprevir with Pegylated interferon-alfa & Ribavirin (SMV/pegIFN&RBV), and Simeprevir with Sofosbuvir (SMV/SOF).

Results—SOF/pegIFN&RBV, yielded a CER ratio of \$6,796.22/QALY, SMV/pegIFN&RBV of \$7,642.60/QALY, and SMV/SOF of \$8,959.11/QALY. SOF/RBV had a higher CER of \$16,295.30/QALY. It is important to note however that SMV/SOF had the highest QALY at 19.08.

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DISCLOSURE STATEMENTS

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Conclusions—After consideration of quality of life, treatment regimens and treatment side effects, the simeprevir and sofosbuvir regimen yields acceptable cost-effective ratios with high quality-adjusted life years.

Keywords

Hepatitis C; Protease Inhibitor; Simeprevir; Sofosbuvir; Cost-Benefit Analysis

INTRODUCTION

Burden of disease

Hepatitis C is an infectious disease that has become a major health problem worldwide [1]. Caused by the hepatitis C virus (HCV), the disease is predominantly transmitted via contact of blood from an infected individual. According to the 1999–2002 National Health and Nutritional Examination Survey (NHANES), 1.6% or 4.1 million Americans were infected with HCV [6]. The NHANES reported that the prevalence of HCV infection has decreased from the 1988–1994 study to the 2007–2008 study, especially among those with the highest risk factors (MSM and IDUs) [7]. There was a decrease in prevalence of 0.9% for males and 0.2% for females during this time period [7]. A recent article by Chak et al. pointed out that the NHANES survey doesn't include the incarcerated, homeless, nursing home residents, the hospitalized, those on active military duty, and immigrants in their survey population [6]. Since transmission rates in these subgroups can be considerably high, Chak et al. concluded that the NHANES underestimated the prevalence of HCV disease in the USA and stated that at least 5.2 million people, using conservative estimates, were living with HCV in the USA in January 2011 [6].

Approximately 20,000 Americans are newly infected with HCV annually [5]. It is estimated that 65–75% of infected individuals in the USA are unaware of their positive disease status and thus not receiving the needed treatment [5]. It is estimated that over 10,000 people die each year from liver failure related to HCV [8, 2]. Although the incidence of HCV has decreased in recent years, the prevalence of the long term complications from HCV has increased. Over the last few decades, rates of liver cancer have tripled with chronic HCV causing half of the cases [5]. It is expected that about 150,000 Americans will die in the next decade due to HCV associated liver cancer or end-stage liver disease [5].

According to the NHANES survey, individuals born between 1945 and 1964 (the baby boomer generation) [6, 7] carry a high burden of disease. The national survey also found that individuals with ages ranging from 46 to 64 had a 1 in 33 rate of HCV infection [5]. African Americans also demonstrated high rates of HCV infection (two times the general population). Individuals with HIV or AIDs had higher rates of HCV infection when compared to the general public [5].

Screening

With expanded health insurance coverage under the Affordable Care Act, the need for increased access to prevention and screening for HCV is being emphasized by many [5]. Multiple organizations, including the U.S. Preventive Services Task Force (USPSTF) and the

CDC have endorsed screening guidelines. Most agree that high-risk individuals should be periodically tested if they continue to participate in risky behavior. The CDC recommends a single serologic screen for all individuals born from 1945 to 1965 who have not been previously tested [3].

Initial screening should be performed using an enzyme-linked immunosorbent assay (ELISA) testing), which tests for HCV antibodies. This ELISA test has a sensitivity of 98.9–100% and a specificity of 99.3–100% [3]. A confirmatory test using polymerase chain reaction (PCR) to measure HCV RNA should be performed if the ELISA test is positive. If both ELISA and PCR test are positive, an individual is diagnosed with a HCV infection [3].

Treatment

For years the backbone of HCV treatment was combination therapy with pegylated interferon-alfa (pegIFN) and ribavirin (RBV). This changed in 2011 when the first oral protease inhibitors, boceprevir and telaprevir, were approved for use in the United States [3]. Since their introduction, the standard of care (SOC) for HCV genotype 1 infection has incorporated the use of either boceprevir (BOC) or telaprevir (TVR) in combination with pegIFN and ribavirin. The standard of care for all other genotypic HCV infections remained pegIFN and ribavirin [10]. In late 2013, the second generation of protease inhibitors, simeprevir (SMV) and sofosbuvir (SOF), were approved for use in the United States. Both are oral drugs with once-a-day dosing and, when used in combination therapy with pegIFN and/or ribavirin, have increased efficacy and reduced duration of treatment in some patients [11].

Simeprevir is indicated for combined treatment with pegIFN and ribavirin in patients with chronic hepatitis C genotype 1 infection [12]. Clinical trials have shown sustained virological response (SVR) rates of 80% at 12 weeks with the SMV/pegIFN/RBV triple therapy [13, 12] (Table 1). Sofosbuvir can also be used to treat HCV genotypes 1, 2, 3, and 4 in combination therapy. Treatment with sofosbuvir, pegIFN, and ribavirin for 12 weeks is indicated for patients with HCV genotype 1 infection [14]. Patients with genotype 1 infection who are unable to tolerate pegIFN can be treated with 24 weeks of sofosbuvir and ribavirin [14]. SVR rates for patients with HCV genotype 1 is 90–91% after 24 weeks of triple therapy with SOF/pegIFN/RBV [14, 15]. Treatment regimens utilizing sofosbuvir and ribavirin in patients with HCV genotype 2 and 3 have been shown to produce SVR rates at 12 weeks of 93–97% and 57–61%, respectively, in multiple phase 3 clinical trials [14, 16]. In the VALENCE clinical trial, higher SVR rates (85%) were seen in patients with hepatitis C genotype 3 infection who were treated for 24 weeks [17, 14]. Thus it is recommended that patients with hepatitis C genotype 3 be treated for longer periods of time (24 weeks with sofosbuvir and ribavirin). Clinical trials have also demonstrated great promise for sofosbuvir and simeprevir combination therapy in HCV genotype 1 infected patients, demonstrating 12 week SVR rates up to 93% [18]. Considering the variety and cost of the new treatment regimens it becomes important to assess the cost-effectiveness of various treatment strategies in order to provide adequate information to clinicians and decision-makers. Although a few cost-effectiveness and cost-benefit analyses have been published specific to the second generation protease inhibitors, these studies do not take into account or compare all the

treatment options available [19]. This study estimates the cost effectiveness of multiple treatment regimens available for Hepatitis C treatment using the new generation of oral protease inhibitors along with sofosbuvir and ledipasvir (LDV) as rescue therapy.

METHODS

The Markov Model in Figure 1 was constructed to simulate the progression of a cohort of 50-year-old patients with genotype 1 chronic hepatitis C disease [19]. This age was selected due to the high prevalence of chronic HCV disease in this age group according to the CDC report [7]. The cohort model included treatment naïve patients only without liver failure. Four treatment options were studied: SOF/pegIFN&RBV, SOF/RBV, SMV/pegIFN&RBV, and SMV/SOF. These treatment options were chosen as they represent the newer regimens for treatment of genotype 1 chronic hepatitis C disease. Rescue therapy was chosen as the combination treatment with sofosbuvir and ledipasvir. Treatment duration was determined based on recent guidelines for each drug regimen. The SVR rates were obtained from the most recent data available at the time of this study (see Table 1 for further information).

The decision tree used with the Markov model is presented in Figure 2. The decision tree was used to calculate cost while the Markov model was used to simulate the progression of patients through the study. In the decision tree, individuals were either treated in which case the cost due to treatment was tabulated or they had no treatment and the disease progressed. The Markov model assumes that individuals are evenly distributed to each disease stage and either received treatment or were allowed to progress to a more advanced stage. Patients in whom the treatment failed would receive rescue therapy and either reach SVR or continue to have disease progression. Parameters under consideration included chronic HCV disease history, treatment, treatment outcomes, and re-treatment (Table 3 in the Appendix). The cost used in the model was based on the current wholesale cost published for each medication in the United States (Table 3). The possibility of death existed at any stage of the model. Health outcomes were evaluated based on quality-adjusted life year (QALY). Since discounting of QALYs is controversial and can vary on an individual basis, no discounting was used. Instead, different rates of QALYs were used depending on each stage of the disease before and after SVR. The mortality rate before SVR for HCV was estimated to be 2.37 times higher than the normal population (non-infected individuals) [20]. The mortality rate decreased to 1.4 times the normal population mortality rate after SVR was achieved [21]. After each stage in the model, cost and QALY were summed for each individual. QALY prior to SVR was set as follows: 0.82 for mild to moderate disease, 0.81 for severe disease, 0.76 for compensated cirrhosis, and 0.69 for decompensated cirrhosis [22]. Mild disease was defined as individuals with no liver fibrosis (F0) or portal fibrosis without septa (F1). Moderate disease included those with portal fibrosis and few septa (F2). Severe disease included those with numerous septa without cirrhosis (F3). QALY after SVR was set as 0.92 for mild to moderate disease, 0.86 for severe disease, and 0.83 for compensated cirrhosis (F4) [19]. Rate of progression from no fibrosis to portal fibrosis without septa was set as 0.117, from mild disease to moderate disease as 0.085, from moderate to severe disease as 0.120, from severe disease to compensated cirrhosis as 0.116, and from compensated cirrhosis to decompensation as 0.11 [23, 24]. It was assumed that one fifth of the cohort was at each disease stage (F0–F4) at baseline. Each individual was modeled for their lifetime in

order to assess the cost and QALY. The QALY was used as the unit of effectiveness, in order to calculate cost effective ratios (CER). The CERs were the average outcome for the all individuals in the cohort based on their treatment regimen, irrespective of disease stage or progression. A program was developed using Visual Basic that modeled the progression of individuals in the cohort through the disease process using the parameters mentioned above and in Table 3 in the Appendix. The program was based on Markov Chain Monte Carlo simulations that used a random decision generator based on probability distributions in order to simulate the progression of disease for each individual.

RESULTS

At the end of the modeled cohort study, three of the treatment plans, SOF/pegIFN&RBV, SMV/pegIFN&RBV, and SMV/SOF yielded similar CER of \$6,796.22/QALY, \$7,642.60/QALY, and \$8,959.11/QALY respectively (Table 2). SOF/RBV had a higher CER of \$16,295.30/QALY. It is important to note however that the SMV/SOF treatment regimen had the highest quality-adjusted life years of any treatment plan (19.08). This in-turn helped to off-set the higher modeled cost of the SMV/SOF treatment plan even though the plan is \$48,540 more expensive than the lowest modeled drug cost. Sensitivity analysis was performed using the One-at-a-time (OAT) methodology. The analysis showed that modification of any of the parameters still resulted in SMV/SOF treatment regimen as having the highest QALYs.

DISCUSSION

Total health care spending for the treatment of Hepatitis C and its complications has skyrocketed in the face of mediocre outcomes. The availability of safe and effective antiviral therapy stands to alter the status quo. Earlier treatment interventions that produce SVR will prevent progression of disease and reduce the need to treat advanced cirrhosis and its complications. Patients will experience fewer hospitalizations, less end stage disease, and fewer liver transplants, resulting in significant cost savings as well as reductions in morbidity and mortality. In order to determine and recommend treatment options it is critical to analyze and determine acceptable cost-effective treatment strategies that also provide high quality-adjusted life years.

Although SOF/pegIFN&RBV, SMV/pegIFN&RBV, and SMV/SOF yielded a similar cost effective ratio not all treatments are shown to be equivalent when the drugs themselves are considered. PegIFN is dosed as a weekly injection and is associated with multiple side effects including headache, fatigue, flu-like illness, and hematologic toxicity. RBV requires twice daily dosing and can cause rash, fatigue, and itching as well as potentially serious side effects such as hemolytic anemia and birth defects [28].

Once we determine the best treatment plan the next question that arises is who to treat. The modeled cohort shows that individuals with earlier stages of disease (fibrosis stages 0, 1, and 2) had better overall outcomes and improved QALY. Patients with risk factors for more advanced disease should be screened earlier in order to intervene in the disease process at an

earlier stage. These patients will be able to lead healthier and more active lives than their untreated counterparts.

This study has certain limitations. First of all the study used a simplified model of patients who already have the disease. This model did not control for potential confounders such as co-morbidities, higher hospitalization rates, health disparities, and higher overall health costs. The higher overall comorbidities and associated health cost of individuals with HCV was also not included in the study. The cost of (and thus access to) these very expensive medication will prevent some patients from obtaining treatment leading to the natural progression of disease. Even though Gilead and Janssen have prescription assistance programs, these programs have rigid qualifications and may not encompass all hepatitis C patients.

The model assumed total compliance with treatment regimen. Non-compliance is problematic within certain patient populations, such as those infected with HCV. Non-compliance is associated with failed initial treatment as well as development of HCV drug resistance. Resistance is a problem with prior BOC and TVR treatment however individuals in this model were assumed to be treatment naïve patients. This model also doesn't take into account the possibility of re-infection or partial failure of treatment in individuals who have good early response with undetectable viral loads but who do not reach SVR. Compliance with treatment protocols depends both on ease of use as well as tolerability of side effects. Since both SMV and SOF are dosed once daily and have a favorable side effect profile, these medications might prove to be a better option for patients even though the cost is higher when compared to other regimens. Additionally, both of these drugs have higher SVR rates. Earlier treatment has the potential to save healthcare dollars that would otherwise be spent treating symptoms and conditions associated with chronic hepatitis C including fibrosis, cirrhosis, ascites, portal hypertension, hepatocellular carcinoma, and liver transplant.

Combination therapy with sofosbuvir and ledipasvir is generally indicated as rescue treatment for those who fail initial therapy. The combination of SOF/LDV was chosen due to its very high SVR rates in clinical trials, with SVR rate at 24 weeks averaging 99% [25]. Therapy for 24 weeks with SOF/LDV is associated with the highest SVR rate. This is noteworthy inasmuch as individuals given SOF/LDV therapy had already failed another treatment regimen. This rescue therapy was used even though ledipasvir was not approved for sale in the United States at the time of this study. Gilead filed for approval for SOF/LDV fixed dose combination tablets; FDA approval was granted in October, 2014 [26]. The cost of SOF/LDV was estimated to be 1.75 times the cost for SOF therapy for 24 weeks (at the time of this study LDV was not yet approved for sale in the US). Some of the drugs in the study (SOF, SMV, and LDV) are still in trials and the SVR rates used were from clinical trials. Some of these trials also had a small number of participants.

The standard mortality rates for this model were based on a study using the Third National Health and Nutrition Examination Survey that had a median follow-up of 14.8 years along with a meta-analysis [24]. Other studies however have shown even more benefit of sustained SVR with an even greater decrease in background mortality rate. This could lead to an underestimation of the benefit of treatment and "cure" of hepatitis C in terms of QALY. The

model also does not take into account hospital expenses, biopsies, and other lab work needed throughout the duration of treatment and only focuses on pharmaceutical costs. Even with all the limitations, it is believed that this model can help determine treatment regimen for hepatitis C patients in order to increase quality-adjusted life years with acceptable overall cost ratios.

The SMV/SOF treatment regimen yields acceptable cost-effective ratios with high quality-adjusted life years. It is easily administered and has an acceptable side effect profile. Our modeled cohort study analysis confirms that this should be the preferred initial treatment plan for hepatitis C patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1.
Simplified Markov Model [19].

Fig 2.
Decision Tree.

Table 1

Treatment Duration and SVR Rates

Treatment Plan	Duration	SVR	Reference
SOF*/pegIFN&RBV	12 weeks	0.90	[14–16]
SOF/RBV	24 weeks	0.68	[14, 27]
SMV/pegINF&RBV	12 weeks	0.80	[13, 12]
SMV/SOF	12 weeks	0.93	[13, 12, 18]
SOF/LDV	24 weeks	0.99	[25]

* SOF: sofosbuvir
RBV: ribavirin
LDV: ledipasvir
pegIFN: pegylated interferon-alfa
SMV: simeprevir

Table 2

Modeled Cost, Quality-Adjusted Life Years, and Cost Effective Ratio

Treatment Plan	Whole Sale Cost	Modeled Cost	QALY	CER
SOF*/pegIFN&RBV	\$93,000	\$122,400	18.01	6,796.22
SOF/RBV	\$173,000	\$267,080	16.39	16,295.30
SMV/pegIFN&RBV	\$75,360	\$129,160	16.90	7,642.60
SMV/SOF	\$150,360	\$170,940	19.08	8,959.11

* SOF: sofosbuvir
 RBV: ribavirin
 pegIFN: pegylated interferon-alfa
 SMV: simeprevir