

# Revolutionizing Treatment Outcomes in Hepatitis C: Managed Care Implications and Considerations—The New and Evolving Standards of Care

Gary M. Owens, MD

To date, the main objective of hepatitis C virus infection (HCV) treatment has been to achieve sustained virologic response (SVR; an undetectable viral load or “cure”). Achievement of an SVR is associated with better clinical outcomes related to liver disease—including cirrhosis, hepatocellular carcinoma (HCC), and the need for a liver transplant—and decreased all-cause mortality compared with a lack of SVR achievement.<sup>1</sup> With the addition of the 2 new direct-acting antivirals (DAAs) sofosbuvir and simeprevir in 2013, SVR rates up to 95% were experienced in patients after only 12 to 24 weeks of treatment with DAAs in combination with standard pegylated interferon (PEG-IFN)/ribavirin therapy, and in combination with each other. Approval of the fixed-dose combinations of ledipasvir and sofosbuvir and of paritaprevir/ritonavir, ombitasvir, and dasabuvir in late 2014 made available all-oral treatment options with high SVR rates for patients with HCV genotype 1. Several additional agents currently in late-stage clinical trials also show great promise for the treatment of chronic HCV infection.

Treatment decisions for patients with HCV infection are often challenging, and therapies used prior to the introduction of all-oral regimens can be complicated by a high incidence of adverse effects, treatment resistance, and medication adherence issues, often resulting in treatment discontinuation and non-achievement of an SVR, resulting in poorer overall outcomes. With a multitude of new therapies and treatment strategies now approved for clinical use and others continuously emerging, including interferon-free regimens and fixed-dose combination therapies, all-oral regimens are now becoming the standard of care. It is imperative for managed care clinicians and providers to improve their knowledge and competence surrounding the clinical and economic burden of HCV infection in the United States if they are to optimize their critical role in the management of patients.

## The Economic Implications of HCV Infection and Its Management

### Cost Burden of HCV Disease

Managed care clinicians and providers must carefully

### Abstract

Although the prevalence of hepatitis C virus (HCV) infection is declining, overall costs associated with HCV infection and the burden of advanced liver disease are projected to increase. The recent approval of all-oral, fixed-dose combination treatments for patients with HCV infection has resulted in unprecedented rates of treatment success, and in debate regarding treatment costs and appropriation. With all-oral therapies becoming the standard of care for HCV infection, high drug costs and improved clinical outcomes—now including the eradication of disease—must be weighed when selecting the most appropriate therapy. Patient “warehousing” has reached an all-time high as payers and providers strive to strike the fine balance between clinical efficacy and cost-effectiveness of currently available treatments, and this “wait and see” period may very well continue until an acceptable balance has been achieved. As such, it is imperative that managed care clinicians maintain an informed understanding of the disease burden and current climate of HCV infection in the United States.

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## Reports

consider the cost-effectiveness of new and emerging treatments for HCV infection in the context of disease costs and the impact of treatment costs on patient outcomes. An informed understanding of both the burden and the costs associated with HCV infection and its complications is required for the effective management of patients. At the same time, the potential costs and values of new and emerging treatments must be taken into consideration. A recent analysis by Razavi and colleagues aimed to predict HCV disease progression and associated costs in the United States in the next few decades.<sup>2</sup> Using a system dynamic model, which was developed with 36 cohorts to provide improved forecasting and flexibility, the prevalent population was tracked by the model beginning in 1950, and the sequelae population was forecasted to 2030. The model consisted of 17 five-year age cohorts and 1 age cohort for individuals at least 85 years of age; these were developed for each sex to provide maximum flexibility for changing inputs such as incidence rate, age at infection, and other variables. Future costs (2012-2030) were estimated using the 2011 annual medical inflation rate of 3.06% (2.88%-5.22%). The incidence of new infections in 2010 was forecasted at 16,020 (95% CI, 13,510-19,510), compared with a reported incidence of 17,000. The viremic prevalence of HCV peaked at 3.3 million in 1994 and is expected to decline by two-thirds in 2030. The incidence of HCV infection has fallen significantly since its peak in 1989 due to the changing epidemiology of intravenous drug users,<sup>3</sup> the implementation of HCV antibody screening of the blood supply in 1992,<sup>4</sup> and universal donor screening for viral ribonucleic acid via nucleic acid testing in 1999.<sup>5</sup> The authors stated that the total cost of \$6.5 billion (in 2011 US\$) is expected to increase and peak in 2024 at \$9.1 billion.<sup>2</sup> Although the prevalence of HCV infection is declining, and the 2030 prevalence is predicted to be one-third of the peak, the prevalence of advanced liver disease will continue to increase, along with the total healthcare costs associated with HCV infection. It was further projected that the prevalent populations with compensated and decompensated cirrhosis will peak in 2015 (626,500 cases) and 2019 (107,400 cases), respectively.<sup>2</sup>

Of note, the analysis by Razavi and colleagues did not consider the effects of recent changes in the HCV treatment landscape; however, the authors did point out that if the number of treated patients is doubled and kept constant between 2012 and 2030 at 126,000 per year, and the average SVR rate increases to 70%, the projected prevalent population would be fewer than 100,000 cases.

They concluded that it is possible to achieve substantial reductions in HCV infection through active and appropriate management.<sup>2</sup>

One systematic literature search published in 2012 identified 50 studies that reported the costs of HCV sequelae in the United States, where costs were compiled and adjusted to 2010 constant US dollars using the medical component of the consumer price index. Several very substantial costs relating to the disease were delineated per person per year, including<sup>6</sup>:

- Liver transplants: \$178,760 to \$233,460
- HCC: \$23,755 to \$44,200
- Variceal hemorrhage: \$25,595
- Compensated cirrhosis: \$585 to \$1110
- Refractory ascites: \$24,755
- Hepatic encephalopathy: \$16,430
- Diuretic sensitive ascites: \$2450

Associated indirect costs of HCV infection, including lost earnings or work production due to hospitalization, ambulatory care, work loss owing to acute or chronic infection, and premature death, also carry substantial impact. Total indirect costs ranged from \$51 million to \$3.3 billion,<sup>7-11</sup> with the lower end of the range including only the loss of work-related productivity income,<sup>9,11</sup> and the higher end considering the loss of production due to early death (age 75 years).<sup>7</sup> In many cases, indirect costs are greater than direct costs. For instance, a 2008 publication by the National Institutes of Health reported that indirect costs related to HCV infection (\$1.78 billion in 2004) were 67% higher than the estimated direct costs.<sup>7</sup>

Of note, HCV genotype is frequently associated with disease severity and the likelihood of treatment response. At least 6 HCV genotypes have been identified worldwide, with substantial geographic variation in terms of prevalence.<sup>12</sup> Genotypes 1a and 1b are the most common types in the United States and Europe. HCV 2a and 2b are also relatively common in these locations, and genotype 3a is frequently found in intravenous drug abusers in both the United States and Europe. Genotypes 4, 5, and 6 appear to be prevalent in North Africa and the Middle East, South Africa, and Hong Kong, respectively.<sup>12</sup>

HCV genotypes display distinct clinical characteristics. For example, although steatosis occurs with all HCV genotypes, patients with genotype 3a experience resolution of steatosis with viral clearance, unlike those with other genotypes.<sup>13,14</sup> In addition, studies have demonstrated that genotype 1b may be associated with a more

severe clinical course compared with other genotypes, including the development of HCC<sup>15,16</sup>; however, the exact role of HCV genotype in disease progression or severity has yet to be delineated.<sup>17</sup>

#### *Cost Implications of Therapy in the Management of HCV: What Do the Data Tell Us?*

Prior to 2011, the majority of published studies concluded that HCV treatments, including PEG-IFN/ribavirin and the first-generation protease inhibitors, were cost-effective.<sup>18</sup> The recent approval of several novel agents for treatment of HCV infection, including the first-generation protease inhibitors boceprevir and telaprevir in 2011, and the DAAs simeprevir and sofosbuvir in 2013, have laid the foundation for an evolving HCV therapeutic landscape. The addition of boceprevir or telaprevir to PEG-IFN/ribavirin standard therapy led to the achievement of an SVR in 50% to 80% of patients after 24 weeks of treatment, with higher rates in patients with genotype 2 or 3 compared with genotype 1.<sup>19</sup> The availability of these agents, and those in late clinical studies, have led to new concerns about cost analyses and cost-effectiveness determinations. Although the cost-effectiveness of traditional therapies (eg, PEG-IFN/ribavirin) is known, economic evaluations of DAAs are few at this time. Actual drug costs for newly approved agents are extremely high, leading to uncertainty regarding their true short- and long-term value in terms of healthcare costs versus benefits.<sup>20</sup>

Direct comparison of the relative efficacy of traditional agents versus DAAs is difficult due to a lack of head-to-head trials. In a network meta-analysis of data from 21 studies that synthesized direct and indirect evidence from clinical trials, Ollendorf and Pearson aimed to describe the potential clinical and economic impact of the recently approved DAAs sofosbuvir and simeprevir in California compared with previous standard therapies. A cohort model was developed that assessed these effects over time periods of 1, 5, and 20 years. Outcomes were examined in hypothetical cohorts by genotype, prior treatment status, and interferon therapy eligibility.<sup>21</sup>

The authors concluded that therapeutic regimens that include sofosbuvir or simeprevir may substantially increase the number of patients achieving an SVR, but for some patient subsets, these agents could come at high cost due to the need for retreatment if an SVR is not achieved. For example, the model suggests that in treatment-naïve patients with HCV genotype 1, the increased drug costs would be offset by downstream savings from

reductions in liver-related complications and a greater number of patients achieving an SVR. However, for other comparisons with previously standard treatments, the incremental cost required to achieve 1 additional SVR with a newer regimen may be greater than \$300,000, and the average increase in treatment costs was estimated to be \$70,000 per patient with newer agents.<sup>21</sup>

In patients with HCV genotype 1 infection, the first-generation protease inhibitors increased the sustained viral response 12 weeks after therapy (SVR12) from approximately 40% with PEG-IFN/ribavirin to about 70%.<sup>20,21</sup> Unfortunately, the pill burden is substantial, ranging from 6 to 12 pills per day depending on the regimen, and adverse effects can be both bothersome and serious.<sup>22</sup> Possible adverse effects include an increase in anemia, nausea, taste disturbance (boceprevir), and pruritis (telaprevir).<sup>20,23</sup> Also of importance is the large number of drug-drug interactions associated with these agents.<sup>20</sup> Despite these issues, triple therapy involving one of these agents with PEG-IFN/ribavirin was considered standard therapy until the arrival of simeprevir and sofosbuvir in 2013.<sup>20</sup>

In patients with HCV genotype 2 infection, the combination of sofosbuvir plus ribavirin is clinically more effective compared with standard treatment options. A large increase in SVR12 among untreated patients was observed in the randomized, open-label, phase 3 FISSION trial; the SVR12 value for patients receiving treatment was 90%. In the FISSION trial, SVR rates in patients receiving 12 weeks of sofosbuvir/ribavirin and in those receiving 24 weeks of PEG-IFN/ribavirin were both 67%.<sup>22</sup> Neutropenia was not observed in patients receiving sofosbuvir, but occurred in 30% of patients receiving PEG-IFN/ribavirin. Discontinuation of treatment due to AEs occurred in 1% of patients receiving sofosbuvir/ribavirin and 11% of patients receiving PEG-IFN/ribavirin. In patients with genotype 3, response rates in the sofosbuvir/ribavirin group were lower compared with genotype 2 (56% vs 97%).<sup>22</sup>

Given the newly approved agents for treatment of HCV genotype 1 infection, patients with genotype 3 have become the more difficult patient population to treat. As noted earlier, correlations have been demonstrated between HCV genotype 3 infection and steatosis and HCC.<sup>24,25</sup> In the randomized VALENCE study of 328 patients with HCV genotype 3 infection, Zeuzem and colleagues reported an SVR of 85% (95% CI, 80%-89%) in patients treated with sofosbuvir and ribavirin for 24 weeks, although lower rates were evident with shorter

## Reports

treatment durations.<sup>26</sup> These results were irrespective of previous treatment status or presence of cirrhosis, and the severity and frequency of AEs were not different with 24 weeks of therapy compared with 12 or 16 weeks.<sup>26</sup>

In October 2014, the FDA approved the combination of ledipasvir and sofosbuvir, the first all-oral combination treatment for HCV genotype 1 infection.<sup>27</sup> Studies suggest that this combination with or without ribavirin has the potential to cure most patients with HCV genotype 1 infection, irrespective of treatment history and including those with compensated cirrhosis.<sup>28</sup>

The combination of sofosbuvir and simeprevir in the management of HCV genotype 1 infection appears promising. In early November 2014, this combination therapy was approved by the FDA for treatment of patients with genotype 1 HCV infection.<sup>29</sup> Both simeprevir and sofosbuvir have demonstrated efficacy when utilized in combination regimens to treat adults with HCV infection and concomitant complications such as compensated liver disease, cirrhosis, human immunodeficiency virus (HIV) coinfection, and HCC. These agents achieve an SVR within 12 to 24 weeks of treatment in up to 95% of patients.<sup>29</sup> The COSMOS study enrolled patients with genotype 1 HCV infection who had previously failed PEG-IFN/ribavirin therapy or who were treatment-naïve, and randomly assigned them to treatment with simeprevir plus sofosbuvir with or without ribavirin for 12 or 24 weeks. Rates of SVR12 were high (>90%) with the combination of simeprevir and sofosbuvir at 12 weeks, with or without ribavirin. This trial also demonstrated that in patients previously treated with other agents, the combination of simeprevir and sofosbuvir achieved an SVR12 of at least 90%.<sup>23</sup> Treatment guidelines developed by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD/IDSA) in 2014 recommend the use of these agents in combination or with standard PEG-IFN and/or ribavirin for individualized management of HCV infection. Specific treatment recommendations depend on HCV genotype, previous treatment status, and disease sequelae, among other factors.<sup>30</sup>

A recent study evaluated the cost-effectiveness of sofosbuvir in combination with ribavirin versus a dual DAA combination with simeprevir. A decision-analytic Markov model was constructed to simulate the progression of a 50-year-old cohort of patients with HCV genotype 1 infection through natural history of disease and therapy with both of the treatment combinations, using a societal perspective over a lifetime horizon.<sup>31</sup>

Costs and quality-adjusted life-years (QALYs) associated with illness and treatments accumulated at the end of each stage (model year). The cost-effectiveness analysis accounted for drug costs, treatment-related medical care, re-treatment if an SVR was not achieved, and natural disease progression in the case of treatment failure. In the base case scenario, the dual DAA combination surpassed the combination of a DAA/ribavirin in the modeled 50-year cohort of both treatment-naïve and treatment-experienced patients, excluding those who had previously failed therapy with telaprevir or boceprevir. The dual oral combination of sofosbuvir and simeprevir resulted in lower costs and more QALYs compared with the DAA/ribavirin combination (\$165,336 and 14.69 QALYs vs \$243,586 and 14.45 QALYs, respectively). All-oral treatment dominated standard therapy in the base case analysis across a range of willingness-to-pay thresholds, producing an incremental cost-effectiveness ratio of \$44,514 per QALY. The model was sensitive to drug costs, rates of SVRs, treatment-related medical care, re-treatment for individuals who do not achieve SVR, and the natural history of continued HCV infection following the failure of retreatment. The all-oral regimen was demonstrated to be the most cost-effective for subjects with HCV genotype 1 infection; however, it was also cost-effective for genotypes 2 and 3 ( $\geq 80,000$ /QALY). These effects were maximized in younger treatment cohorts (<50 years of age).<sup>31</sup> The degree of cost-effectiveness varied according to willingness-to-pay threshold and the cost of drug combinations.<sup>31,32</sup>

The authors calculated cost savings per SVR. The combination therapy resulted in cost savings of \$91,590 per SVR compared with sofosbuvir and ribavirin in the base case analysis.<sup>31</sup>

Despite the paucity of direct comparison data with these new agents, it is clear that the changing treatment landscape for HCV infection brings with it effective strategies for virus eradication. Given the high up-front drug costs involved, it is critical that clinicians understand and distinguish between which treatments are most likely to result in positive outcomes for particular patient groups.

### ***Going for Goal: The Cost-effectiveness of Achieving SVR/Cure***

The goal of HCV infection management has focused on achieving an SVR, which indicates an undetectable viral load (ie, cure). Achievement of an SVR is associated with a greatly reduced risk of clinical outcomes related to

■ **Table.** Estimated Medication Cost for Treatment of Genotype 1 Chronic HCV Infection<sup>34,35</sup>

Regimen and Duration	Regimen Cost
Sofosbuvir + ribavirin + PEG-IFN for 12 weeks	\$97,000
Sofosbuvir for 12 weeks + PEG-IFN/ribavirin for 24 weeks	\$109,000
Sofosbuvir/ledipasvir for 12 weeks	\$94,500
Sofosbuvir + ribavirin for 24 weeks	\$169,000
Sofosbuvir + simeprevir ± ribavirin for 12 weeks	\$150,000
Simeprevir for 12 weeks + PEG-IFN/ribavirin for 24 weeks	\$79,000
Simeprevir for 12 weeks + PEG-IFN/ribavirin for 48 weeks	\$104,000

HCV indicates hepatitis C virus; PEG-IFN, pegylated interferon. Adapted from Spach DH, Kim HN. Hepatitis C online: treatment of HCV genotype 1. <http://www.hepatitisc.uw.edu/go/treatment-infection/treatment-genotype-1/core-concept/all>. Accessed October 24, 2014; and Gish RG. Treatment of chronic HCV genotype 1. [http://depts.washington.edu/hepstudy/presentations/uploads/118/m5\\_j1\\_treatment\\_of\\_gt1.pdf](http://depts.washington.edu/hepstudy/presentations/uploads/118/m5_j1_treatment_of_gt1.pdf). Accessed January 28, 2015.

liver disease, including cirrhosis, end-stage liver disease, HCC, and the need for liver transplantation. In addition, an SVR is associated with a decrease in all-cause mortality compared with a lack of SVR achievement.<sup>33</sup>

Unfortunately, the eradication of HCV infection comes with an extremely high price tag in terms of direct drug costs. The **Table**<sup>34,35</sup> illustrates the approximate costs of various regimens used to treat patients with HCV infection genotype 1 (cost estimates are based on wholesale acquisition cost data).

### Implications of New Drug Therapies on Managed Care

#### Current Status

Managed care payers and providers are currently in a “wait and see” position in terms of possessing all the information needed to distinguish between treatments for clinical efficacy and cost-effectiveness. Just a few months ago, patient “warehousing” (ie, holding off on HCV treatment) reached an all-time high. Prior to this, standard interferon-based therapies were considered the first-line treatment and were utilized across the board in treatment of patients with HCV infection. It is conceivable that this “wait and see” period will continue until payers and caregivers are comfortable with choosing the most clinically effective and cost-effective regimen for patients with consideration of individual status (eg, genotype, prior treatment status, extent of hepatic involvement).

According to study results published in late 2013, 90% of physicians are warehousing at least some of their patient caseload while waiting for more efficacious, tolerable therapies. Pharmaceutical companies are now in a race to release interferon-free treatments in addition to the newly available agents sofosbuvir and simeprevir.<sup>36</sup>

However, some evidence exists that this status is changing. Study results presented in October 2014 at the Academy of Managed Care Pharmacy’s (AMCP’s) Nexus meeting indicated that 90% of newly diagnosed patients begin treatment with a sofosbuvir-based regimen. In addition, 39% more patients began an HCV infection therapeutic regimen between December 2013 and May 2014 (n = 384) than between June 2013 and November 2013 (n = 276). This change in prescribing behavior, combined with a greater number of patients receiving treatment for HCV infection, has added substantial economic burden to overall pharmacy expenditure when drug costs alone are considered.<sup>37</sup>

Study results presented by Aggarwal et al at the same AMCP meeting evaluated the budget impact of new HCV infection treatments on US managed care in 5 states (Florida, Illinois, New York, Texas, and California). Of 426 coverage policies identified for the 4 treatments (telaprevir, boceprevir, sofosbuvir, and simeprevir), 69% were for telaprevir and boceprevir, and 31% were for sofosbuvir and simeprevir. They concluded that new HCV infection treatments such as sofosbuvir and simeprevir are associated with lower managed care access compared with older agents.<sup>38</sup> These differences likely represent the lack of availability of cost-effectiveness data for sofosbuvir and simeprevir in specific clinical situations.

#### Future Implications

The healthcare and cost implications of new and emerging HCV infection treatments are still not clearly delineated, but it is evident that the main questions to be answered encompass the following: (1) What type of patient will most likely benefit from early treatment versus late? (2) Which treatment is most efficacious for which patients? and (3) What is the balance between

## Reports

efficacy and cost-effectiveness in individual patients with HCV infection that will tip the scales in the direction of achieving the most positive outcomes with the least economic impact? Research is under way to answer these questions.

Available results are encouraging in that all-oral and interferon-free regimens will prove cost-effective if treatments are individualized based on patient/disease characteristics. Of note, HCV infection guidelines are constantly being updated to keep abreast with the ever-changing HCV infection treatment landscape and to identify the most appropriate treatments for individual patients.

The prioritization of patients who should receive early treatment for HCV infection is an important factor for consideration to appropriately balance the likelihood of optimal clinical outcomes and minimize risk for adverse treatment-related effects. However, guideline recommendations are new and not yet widely practiced. In August 2014, the AASLD and the IDSA prioritized which patients should be treated for HCV infection. They recommended that top treatment priority be given to patients at highest risk for severe complications, including those with fibrosis and stage 3 or 4 compensated cirrhosis and organ transplant recipients. Next in order of priority (labeled “high priority”) are 2 categories of patients: (1) those at high risk for complications (eg, those with stage 2 fibrosis or coinfection with HIV or hepatitis B); and (2) those with high HCV transmission risk (active injection drug users, incarcerated patients, and HIV-positive men with high-risk sexual practices).<sup>33</sup>

What is the rationale for treating patients at high risk for transmission? Recommendations by the AASLD and IDSA state: “Persons who have successfully achieved an SVR (virologic cure) no longer transmit the virus to others...successful treatment benefits public health.”<sup>33</sup> Virologic cure rates are 90% to 100% for HCV genotype 1 infection and are high for other genotypes as well.<sup>39</sup> The development of treatments is rapidly progressing, and shorter durations of therapy are becoming a reality. Therefore, stopping HCV before it spreads (ie, curing it early) is critical.

It is important to recognize that there are risks associated with waiting to treat HCV infection. Patients with cirrhosis and fibrosis risk progression of disease and decompensation, which are associated with other morbidities and can lead to less benefit when treatments are given at a later date. Patients with HCV-related symptoms and those with extrahepatic manifestations

such as renal disease may benefit more from early treatment. In addition, waiting to treat the infection may not be prudent in patients with risk factors associated with progression of fibrosis (eg, excessive alcohol consumption, steatosis, HIV coinfection, prolonged immunosuppression).<sup>40</sup>

HCV treatments are generally more cost-effective in patients at high risk of experiencing adverse outcomes such as liver-related complications.<sup>30</sup> For example, in a patient with advanced fibrosis and/or HIV infection, an SVR can prevent morbidity, mortality, and expenditures that would otherwise have been imminent. Other patients who should receive treatment include those at risk for accelerated fibrosis progression.<sup>30</sup> The potential risks associated with waiting to treat include progression of these complications, resulting in poor clinical outcomes and increased expenditures.

Which patients should not receive treatment for HCV infection? According to the AASLD/IDSA guidelines, patients with limited life expectancy (ie, less than 12 months) for non-liver related comorbid conditions would likely not benefit from treatment, and palliative care strategies should be the focus.<sup>30</sup>

Treatment adherence is critical to achieving positive outcomes such as an SVR. A retrospective Veterans Affairs-based study in 5706 patients with HCV infection reported that early virologic response increased with higher levels of adherence to interferon and ribavirin therapy.<sup>41</sup> Positive treatment outcomes are associated with adherence to therapy, which in turn is linked with reduced overall costs of care in patients with HCV infection.<sup>42</sup> In a recent study, pharmacy and medical claims data from approximately 40 managed healthcare plans and 50 million patients between 2002 and 2006 were searched for a diagnosis of HCV infection.<sup>42</sup> Patients were required to have a prescription claim for at least 1 HCV infection medication within 6 months prior to or any time after diagnosis. Treatment cost, prescribing patterns, and duration of treatment were assessed over the therapy period. Treatment adherence rates were lower for patients with more severe disease (50%, compared with 65% and 62% for those with mild or moderate disease, respectively). Patients who were adherent to treatment had greater total HCV-related costs compared with non-adherent patients (\$20,132 vs \$12,259;  $P < .01$ ); this was primarily due to higher pharmacy costs from stricter refill compliance by adherent patients. When pharmacy costs were excluded, total HCV-related costs were lower for adherent patients compared with nonadherent patients

(\$1370 vs \$2463;  $P < .01$ ). Inpatient costs were also higher for nonadherent patients (\$13,162 vs \$8733;  $P < .01$ ).<sup>42</sup>

A recent study assessed the development of an adherence monitoring and appropriateness of therapy program for patients prescribed sofosbuvir at a single healthcare center; this program involved clinical pharmacists, nurse care managers, dispensing pharmacists, and prescribers. Although only a few patients have entered the program thus far, the authors suggested that such a program is necessary to promote adherence and appropriateness of this high-cost treatment.<sup>43</sup>

Several treatment-related factors may lead patients to terminate therapy early, such as longer treatment durations, higher complexity regimens, and frequent or intolerable AEs.<sup>44</sup> The selection of a regimen with the best chance of virologic cure, along with provision of medication adherence monitoring and overall therapy management, is critical to treatment success.

Results from a study aimed to promote cost-effective regimens for the treatment of HCV infection via telephonic prescriber outreach were presented at the 2014 AMCP Nexus meeting. The goals of the telephonic prescriber program were to promote use of a cost-effective regimen through telephonic prescriber outreach on prior authorization requests, monitor patient adherence to treatment using pharmacy claims data, and identify patients achieving virologic cure by conducting prescriber outreach. A total of 396 patients were included in the program at that time; 113 prescribers of these patients were contacted to discuss alternative regimens. Of these, 27 regimens were approved, leading to an estimated cost avoidance of \$569,000 to \$1,200,000. In addition, 105 prescribers were contacted for 181 members who were past due or nearly due for a medication refill. The authors concluded that telephonic interventions may assist prescribers in the management of patients who are potentially nonadherent to a prescribed drug regimen.<sup>45</sup>

Russell and colleagues<sup>46</sup> reported on the implementation of a center of excellence model for the management of HCV infection utilizing a multidisciplinary healthcare team including pharmacists, physicians, and nurses. They noted that appropriate patients are receiving necessary treatment and care from this team approach, thereby improving correct utilization of HCV infection medications. Importantly, the authors reported that the program included strong clinical experts with a history of producing superior patient outcomes and alignment of benchmark measurement criteria with policy criteria.<sup>46</sup>

### The Future Direction of HCV Infection and Managed Care

The appropriate management of HCV infection is complex and depends heavily on clear communication and collaboration between patients and members of the healthcare team to minimize adverse treatment effects, prevent drug-drug interactions, and ensure treatment adherence. New treatment options with novel mechanisms of action that have been approved by the FDA over the last few years represent groundbreaking opportunities that were historically unavailable to eradicate HCV in many patients with chronic infection. Emerging drugs offer even more choices to optimize treatment outcomes.

On October 10, 2014, the combination of ledipasvir and sofosbuvir, the first all-oral combination treatment for HCV genotype 1 infection, was approved by the FDA.<sup>47</sup> Within days of this approval, Bristol-Myers Squibb announced it would no longer pursue approval for its combination of asunaprevir (an NS3/4A protease inhibitor) and daclatasvir for the treatment of HCV genotype 1b infection, citing the rapidly evolving treatment landscape for HCV treatment in the United States.<sup>47</sup>

Abbvie's fixed-dose "3D" combination of the protease inhibitor paritaprevir and ritonavir (ABT-450/r) coformulated with the NS5A inhibitor ombitasvir (ABT-267) and the non-nucleoside polymerase inhibitor dasabuvir (ABT-333) was approved by the FDA in December 2014 for treatment of HCV genotype 1 infection. This direct-acting 3D combination therapy demonstrated SVR12 rates of 98.7% and 99.3% with and without ribavirin, respectively.<sup>48,49</sup>

Of note, pricing wars between companies supplying recently approved all-oral HCV infection treatments may prove beneficial for payers and patients, as these competitions are beginning to drive drug prices down. This has resulted in the ability of drug providers to secure discounts that may make treatments accessible for more patients with HCV infection. Outside of the HCV infection treatment landscape, such competitions may result in discussions about drug pricing earlier in the development process, and more detailed evaluations of patients who are likely to benefit most from treatment.<sup>50</sup>

Several agents are in late-phase studies and are likely to be available in 2015. The combination of daclatasvir and sofosbuvir demonstrated SVR12 rates of 90% and 86% in treatment-naïve and treatment-experienced patients with genotype 3 infection, according to ALLY-3, a phase 3 open-label trial ( $n = 152$ ). These results are promising for treatment of genotype 3, which has become

## Reports

one of the most difficult HCV genotypes to treat and the second-most common genotype worldwide. Results from ALLY-3 indicate the possibility of eradicating HCV genotype 3 infection using an all-oral regimen administered for 12 weeks.<sup>51</sup>

Other emerging HCV infection medications include grazoprevir (MK-5172), elbasvir (MK-8742), and sofosbuvir in combination with the NS5A inhibitor GS-5816 and ribavirin.<sup>52</sup>

Achieving an SVR should be the ultimate treatment goal for patients with HCV infection, particularly for those who are at high risk for reinfection or may further spread the virus. As Bruce Bacon, MD, of Saint Louis University noted in an expert interview (May 25, 2014), “While costs are higher with newer DAAs, one must consider the fact that achieving cure more quickly with these drugs essentially removes the patient from the HCV healthcare system and its associated expenses, potentially saving significant costs in the long run.” Now that all-oral treatment regimens for HCV infection have become the standard of care, the balance between high drug costs and improvements in clinical outcomes—including eradication of the HCV—must be considered. Individualized, targeted treatment plans based on HCV subtype, patient characteristics, and drug safety profiles are the key to optimizing outcomes with the minimum expense.

**Author affiliation:** Gary Owens Associates, Ocean View, DE.

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**Address correspondence to:** gowens99@comcast.net.

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