Real-World Drug Costs of Treating Hepatitis C Genotypes 1-4 with Direct-Acting Antivirals: Initiating Treatment at Fibrosis 0-2 and 3-4

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ABSTRACT

BACKGROUND: Direct-acting antivirals (DAA) for the treatment of hepatitis C virus (HCV) have drastically improved outcomes but are also very costly. For this reason, priority for treatment is often given to patients with a higher fibrosis score at baseline by payers and providers rather than treating all eligible patients. Simulation studies have suggested that waiting to treat patients until fibrosis 3-4 may be more costly and result in worse outcomes; however, real-world implications are unknown.

OBJECTIVE: To determine drug costs and outcomes for treating hepatitis C in patients with fibrosis scores of 0-2 and 3-4 at baseline in a real-world ambulatory care setting.

METHODS: A total of 322 patients at 36 clinical sites in Massachusetts with HCV genotype 1-4 and a prescription for at least 1 DAA medication between May 2011 and October 2015 were included. Retrospective and prospective chart reviews were completed by the primary investigator. Data were collected through April 2016. The primary outcome for the study was to determine the mean drug cost per sustained virologic response (SVR) achieved for patients with fibrosis scores of 0-2 and 3-4. Drug costs were calculated using average wholesale price and only included the cost of HCV medications, not for adjunctive medications, blood work, hospitalizations, anticipated complications, or any other projected medical costs.

RESULTS: The mean $\pm$ SD (median) drug cost per patient was \$130,391 $\pm$ 46,787 (113,400) and completed treatment duration was 15.0 $\pm$ 8.9 (12) weeks. The mean drug cost per SVR was \$155,662 for all patients with a mean drug cost per SVR of \$122,452 and \$178,401 for patients with fibrosis scores of 0-2 and 3-4, respectively. SVR rates were 83.5% (269/322) for all patients and 92.2% (107/116) and 78.6% (162/206) for patients with fibrosis scores of 0-2 and 3-4, respectively. Ledipasvir/sofosbuvir; sofosbuvir + ribavirin; ledipasvir/sofosbuvir + ribavirin; sofosbuvir + interferon + ribavirin; boceprevir + interferon + ribavirin; sofosbuvir + simeprevir; and telaprevir + interferon + ribavirin had a mean drug cost per SVR of \$123,559; \$153,347; \$157,969; \$184,800; \$248,640; \$251,550; and \$373,333; respectively.

CONCLUSIONS: Real-world knowledge about outcomes and drug costs may influence future decisions. Further studies are needed to evaluate emerging treatment options and to reflect changes in treatment guidelines.

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- Direct-acting antivirals (DAAs) have drastically improved sustained virologic response (SVR) rates, tolerability, and shortened treatment durations for HCV compared with older treatment options.
- It has been estimated that payers would need \$136 billion to cover medication costs for all eligible patients with HCV from 2015-2020, of which \$61 billion would need to be paid by the government; for this reason, some payers restrict access to DAA medications to patients with a fibrosis score of 3-4.

What this study adds

- This study shows that nearly \$42 million were spent on 322 treatments, resulting in an average cost of \$130,391 per patient; 269 SVRs were achieved for a mean drug cost per SVR of \$155,662.
- The total cost spent on treatments, mean drug cost per patient, and mean drug cost per SVR were all higher for patients with a fibrosis score of 3-4 versus a fibrosis score of 0-2, which is likely because of longer treatment durations, lower SVR rates, and more total treatments with this population.
- Mean completed treatment durations were longer for patients with a fibrosis score of 3-4 versus a fibrosis score of 0-2 for all treatment regimens.

Current estimates indicate that nearly 4 million persons in the United States are chronically infected with hepatitis C virus (HCV) as of 2013. Untreated HCV can lead to cirrhosis, end-stage liver disease, and hepatocellular carcinoma and is the leading cause of liver transplantations in the United States.¹ A major predictor of serious complications from HCV is a fibrosis score of F3 or F4 before treatment, a score used to indicate the amount of scarring in the liver.² Successful treatment of HCV has been shown to prevent these complications in addition to reducing mortality and health care costs and improving quality of life.³⁻⁵

New treatments called direct-acting antivirals (DAAs) came to the market in 2011 and have since improved outcomes considerably by increasing sustained virologic response (SVR) rates, shortening duration of treatment, and improving tolerability compared with older interferon (IFN) regimens. In clinical trials, cure rates exceeded 90% for many patient populations.⁶⁻¹⁷ Approval of new therapies has spurred frequent revisions to the HCV treatment guidelines authored in collaboration by the American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the International Antiviral Society-USA.¹⁸

What is already known about this subject

- Nearly 4 million persons in the United States are estimated to be chronically infected with hepatitis C virus (HCV), a slow-progressing infection that can lead to cirrhosis, hepatocellular carcinoma, end-stage liver disease, and death over the course of decades.

Ultimately, the percentage of eligible patients who receive DAA treatment for HCV remains low. In addition to many patients being unaware of their HCV status, lack of knowledge about HCV, social stigma regarding this infection, and medical ineligibility, as well as patient, provider, and medical barriers, contribute to the lack of treatments in the United States.¹⁹⁻²¹ The overwhelming cost of these medications has a significant impact on the health care system. It has been estimated that payers would need \$136 billion to cover medication costs for all eligible patients with HCV from 2015-2020, of which \$61 billion would need to be paid by the government.²² As a result, some payers are restricting access to only those patients in more advanced stages of disease, in some cases requiring fibrosis scores of F3 or F4 before covering a DAA medication, and preference is given by many providers to treat patients with more advanced fibrosis.^{23,24}

Previous simulation studies in various populations have proposed that treating patients with DAA regimens early in the course of infection, regardless of fibrosis staging may be more cost-effective than restricting access to patients with later fibrosis staging.²⁵⁻²⁹ However, these studies use simulations and projected medical costs rather than estimated actual costs. Real-world drug cost implications of restricting treatment to patients in later stages of infection is unknown. The objective of this study was to describe the drug cost implications and outcomes of treating HCV genotypes 1-4 with DAAs early in the course of infection versus late in the course of infection in a large multisite ambulatory care setting.

Methods

This study was a retrospective and prospective chart review of patients treated at 36 clinical sites in the state of Massachusetts. Before retrieval of data, the study protocol was approved by the MCPHS University Institutional Review Board. Eligible patients had at least 1 encounter at Atrius Health documented in the electronic medical record (EMR); had a diagnosis of HCV genotype 1, 2, 3, 4, or a mix of these genotypes; and had a prescription for at least 1 of the study medications between May 2011 and October 2015. Atrius Health is a nonprofit alliance of community-based medical groups that provides primary and specialty care to 675,000 adult and pediatric patients across more than 20 site locations in eastern and central Massachusetts. Atrius Health has 29 medical practices, with more than 50 specialties and 725 physicians.

Study medications included telaprevir (TEL), boceprevir (BOC), simeprevir (SIM), sofosbuvir (SOF), ledipasvir/sofosbuvir (LED/SOF), and ombitasvir/paritaprevir/ritonavir/dasabuvir (referred to as the 3D regimen). Study medications may have been used in combination or with ribavirin (RBV) and/or IFN. Participants were excluded from the study if they had a diagnosis of HCV genotype 5 or 6, did not have a documented fibrosis score in the EMR, did not have relevant

accessible medical records from an outside facility, did not receive a dose of the study medication (e.g., insurance rejected the claim), or did not have a documented HCV-ribonucleic acid (RNA) at least 12 weeks after completion of therapy in order to test for SVR by the end of data collection.

The primary outcome for the study was to determine the mean drug cost per SVR achieved for patients with a fibrosis score of 0-2 and of 3-4. Secondary outcomes included determining the mean drug cost per SVR achieved for each treatment regimen, determining SVR rates for each treatment regimen, determining SVR rates for patients with fibrosis scores of 0-2 and 3-4, determining the mean duration of treatment for each treatment regimen, and determining the mean duration of treatment for patients with fibrosis scores of 0-2 and 3-4.

A predetermined sample size of 300 patients was identified based on the anticipated number of patients that would meet inclusion criteria at Atrius Health and was determined adequate for reflecting the local drug cost impact of DAA medications in the given time frame. Eligible patients were identified through the use of the institution's EMR, as well as claims data for accessible payers. If a patient had more than 1 treatment course with a study medication, each treatment course was documented and reflected as a unique patient in the data. For example, a patient may have received treatment with TEL triple therapy in 2011 and then SOF + RBV in 2014. These treatment courses would be reflected as 2 unique patients and regimens in the data. An in-depth chart review was conducted by the primary investigator to obtain the following: patient age, gender, race/ethnicity, body mass index (BMI), past history of treatment, HCV genotype, most recent fibrosis score before initiation of treatment, human immunodeficiency virus (HIV) history, current HCV treatment regimen, treatment duration, and presence or lack of SVR at least 12 weeks after treatment. Data were collected through April 2016. All statistical analyses, including means, standard deviations, medians, percentages, and cost analyses were conducted by the primary investigator using Microsoft Excel 2010 (Microsoft, Redmond, WA).

If a patient had more than 1 fibrosis score or liver biopsy, results from the most relevant test (most recent before the time of treatment) were recorded. Fibrosis scores were documented according to the following: a fibrosis score of F0 was recorded as 0; scores of F1, F0/F1, or F1[F1-2] were recorded as 1; scores of F2, F1/F2, F2[F1-2], F2[F2-F3], or F2[F1-F3] were recorded as 2; scores of F3, F2/F3, F3[F2-4], or F3[F3-4] were recorded as 3; and scores of F4, F3/F4, liver biopsy consistent with cirrhosis, or diagnosis of cirrhosis in the EMR were recorded as 4. An algorithm was developed because results were reported differently depending on the specific test used (some tests reported ranges; some reported a probable fibrosis score; and some reported both). If there was only a range of numbers, the algorithm used the highest number in the range (e.g., F2/3 = 3). If there is a range with a probable fibrosis score, the probable

FIGURE 1 Study Cohort

BOC=boceprevir; DAS=dasabuvir; HCV=hepatitis C virus; IFN=interferon; LED=ledipasvir; OMB=ombitasvir; PAR=paritaprevir; RBV=ribavirin; RNA=ribonucleic acid; SIM=simeprevir; RIT=ritonavir; SOF=sofosbuvir; TEL=telaprevir.

fibrosis score (e.g., F2[F2-3]=2) was used. The format F2[F2-3] means that a fibrosis score of 2 is probable; however, it could also be a fibrosis score of 3.

Patients included in the study may have been treated in correspondence with other local institutions. SVR was defined as an undetectable HCV-RNA at least 12 weeks after therapy completion. SVR at 12 weeks is currently used for approval of new treatments. Previous trials used 24 weeks as a marker for SVR; however, 12 weeks has been shown to be an adequate predictor of treatment success with a positive predictive value of 98% and has been more commonly used in recent trials.³⁰ HCV-RNA tests were able to detect viruses with an HCV-RNA of at least 15 IU/mL. Any relapse at least 12 weeks after therapy completion was considered a treatment failure, unless there was proven documentation of reinfection.

Because of the time frame of data collection, as well as frequent delays in starting treatment due to prior authorizations and appeals, a number of patients had not completed their full course of treatments or were pending blood work at the completion of data collection (Figure 1). Additionally, many patients were treated at outside institutions, and blood work was not always accessible in a timely manner. For these reasons, it was determined not to use an intent-to-treat analysis, since this would have underestimated SVR rates in the present study.

All cost analyses were performed using average wholesale price (AWP). Mean drug cost per SVR was calculated using the total cost of study medication (including IFN and RBV) in the numerator accounting for duration of treatment and the total number of SVRs achieved with that regimen in the denominator. Duration of completed treatment was estimated based on the chart review and accounted for early discontinuation of treatment due to adverse drug reactions (ADRs), poor response, or any other reason. If a patient discontinued treatment early for any reason, the duration the patient actually received was used for the cost (but was rounded up to the nearest 4 weeks, since mail-order pharmacies typically send 4 weeks of medication at a time). For example, if a patient stopped treatment at 10 weeks, the cost analysis used 12 weeks because this is most likely the amount paid for by the health care system. If the date of early discontinuation was unknown, 12 weeks was used for early discontinuation because of ADRs with BOC or TEL triple therapy, and 24 weeks was used for early discontinuation because of poor response with BOC or TEL triple therapy. These estimates were based on observations from other treatments, as well as on treatment protocols. Cost analyses only included drug costs for HCV medications and did not take into account cost of adjunctive medications, costs of switching DAA regimens, hospital visits, blood work, complications, or any other medical cost.

Results

A total of 446 patients were assessed for eligibility, with 124 patients excluded. The most common reasons for exclusion included unknown fibrosis score according to the EMR, inability to access relevant records, patient never receiving treatment with a study medication, and HCV-RNA unavailable at the time of data analysis (Figure 1). Some patients were treated at outside institutions, so not all relevant records were accessible for review, and patients were excluded accordingly. Some patients received valid prescriptions, but claims were rejected by their insurance, and they never received treatment. Some patients were pending blood work at the termination of data collection and were excluded accordingly. A total of 322 patients met inclusion into the study. The majority of patients in this study were older, white males with genotype 1 infection. The mean age was around 60 years, and the mean BMI was 29 kg/m². About half of the total population was treatment naïve and half was treatment experienced (Table 1).

During the study, 5 of 322 (1.6%) patients reported missing doses of their study medications. Reasons given for these missed doses included forgetting a dose, not taking the medication because of a stomach bug, delay in shipment of the medication because of insurance issues, and losing a tablet. Of these patients, 5 of 5 (100%) achieved SVR.

SVR rates with 3D and LED/SOF were 100% (2/2) and 97.0% (160/165), respectively. The SVR rate with SOF+RBV was

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TABLE 1 Patient Characteristics

Characteristic	Total N=322	Fibrosis 0-2 n=116	Fibrosis 3-4 n=206
Age, years±SD	59.9±10.6	56.4±10.6	61.8±10.5
Age, n (%)			
<45 years	26 (8.1)	18 (15.5)	8 (3.9)
45-54 years	36 (11.2)	18 (15.5)	18 (8.7)
55-65 years	180 (55.9)	64 (55.2)	116 (56.3)
>65 years	80 (24.8)	16 (13.8)	64 (31.1)
Born between 1945 and 1965, n (%)	264 (82.0)	88 (75.9)	176 (85.4)
Race or ethnic group, n (%)			
White	208 (64.6)	78 (67.2)	130 (63.1)
Black or African American	75 (23.3)	22 (19.0)	53 (25.7)
Hispanic or Latino	18 (5.6)	6 (5.2)	12 (5.8)
Asian	7 (2.2)	4 (3.4)	3 (1.5)
Unknown or other	14 (4.3)	6 (5.2)	8 (3.9)
Male sex, n (%)	224 (69.6)	65 (56.0)	159 (77.2)
BMI (kg/m ²)±SD	29.0±7.0	28.1±7.0	29.5±7.1
Fibrosis score, n (%) ^a			
0	13 (4.0)	13 (11.2)	–
1	36 (11.2)	36 (31.0)	–
2	67 (20.8)	67 (57.8)	–
3	59 (18.3)	–	59 (28.6)
4	147 (45.7)	–	147 (71.4)
HIV coinfection, n (%)	17 (5.3)	2 (1.7)	15 (7.3)
Treatment history, n (%)			
Naïve	164 (50.9)	78 (67.2)	86 (41.7)
Experienced	158 (49.1)	38 (32.8)	120 (58.3)
Genotype, n (%)			
1	275 (85.4)	93 (80.2)	182 (88.3)
2	25 (7.8)	13 (11.2)	12 (5.8)
3	13 (4.0)	6 (5.2)	7 (3.4)
4	6 (1.9)	4 (3.4)	2 (1.0)
Mixed 1/2	3 (<1.0)	–	3 (1.5)

^aFibrosis score of F0 was recorded as 0; F1, F0/F1, or F1[F1-2] was recorded as 1; F2, F1/F2, F2[F1-2], F2[F2-F3], or F2[F1-F3] was recorded as 2; F3, F2/F3, F3[F2-4], or F3[F3-4] was recorded as 3; and F4, F3/F4, or liver biopsy consistent with cirrhosis or diagnosis of cirrhosis in the EMR was recorded as 4.

BMI=body mass index; EMR=electronic medical record; HIV=human immunodeficiency virus; kg=kilogram; m=meter; SD=standard deviation.

92.3% (36/39); LED/SOF+RBV was 85% (17/20); SOF+SIM was 73.7% (28/38); SOF+IFN+RBV was 73.7% (14/19); 3D+RBV was 50% (1/2); TEL+IFN+RBV was 31.0% (9/29); and BOC+IFN+RBV was 25% (2/8; Table 2). The overall sample sizes for 3D, 3D+RBV, and BOC+IFN+RBV were small, and results should be interpreted accordingly. The overall SVR rate was 83.5% (269/322) for all patients and 92.2% (107/116) and 78.6% (162/206) for patients with fibrosis scores of 0-2 and 3-4, respectively. The overall SVR rate was 90.5% (258/285) for all patients and 98.1% (102/104) and 86.2% (156/181) for patients with fibrosis scores of 0-2 and 3-4, respectively, when BOC and TEL regimens were excluded.

TABLE 2 SVR Rates

Drugs	Total, N=322 n (%)	Fibrosis 0-2, n=116 n (%)	Fibrosis 3-4, n=206 n (%)
3D	2/2 (100.0)	1/1 (100.0)	1/1 (100.0)
LED/SOF	160/165 (97.0)	64/65 (98.5)	96/100 (96.0)
SOF+RBV	36/39 (92.3)	19/19 (100.0)	17/20 (85.0)
LED/SOF+RBV	17/20 (85.0)	3/3 (100.0)	14/17 (82.4)
SOF+SIM	28/38 (73.7)	8/8 (100.0)	20/30 (66.7)
SOF+IFN+RBV	14/19 (73.7)	6/7 (85.7)	8/12 (66.7)
3D+RBV	1/2 (50.0)	1/1 (100.0)	0/1 (0)
TEL+IFN+RBV	9/29 (31.0)	5/9 (55.6)	4/20 (20.0)
BOC+IFN+RBV	2/8 (25.0)	0/3 (0)	2/5 (40.0)
Total	269/322 (83.5)	107/116 (92.2)	162/206 (78.6)
Total excluding BOC and TEL regimens	258/285 (90.5)	102/104 (98.1)	156/181(86.2)

3D=ombitasvir/paritaprevir/ritonavir/dasabuvir; BOC=boceprevir; IFN=interferon; LED=ledipasvir; RBV=ribavirin; SI=simeprevir; SOF=sofosbuvir; SVR=sustained virologic response; TEL=telaprevir.

The mean duration±standard deviation of treatment was 15.0±8.9 weeks for all patients and 13.1±8.8 weeks and 16.1±8.9 weeks for patients with fibrosis scores of 0-2 and 3-4, respectively. The mean duration of treatment was 13.3±6.7 weeks for all patients and 11.8±6.6 weeks and 14.1±6.6 weeks for patients with fibrosis scores of 0-2 and 3-4, respectively, when BOC and TEL regimens were excluded. The overall median duration of treatment was 12 weeks, which was consistent with the median duration for all treatment regimens except first generation protease inhibitor regimens.

An estimated total of \$41,873,160 was spent on 322 regimens for a mean estimated cost of \$130,391±46,787 per regimen. Total mean drug cost per SVR was \$155,662 for all patients with a mean drug cost per SVR of \$122,452 and \$178,401 for patients with fibrosis scores of 0-2 and 3-4, respectively. When BOC and TEL regimens were excluded, the total mean drug cost per SVR was \$147,348 for all patients, with a mean drug cost per SVR of \$116,579 and \$167,467 for patients with fibrosis scores of 0-2 and 3-4, respectively. Mean drug cost per SVR with LED/SOF was \$123,559; SOF+RBV was \$153,347; LED/SOF+RBV was \$157,969; SOF+IFN+RBV was \$184,800; BOC+IFN+RBV was \$248,640; SOF+SIM was \$251,550; and TEL+IFN+RBV was \$373,333 (Table 3). Because of the lack of 3D and 3D+RBV regimens, an adequate cost analysis could not be performed.

Discussion

Over 80% of patients in this study were born between 1945 and 1965, which is possibly a result of implementation of CDC recommendations to screen any individual born in this time period.¹ The majority of patients had a fibrosis score

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TABLE 3 Drug Cost Analysis

Drugs	Number of Patients Treated	Mean Drug Cost per Patient $\pm$ SD (Median)	Total Mean Drug Cost per SVR (Total Drug Cost/Number of SVRs Achieved)	Number of Patients Treated with Fibrosis Score 0, 1, 2	Mean Drug Cost per SVR (Total Drug Cost/Number of SVRs Achieved) for Fibrosis Score 0, 1, 2	Number of Patients Treated with Fibrosis Score 3, 4	Mean Drug Cost per SVR (Total Drug Cost/Number of SVRs Achieved) for Fibrosis Score 3, 4
LED/SOF	165	119,815 $\pm$ 43,706 (113,400)	123,559 (19,769,400/160)	65	100,997 (6,463,800/64)	100	138,600 (13,305,600/96)
SOF + RBV	39	141,106 $\pm$ 49,130 (104,160)	153,347 (5,520,480/36)	19	137,053 (2,604,000/19)	20	171,558 (2,916,480/17)
LED/SOF + RBV	20	134,274 $\pm$ 42,775 (116,760)	157,969 (2,685,480/17)	3	137,200 (350,280/3)	17	220,500 (2,335,200/14)
SOF + IFN + RBV	19	136,168 $\pm$ 44,057 (117,600)	184,800 (2,587,200/14)	7	116,760 (823,200/6)	12	166,800 (1,764,000/8)
SOF + SIM	38	185,353 $\pm$ 29,297 (180,600)	251,550 (7,043,400/28)	8	180,600 (1,444,800/8)	30	279,930 (5,598,600/20)
BOC + IFN + RBV	8	62,160 $\pm$ 21,533 (57,960)	248,640 (497,280/2)	3	N/A ^a (140,280/0)	5	178,500 (357,000/2)
TEL + IFN + RBV	29	120,352 $\pm$ 19,836 (113,400)	373,333 (3,360,000/9)	9	188,160 (1,071,000/5)	20	604,800 (2,419,200/4)
Total ^b	322	130,391 $\pm$ 46,787 (113,400)	155,662 (41,873,160/269)	116	122,452 (13,102,320/107)	206	178,401 (28,901,040)
Total excluding TEL and BOC regimens^b	285	133,328 $\pm$ 45,930 (113,400)	147,348 (38,015,880/258)	104	116,579 (11,891,040/102)	181	167,467 (26,124,840/156)
Total excluding all 24-week regimens ^b	281	116,540 $\pm$ 30,266 (113,400)	140,985 (32,426,520/230)	109	116,256 (11,625,600/100)	172	161,009 (20,931,120/130)
Total excluding all 24-week regimens and TEL and BOC regimens ^b	244	117,870 $\pm$ 46,787 (113,400)	130,453 (28,569,240/219)	97	109,624 (10,414,320/95)	147	146,411 (18,154,920/124)

Note: All costs are in U.S. dollars and are calculated using average wholesale price. Cost analyses only include cost of HCV medications, not adjunctive medications, hospital costs, or projected medical costs.

^aNo patients achieved SVR with BOC + IFN + RBV with fibrosis score 0-2, so a mean drug cost per SVR could not be calculated.

^b3D and 3D + RBV are included in the totals, but only 2 patients were treated with each regimen (4 total), so an individual cost analysis for these regimens was not completed.

3D = ombitasvir/paritaprevir/ritonavir/dasabuvir; BOC = boceprevir; HCV = hepatitis C virus; IFN = interferon; LED = ledipasvir; N/A = not available; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; SD = standard deviation; TEL = telaprevir.

of 3-4, accounting for over 60% of treatments, which likely reflects payer restrictions and provider preference to treat this population with higher priority. Patients with a fibrosis score of 3-4 were older, had a higher mean BMI, were more likely to be coinfecting with HIV, more likely to be genotype 1, more likely to be male, and more likely to be treatment experienced compared with patients who had fibrosis scores of 0-2. Differences in patient characteristics may have affected SVR rates. Increased age and HIV coinfection have been shown to be independent risk factors for progression of fibrosis in intravenous drug users in previous studies, which possibly explains the distribution seen in this study.^{31,32} Among patients with HIV coinfection, 100% (17/17) successfully achieved SVR; therefore, HIV coinfection did not appear to affect SVR rates in this study, regardless of fibrosis score.

In this study, only 5 (1.6%) patients reported missing doses of their study medication or taking the medication incorrectly. Although adherence was addressed and strongly encouraged

during many follow-up visits and phone encounters, this number is likely an underestimation of the actual number of patients who missed their medication doses. This study was observational with multiple sites; therefore, there was no set protocol in place to assess for adherence during every encounter. It is unlikely that adherence was addressed and reported for every patient included in the study, and the actual reporting of nonadherence is underestimated. Other methods for assessing adherence were considered and are addressed in the Limitations section.

For patients with a fibrosis score of 0-2, LED/SOF had the shortest treatment duration of 10.5 (SD $\pm$ 6.6) weeks, likely because of the use of 8-week regimens in qualifying patients (Table 4). Criteria for LED/SOF 8-week treatment is genotype 1 treatment-naïve, baseline HCV-RNA level of less than 6 million IU/mL, without compensated cirrhosis.

Because of low SVR rates and longer duration of treatment (with an average completed duration of 28.3 weeks), BOC and TEL regimens had a relatively high drug cost per SVR at

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TABLE 4 Mean±SD (Median) Completed Treatment Duration

Drugs	Total N=322 Weeks	Fibrosis Score 0, 1, 2 n=116 Weeks	Fibrosis Score 3, 4 n=206 Weeks
LED/SOF	12.7±6.7 (12)	10.5±6.6 (12)	14.1±6.6 (12)
SOF+RBV	16.3±5.8 (12)	15.8±6.1 (12)	16.7±4.8 (12)
LED/SOF+RBV	14.1±6.0 (12)	12.0±0 (12)	14.1±6.0 (12)
SOF+SIM	12.3±2.6 (12)	12.0±0 (12)	12.4±5.8 (12)
SOF+IFN+RBV	13.9±5.8 (12)	12.0±0 (12)	15.0±5.8 (12)
TEL+IFN+RBV	29.0±8.6 (24)	28.0±8.6 (24)	29.4±8.4 (24)
BOC+IFN+RBV	27.0±8.9 (24)	16.0±3.7 (12)	33.6±8.9 (36)
Total ^a	15.0±8.9 (12)	13.1±8.8 (12)	16.1±8.9 (12)
Total excluding TEL and BOC regimens^a	13.3±6.7 (12)	11.8±6.6 (12)	14.1±6.6 (12)

^aTwo 12-week 3D regimens and two 12-week 3D+RBV regimens are included in the totals. Because of the small number of treatments, these regimens were not included as individual rows in the chart.

BOC=boceprevir; IFN=interferon; LED=ledipasvir; RBV=ribavirin; SIM=simeprevir; SOF=sofosbuvir; SD=standard deviation; TEL=telaprevir.

\$248,640 and \$373,333, respectively, compared with other regimens. Sethi et al. (2015) demonstrated a mean cost per SVR of \$172,889 for all patients and a mean cost per SVR of \$266,670 for patients with cirrhosis when treated with first-generation protease inhibitors.³³ Patients in the study had an SVR of 48.5%, and hospital costs were included in addition to drug costs.³³ Bichoupan et al. (2014) found a median cost per SVR of \$189,338 for patients treated with TEL triple therapy, with an overall SVR rate of 44%.³⁴ The Bichoupan et al. study also took into account the cost of lab tests, professional fees, and ADR management; however, these costs accounted for less than 6% of total costs.³⁴ The cost analysis in the present study did not account for hospital costs, lab tests, ADR management (including erythropoiesis-stimulating agents or blood transfusion), or cost of additional office visits/phone encounters and underestimates the total cost per SVR; inclusion of these incremental costs would result in slight increases in total cost per SVR. This study used AWP to determine drug costs, while Sethi et al. used wholesale acquisition cost, and Bichoupan et al. used data from Medicare reimbursement databases, RED BOOK, and the Healthcare Cost and Utilization Project database.^{33,34} Differences in medication costs used also accounts for the differences with this study and previous cost analysis studies.

LED/SOF had the lowest mean drug cost per SVR at \$123,559, primarily because of higher SVR rates and shorter duration of treatment, compared with other regimens. The overall SVR rate for LED/SOF regimens was 97.0%. This SVR rate included all patient groups, including treatment-naïve and experienced patients and those with and without cirrhosis and HIV coinfection. The SVR rate with LED/SOF was higher for patients with a fibrosis score of 0-2 at 98.5% than for patients

with a fibrosis score of 3-4 at 96.0%. The SVR rate found in this study is similar to that found in clinical trials, which ranges from 94%-99%, depending on duration of treatment and patient population.⁶⁻⁸ Among genotype 1 treatment-naïve patients treated in this study with LED/SOF 8-week regimens, the SVR rate was 100% (32/32), with a mean drug cost per SVR of \$75,600. Among patients treated for 12 weeks, the SVR rate was 94.4% (34/36), with a mean drug cost per SVR of \$120,071. Although this study had a smaller sample size than other clinical trials, the results suggest that using 8 weeks of LED/SOF for appropriate genotype 1 treatment-naïve patients without cirrhosis may be a viable option and may result in lower drug costs than 12-week regimens.

A previous simulation study in genotype 1 treatment-naïve patients concluded that treating patients earlier in the course of infection resulted in better outcomes and was more cost-effective than waiting, but this course of action also increased the total number of health care dollars spent.¹² Younossi et al. (2015) used a hybrid decision-tree and Markov state-transition model and found that initiating treatment in patients at earlier stages of fibrosis reduced mean cost per SVR and long-term costs for genotype 1 patients.³⁵ Their model also demonstrated that LED/SOF was more cost-effective than all comparator treatments.³⁵ The present study aimed to determine the mean drug cost per SVR for treating patients at fibrosis scores of 0-2 and 3-4 in patients with genotypes 1-4. The mean drug cost per SVR was 30% lower for patients with a fibrosis score of 0-2 versus 3-4, which was maintained with the exclusion of BOC and TEL regimens. This cost difference resulted primarily from a lower SVR rate for patients with a fibrosis score of 3-4 and longer duration of treatment for patients with cirrhosis. The mean drug cost per SVR for patients with a fibrosis score of 0-2 was lower for all treatments regimens, indicating that this cost difference is not the result of poor outcomes or overuse of one particular regimen.

In the past, 24-week regimens were used more for patients with cirrhosis than they are currently and contributed significantly to the higher cost for treating these patients. A 24-week regimen costs twice that of a 12-week regimen and 3 times as much as an 8-week regimen and can quickly raise overall drug costs, regardless of effectiveness. A decrease in the use of 24-week regimens after 2015 can be seen in the prescribing patterns of this study, which is consistent with guideline changes that were made to allow the option for shorter treatment regimens. A separate cost analysis was completed, which excluded all 24-week regimens in order to determine the effect on cost. After removing all 24-week regimens, the mean drug cost per SVR for patients with a fibrosis score of 0-2 was \$116,256; \$161,009 for patients with a fibrosis score of 3-4; and \$109,624 and \$146,411 when BOC and TEL regimens were excluded. With the removal of all 24-week regimens, this represented a 25% cost difference between patients with

fibrosis scores of 0-2 and 3-4. Some 24-week regimens are still recommended by guidelines; therefore, this additional cost analysis is not fully reflective of best practice and is only used as a demonstration. This analysis does not account for health care costs for hepatocellular carcinoma; liver transplantations; decompensated cirrhosis; or procedures, additional lab work, and additional office visits that may be avoided by treating patients earlier in the course of infection.

Results from this study will help to influence future decisions. A number of factors not measured in this study influence treatment choice, outcomes, and cost and should be taken into consideration. Among these are genotype and subgenotype, baseline RNA, presence of decompensated cirrhosis, presence of hepatocellular carcinoma, liver transplantation, renal impairment/dialysis, acute versus chronic infection, pill burden and regimen complexity, payer and organization formulary, and availability of medication.

Results and analyses from this study may not be generalizable to all other geographic regions. Genotype 1 accounted for over 80% of infections in this study. The distribution of genotype 1 has been estimated at 70% for other studies.^{4,36} LED/SOF prescriptions accounted for over half of the prescriptions in this study, which may vary from other areas based on provider and payer preferences and genotype distributions. Only 5.3% of patients in this study were coinfecting with HIV, which is lower than other studies that have demonstrated coinfection rates ranging from 11%-34%.^{32,34} Distribution of fibrosis scores may also vary from other regions, since this was primarily driven by prior authorization criteria for local payers and provider preference.

Limitations

This study had several limitations that should be considered. First, this study was a retrospective and prospective chart review and was completely observational and descriptive in nature. It was not designed to directly compare treatment regimens or specific patient populations with one another. Some patient characteristics varied between groups, which may have affected results.

Second, HCV treatment guidelines have changed frequently from 2011 to 2016, so these cost analyses may not represent current best practices. Separate analyses that excluded BOC and TEL regimens, as well as 24-week regimens were used to mimic the current standard of treatment; however, this may not fully account for all guideline changes. New agents were approved at the end of 2015 and early 2016 and were not captured because of the time frame of data collection.

Third, measuring fibrosis has a number of limitations, including use of a variety of tests that are not 100% equivalent or 100% accurate. Among these tests include standard liver biopsy, FibroMeter, Fibroscan, Fibrosure, Fibrotest, Fibrospect, and Hepascore. These tests use ultrasound technology or take

into account direct or indirect markers of liver fibrosis, using different techniques and are not interchangeable.³¹ Although these tests are accurate for determining cirrhosis (F4) and detecting a lack of fibrosis (F0), they are not as accurate for determining in-between stages, and there are also discrepancies between them.³⁷⁻⁴⁰ A number of variables can affect reproducibility of fibrosis staging, including steatosis, increased BMI, food consumption, and lower degrees of fibrosis.⁴¹⁻⁴⁴ Grouping patients into fibrosis 0-2 and 3-4 may have reduced the effect of these inaccuracies; however, this limitation could not be fully overcome. The most common tests used in this study were Fibrosure and Fibrometer; however, the test used was largely driven by payer preference and preference of the treatment site.

Fourth, fibrosis scores may have been underestimated if the patient had undergone fibrosis testing a significant amount of time before starting treatment. In most cases, payers required a recent fibrosis score within a specified time frame (e.g., 6-12 months), but this was not always the case. Some patients had a fibrosis test several years before initiation of treatment, possibly underestimating the true level of fibrosis in their livers during the time of treatment. Fifth, patients with unknown fibrosis scores and those lost to follow-up were excluded from the study, which could lead to potential bias. Excluding patients lost to follow-up and patients with unknown HCV-RNA at the end of data collection may have led to an overestimation of the benefit of DAA regimens in this study.

Finally, this study used patient reports to assess nonadherence to medications, which likely underestimated the number of patients who missed doses or took their medications incorrectly. Other mechanisms for assessing adherence were considered but were not used because of anticipated inaccuracies. Many specialty pharmacies mail prescriptions to patient home addresses on a predetermined schedule; therefore, claims data would have showed 100% adherence in many cases if used as a marker for adherence. Many patients underwent the prior authorization process to obtain their medications weeks or months before their appointments to initiate treatment, so using the date when a prescription was written in the EMR as the initiation date would also be inaccurate.

Conclusions

This study demonstrated a mean drug cost per SVR of \$155,662 in all patients, with a mean drug cost per SVR of \$122,452 and \$178,401 for patients with fibrosis scores of 0-2 and 3-4, respectively (based on AWP). SVR rates were 83.5% (269/322) for all patients and 92.2% (107/116) and 78.6% (162/206) for patients with fibrosis scores of 0-2 and 3-4, respectively. Patients with advanced fibrosis were older, had a higher mean BMI, were more likely to be coinfecting with HIV, more likely to be genotype 1, more likely to be male, and more likely to be treatment experienced. Knowledge about drug costs and

outcomes may influence future decisions. Further research is needed to determine the effect of newer treatment options and changes to treatment guidelines.

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DISCLOSURES

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Study concept and design was primarily contributed by Bach, along with Zaiken. Bach took the lead in data collection, data interpretation, and preparation of the manuscript, along with Zaiken.

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