Health Equity
Volume 1.1, 2017
DOI: 10.1089/heq.2017.0018

Health Equity

Mary Ann Liebert, Inc. publishers

ORIGINAL ARTICLE Open Access

Patterns in Liver-Related Health Outcomes with Hepatitis C Virus Treatments and Health Equity Implications for Decision Makers: A Cohort Analysis of Medicaid Patients

S. Mantravadi*

Abstract

Introduction: Hepatitis C virus (HCV) infection is a blood-borne communicable disease that, in perhaps 20% of cases, results in a chronic disease. However, traditional peginterferon/ribavirin therapies pose many adverse side effects that are difficult to tolerate, and many patients do not complete the therapy. However, healthcare access to these newer, efficacious treatments are reduced, due to inadequate or lack of coverage of direct acting antiviral (DAA) medication. The objective of this study was to evaluate the impact of HCV treatment regimens on outcomes of care for HCV-infected Medicaid beneficiaries without cirrhosis/liver disease scarring.

Methods: A cohort analysis was performed to evaluate the changes in cirrhosis, hepatocellular carcinoma (liver cancer), and liver transplantation with use of HCV treatments in Medicaid beneficiaries with HCV, and was followed over a period of 10 years. The cohort of Medicaid beneficiaries and relevant variables were generated from published literature.

Results: Finally, considering the impact on health expenditures due to improved access to new treatments in Medicaid beneficiaries, DAAs resulted in the lowest decompensated cirrhosis and hepatocellular carcinoma-related healthcare cost per person over the 10-year time frame the cohort was followed.

Conclusions: The risk of liver-related disease is higher in patients with cirrhosis, as reaching treatment success results in continued disease progression, not normal health status; thus, liver cancer healthcare costs are higher in patients with cirrhosis, compared to those without cirrhosis.

Keywords: hepatitis C; Medicaid; health equity

Introduction

Hepatitis C virus (HCV) infection is a blood-borne communicable disease that, in perhaps 20% of cases, results in a chronic disease, spanning an "indolent course."[1] The sequela of HCV infection ranges from acute to chronic forms of liver disease, cirrhosis, and liver cancer.[2] The HCV infection increases the risk of liver-related negative health outcomes. Patients may experience jaundice, dark urine, and nonspecific symptoms such as nausea, fatigue, and anorexia.[3,4] The HCV infection can result in several degrees of liver fibrosis and damage (cirrhosis).

The level of liver damage is classified based on the grade of inflammation and the stage of fibrosis (F0–F4, where F0 mild hepatitis/no fibrosis), depending on the extent of damage to and inflammation of the liver.[5] Patients in the compensated cirrhosis (F4) do not experience symptoms of hepatitis, and have a significantly higher survival rate than those with decompensated cirrhosis.[6]

More than 2.7–3.9 million people with HCV infection live in the United States, and the disease causes long term decreased health related quality of life.[4,7,8–15] A majority of these cases are prevalent rather than incident.[16] The mortality due to HCV infection now exceeds human immunodeficiency virus in cause specific mortality.[4,17] Mortality due to HCV infection and liver cancer is predicted to increase, corresponding with the duration of infection.[18]

University of West Florida, Pensacola, Florida.
*Address correspondence to: S. Mantravadi, PhD, MS, MPH, University of West Florida, Pensacola, FL 32514, E-mail: smantra2013@gmail.com

It was forecasted that although the incidence of HCV infection declined during the 1990s, individuals infected for more than 20 years would increase substantially before cresting in 2015.[19] Due to lack of HCV screening of blood supplies before 1992, individuals who have had blood transfusions/exposure may be at a higher risk for HCV.[20] The peak of HCV infection prevalence occurs in the population younger than 55 years and disproportionally affects the poor.[21,22]

Treatment to reach sustained virologic response is desirable as this reduces the risk for the noted sequelae of HCV infection.[10] Sustained virologic response is attained when the hepatitis C viral RNA cannot be detected in the patient's bloodstream for 6 months.[23,24] Length of treatment for peginterferon and ribavirin regimens can be 48 weeks, with weekly peginterferon injections and ribavirin pills taken once daily, orally.[25] However, traditional peginterferon/ribavirin therapies pose many adverse side effects that are difficult to tolerate, and many patients do not complete the therapy.[26] A new wave of treatments for HCV infection entered the market, with the approval of direct acting antivirals (DAAs) by the Food and Drug Administration. Currently approved DAA treatments include simeprevir, sofosbuvir, ledipasvir, ombitasvir/paritaprevir/ritonavir with dasabuvir, daclatasvir–sofosbuvir, elbasvir–grazoprevir, and most recently, sofosbuvir–velpatasvir.[4,27–29]

Before the newly approved oral DAA agents, most newly detected cases of HCV infection did not prompt antiviral medication due to side effects and limited efficacy of peginterferon/ribavirin regimens. Health disparities arise since the disease progresses slowly and chronic HCV-infected patients often play a waiting game for treatment, either due to efficacy or affordability of effective treatments, putting health outcomes at risk.

Risk of HCV infection and subsequent health disparities are higher for certain populations, including low income.[30,31] The presence of HCV infection was found to be associated with Medicaid and public insurance usage.[32] There will be a reduction in the number of low-income individuals who are uninsured, as with the Affordable Care Act there is increased eligibility for Medicaid services and coverage.[31,33,34] This results in a large number of HCV-infected individuals who qualify for Medicaid.[34] In addition, HCV infection screening/testing for high-risk patients is usually considered part of routine preventive services in non-grandfathered traditional Medicaid plans[15]; the Department of Health and Human Services is encouraging HCV testing[35] and screening initiatives.

The number of Medicaid beneficiaries with HCV infection is high, and the number is rising, as the proportion of new Medicaid beneficiaries identified as infected with HCV will continue to increase.[31,33] There are 377,000 Medicaid beneficiaries who are HCV positive (all HCV genotypes), reported in 2013.[31] In 2015, the payer forecasts that the number of HCV-infected Medicaid beneficiaries will be from 401,390 to 444,010.[31] Hence, the Medicaid population is at greater risk; treatment of HCV infection is a priority for Medicaid.

However, healthcare access to these newer, efficacious treatments is reduced, due to inadequate or lack of coverage of DAA medication. Sofosbuvir has been considered a nonpreferred drug on the tiered formularies in a majority of Medicaid programs; many states also consider liver disease severity/presence of cirrhosis as a criteria for coverage of DAA medications.[30,36] Restricting treatment coverage has negative consequences on health of patients, public health of the population, opportunities for reduction of transmission among Medicaid beneficiaries, and treatment affordability/availability.[37,38]

Many dimensions of HCV health disparities influence access to DAA treatment, including socioeconomics, availability of/access to care, and health insurance coverage. Individuals with inadequate health insurance coverage, as often occurs with Medicaid, have a lower chance of receiving appropriate medical care, and are more likely to have poor health status.[39] Furthermore, several barriers arise when considering access to services—including high costs/low affordability of services/treatment, lack of insurance coverage of services (Healthy people, 2020).

Such barriers lead to preventable hospitalizations and negative health outcomes, delays in care, and unmet preventive services.[39] In the case of HCV patients on Medicaid, lack of coverage for DAA medications leads to cases of potentially preventable negative liver-related health outcomes, treatments for liver cancer, and liver transplantations.

Health outcomes for HCV-infected Medicaid patients are already at a disadvantage. What would happen if you introduce DAA as a treatment, compared to current options for treatment? This is further explored in this study.

Materials and Methods

The objective of this study was to evaluate the impact of HCV treatment regimens on outcomes of care for HCV-infected Medicaid beneficiaries without cirrhosis/liver disease scarring. Specifically, this study aimed to compare what happens to a cohort of patients without

cirrhosis on Medicaid, and follow such a cohort over 10 years.

A cohort analysis was performed to evaluate the changes in cirrhosis, hepatocellular carcinoma, and liver transplantation with use of HCV treatments in Medicaid beneficiaries with HCV, and was followed over a period of 10 years. The cohort of Medicaid beneficiaries used a sample generated from published literature. The target population was the noninstitutionalized Medicaid population in the United States with a diagnosis of HCV infection. The data source is from published literature[31] and publically available reports.[15] The model considered 72,164 patients with HCV with cirrhosis on Medicaid, using data from public literature estimates,[40] and age/genotype distributions of HCV. The study cohort was limited to Medicaid beneficiaries, 55 years and younger.

The National Average Drug Acquisition Cost values, as published by Mediciad,[41] as well as wholesale cost were used for medication costs of American Association for the Study of Liver Diseases and the Infectious Diseases Society of America[42] recommended treatments for HCV genotype 1a patients without cirrhosis. The treatments considered in this cohort analysis were ribavirin, peginterferon, sofosbuvir, simeprevir–sofosbuvir, sofosbuvir–velpatasvir, ombitasvir/paritaprevir/ritonavir, and dasabuvir. Furthermore, the effectiveness of each DAA treatment was extracted from published articles on clinical trials. Table 1 illustrates the data used in the cohort analysis.

These American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommended medications were evaluated in the context of a watch/wait scenario (no treatment for oncogenic disease) and peginterferon–ribavirin. Since DAAs are not fully covered for Medicaid patients due to high medication costs, peginterferon–ribavirin is considered as an alternative treatment option. Furthermore, since many providers are reluctant to treat patients with peginterferon–ribavirin due to side effects and low efficacy, a watch and wait strategy is often considered.

The cohort progressed through the natural history of HCV disease stages. The treatment is successful if the individual reaches sustained virologic response. All patients in the cohort analysis began at a baseline of HCV infection, without liver cirrhosis/scarring (F0–F3). The individual is treated, by one of the noted regimens, and either (1) reaches sustained virologic response or (2) fails to reach sustained virologic response. Patients who failed to reach sustained virologic response were modeled to be retreated in year 2; each individual in the Medicaid cohort had a 50% chance of retreatment, illustrating the implicit effects of access to care and affordability of DAA medications. If the patient reaches sustained virologic response from F0 to F3, the patient reaches a normal health status. If the patient does not reach sustained virologic response, the patient continues into disease progression stages of liver damage.

Each disease stage had a bivariate decision; the individual with liver damage may stay in the same health stage or progress. At each of the 10 years, each patient can progress from the following:

- F0–F3 to F4/compensated cirrhosis liver damage state.
- From F4 liver damage state to decompensated cirrhosis or liver cancer.
- From decompensated cirrhosis state to liver cancer or liver transplantation.[43,44]

Patients who are in liver cancer state can either continue with liver cancer or move to liver transplantation state.

Thus, liver transplantation, liver cancer, and decompensated cirrhosis are endpoints in the model. Each event in the natural history/disease progression occurs on a yearly basis. All treatment-naive patients were started at the same baseline and will continue through the natural history progression.

This study was based entirely on the use of published literature and costs. These are publicly available, published sources, which omit patient-level, personal identification information. The Medicaid National Average Drug Acquisition Cost data set is an aggregated, publically available data set on costs of medications. In addition, published literatures on HCV infection were used. Since there was no risk posed to human subjects in this research, this study met the exempt status by the University of Texas Health Science Center Committee for Protection of Human Subjects.

Over the 10-year period of time, the all-cause healthcare costs in the Medicaid HCV cohort for liver-related outcomes (decompensated cirrhosis, compensated cirrhosis, hepatocellular carcinoma, and liver transplantation) that were averted by each treatment were evaluated. The Medicaid cohort's disease progression through the HCV natural stages was also determined.

Results

The cohort analysis of Medicaid beneficiaries without cirrhosis indicated that patients on DAA treatments

Table 1. Cohort Analysis: Values for Simulated Cohort

Input value/variable	References	Base case value (range)/probabilities
Rate variable: treatment response rate (SVR reached)		
No treatment	[43]	1% (0.7–1.7%)
Peginterferon–ribavirin	Pegasys, Pegintron, Copegus, Rebetol	41% (38–44%)
Elbasvir–grazoprevir, 12 weeks	C-EDGE TN	92% (94%)
Harvoni (sofosbuvir–ledipasvir), 12 weeks	ION 1,3; NEUTRINO trial; ION 1, double blind; NEUTRINO, open label	96% (89–100); Gilead'16; range—genotype 1 Rx naive NC; ION 1, 96–100; ION 3, 95–98; NEUTRINO, 89–95
Simeprevir–sofosbuvir without ribavirin, 12 weeks	ION 1,3; NEUTRINO trial; ION 1, double blind; NEUTRINO, open label	97% (97%); Base case—treatment naive, noncirrhosis genotype 1, range—genotype 1a
Viekira Pak-ribavirin 12 weeks	Pearl IV; Saphire I	95.3% (93–97.6%)
Daclatasvir–sofosbuvir	ALLY-1	96.4%
Transition probabilities for cohort		
F3 to F4	[43]	0.116
F4 with SVR to decompensated cirrhosis	[43]	0.008
F4 without SVR to decompensated cirrhosis	[43]	0.039
F4 with SVR to liver cancer	[43]	0.005
F4 without SVR to liver cancer	[43]	0.014
Decompensated cirrhosis to liver cancer	[43]	0.068
Decompensated cirrhosis to liver transplant	[43]	0.023
Treatment cost/day		$
Pegylated interferon– ribavirin	Medicaid National Average Drug Acquisition Cost	Pegylated interferon (pegasys proclick): 1685.5 (1264.15–2106.8); ribavirin: 0.87 (0.66–1.1)
Elbasvir–grazoprevir	Medicaid National Average Drug Acquisition Cost	Elbasvir–grazoprevir: 650 (487.5–812.5)
Sofosbuvir–velpatasvir	[29]	Sofosbuvir–velpatasvir: 890 (667.5–1112.5)
Sofosbuvir–ledipasvir	Medicaid National Average Drug Acquisition Cost	Sofosbuvir–ledipasvir: 1091.2 (818.4–1364.0)
Simeprevir–sofosbuvir	Medicaid National Average Drug Acquisition Cost	Sofosbuvir: 981.5 (736.13–1226.9) Simeprevir: 781.2 (585.96–76.5)
Ombitasvir–daclatasvir–paritaprevir–ribavirin	Medicaid National Average Drug Acquisition Cost	Viekira Pak: 243.5 (182.65–304.4) Ribavirin: 0.9 (0.7–1.1)
Daclatasvir–sofosbuvir	Medicaid National Average Drug Acquisition Cost	Sofosbuvir: 981.50 (736.1–1226.9) Daclatasvir: 723.625 (542.74–904.53)
Cost: total/all-cause healthcare cost/year		$/year
HCV infection monitoring	[31,43]	14,915.00 (14464–16686)
Decompensated cirrhosis	[31,43]	41,943.00 (38670–44936)
Compensated cirrhosis	[31,43]	16,911.00 (15313–26354)
Liver cancer	[31,43]	58,208.00 (50878–66116)
Liver transplant + medical cost, first and subsequent years	[31,43]	190,995.00 (182,973–199,017) SD = 8022; subsequent years: 54,885.00 (50,476–59,294); SD = 4409.00

F0–F3, where F0 is mild hepatitis; HCV, hepatitis C virus; SD, standard deviation; SVR, sustained virological response.

had lower incidence of liver-related outcomes, as well as all-cause healthcare costs. Since reaching treatment success results in reaching a healthy state, only individuals who do not reach sustained virologic response are at a higher risk for liver-related conditions. Thus, when following the cohort after the 10-year period, the number of individuals and the associated costs of liver-related outcomes are low in patients on DAA treatments. Since treatment success prevents disease progression of HCV natural history, patients without cirrhosis have reduced overall disease progression; among those in the cohort who progressed to end-stage liver disease outcomes, most of the cohort was in early stages. This results in overall improved outcomes, lowered medical costs accrued, and higher savings/averted medical costs.

Furthermore, the cohort analysis, presented in Table 2, of Medicaid beneficiaries illustrated that DAA treatments resulted in the lowest number of individuals in end-stage liver disease-related outcomes, over the 10-year progression of the cohort, as in Table 2. Approximately 600 individuals were in decompensated cirrhosis, after the 10-year time period, while with peginterferon–ribavirin treatment, there were 3334 individuals with decompensated cirrhosis.

The cohort analysis revealed that progression of the patient through disease stages is affected by the treatment choice. DAA treatments resulted in a higher number of

Table 2. Cohort Analysis: Yearly Breakdown of Health Outcomes of Medicaid Beneficiaries Without Cirrhosis

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
No treatment										
F3	72163.52	63157.80519	55831.49978	49355.04581	43629.86049	38568.79668	34094.81626	30139.81758	26643.59874	23552.94128
Compensated cirrhosis	0	8287.675794	6887.058584	12998.49845	18034.76335	22323.23621	25614.0851	28211.53728	30212.54464	31701.93723
DCC	0	0	323.2193559	562.4016793	1018.164566	1628.867361	2351.246644	3136.232518	3951.085313	4769.82579
HCC	0	0	116.0274611	229.7840991	440.8150276	744.9043039	1130.728642	1603.98146	2148.047534	2753.775059
Liver transplantation, year 1/incident cases	0	0	0	12.07514363	22.12660259	41.05038613	67.26012147	99.30781849	136.2926063	176.7968636
Peginterferon–ribavirin										
F3	63811.60285	11596.09724	10250.94996	9061.839768	8010.666354	7081.429057	6259.983287	5533.825225	4891.901499	4324.440925
Compensated cirrhosis	0	2456.217073	1214.967775	2339.684679	3266.854804	4054.168734	4660.743562	5139.882215	5509.392183	5784.854972
DCC	0	0	95.79246586	134.4590947	213.4710196	321.4524941	450.3128978	591.103423	737.7684179	885.497787
HCC	0	0	34.38703903	56.534994	96.17239819	152.5774988	223.8012234	310.7208614	410.4454107	521.3273372
Liver transplantation, year 1	0	0	0	3.578708276	5.353958938	8.756729378	13.49650732	19.30924558	26.02421318	33.38649004
Sofosbuvir–velpatasvir										
F3	66548.76516	3333.022895	2946.392239	2604.610739	2302.475894	2035.38869	1799.283602	1590.566704	1406.060966	1242.957894
Compensated cirrhosis	0	1448.636049	309.8529452	635.2122389	903.680836	1130.062085	1306.273882	1445.758264	1553.638814	1634.399029
DCC	0	0	56.49680591	63.43986143	80.32944864	108.2630214	142.4835078	180.46219	220.424703	260.9579687
HCC	0	0	20.28090468	27.64939253	39.75029875	56.27422101	76.96692616	101.864962	130.3024081	161.830135
Liver transplantation, year 1/incident cases	0	0	0	2.110662723	2.565092514	3.437589269	4.741018333	6.355797725	8.225228849	10.28186449
Elbasvir–grazoprevir										
F3	66548.76516	3746.336692	3311.761636	2927.597286	2587.996001	2287.788465	2022.405003	1787.806023	1580.420524	1397.091743
Compensated cirrhosis	0	1538.215105	353.0496558	718.5023738	1020.023033	1274.322431	1472.166804	1628.740944	1749.803172	1840.392385
DCC	0	0	59.99038908	68.30020025	90.1064746	121.6876837	160.3126793	203.1387308	248.1740031	293.8324926
HCC	0	0	21.53501146	29.69565264	43.21127339	61.89038519	85.20684499	113.3101686	145.3935688	180.9509027
Liver transplantation, year 1/incident cases	0	0	0	2.241179407	2.758730711	3.800899851	5.274432133	7.095465423	9.204597554	11.52374482
S-ledipasvir										
F3	66548.76516	3400.355319	3005.914102	2657.228067	2348.989611	2076.506816	1835.632025	1622.69871	1434.46566	1268.067643
Compensated cirrhosis	0	1477.900828	316.1124732	648.044548	921.9366427	1152.891157	1332.662716	1474.964907	1585.024817	1667.416519
DCC	0	0	57.63813228	64.72144869	81.95223273	110.4501086	145.3619038	184.1078165	224.8776366	266.2297395
HCC	0	0	20.69061159	28.20795474	40.55331874	57.41105081	78.52178189	103.9227981	132.9347264	165.0993641
Liver transplantation, year 1/incident cases	0	0	0	2.153301506	2.61691151	3.507034102	4.83679453	6.484195064	8.391391704	10.4895747
Simeprevir–sofosbuvir										
F3	66548.76516	3318.464735	2933.522826	2593.234178	2292.419013	2026.498408	1791.424592	1583.61934	1399.919496	1237.528835
Compensated cirrhosis	0	1463.195469	307.3925494	631.389392	898.7409189	1123.988866	1299.491272	1438.423487	1545.886886	1626.345542
DCC	0	0	57.06462328	63.86005198	82.67297354	110.2006288	144.0079374	181.5833747	221.1578036	261.322032
HCC	0	0	20.48473656	27.84923717	39.91720271	56.52464967	77.21952209	102.1161588	130.5171107	161.9775733
Liver transplantation, year 1/incident cases	0	0	0	2.131875798	2.582750683	3.4981665	4.795600449	6.400963443	8.261063967	10.30731391
Daclatasvir–sofosbuvir										
F3	66548.76516	3367.384755	2976.768123	2631.463021	2326.213311	2056.372567	1817.833349	1606.96468	1420.556777	1255.772191
Compensated cirrhosis	0	1472.001032	312.6005769	641.3378486	912.5966531	1141.166132	1319.223544	1460.173365	1569.19208	1650.809486
DCC	0	0	57.40804024	64.37533107	83.52935204	111.5194505	145.8766596	184.0516018	224.2496673	265.0414387
HCC	0	0	20.60801444	28.06384868	40.29754713	57.14199432	78.13669544	103.3999701	132.2219073	164.1506975
Liver transplantation, year 1/incident cases	0	0	0		2.603186562	3.533076982	4.850627134	6.480630989	8.369185646	10.44661864
Ombitasvir/paritaprevir/ritonavir/ribavirin										
F3	66548.76516	3458.749614	3057.534659	2702.860639	2389.328805	2112.166663	1867.15533	1650.565312	1459.099736	1289.844166
Compensated cirrhosis	0	1488.282427	322.3359867	659.9261998	938.4819453	1173.254852	1356.083678	1500.801261	1612.724371	1696.505549
DCC	0	0	58.04301464	65.33220378	85.12409503	113.9785983	149.3634851	188.6586714	230.0219815	271.9862316
HCC	0	0	20.83595397	28.46214462	41.00521549	58.29219257	79.84679742	105.794814	135.4030288	168.2065435
Liver transplantation, year 1/incident cases	0	0	0	2.168427496	2.641126472	3.598062805	4.953195463	6.629232053	8.570942001	10.70662672

DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma.

Table 3. Cohort Analysis–Year 10: Health Outcomes of Medicaid Beneficiaries Without Cirrhosis

Treatment regimen	Number of individuals who reached SVR after treatment regimen completion	Total number of individuals in DCC at year 10	Total number of individuals in HCC at year 10	Total number of individuals progressing to liver transplantation at year 10
No treatment	718.0390212	17417.82387	9052.036126	554.9095422
Peginterferon–ribavirin	21463.03262	3334.065134	1771.579724	109.9058527
Sofosbuvir–velpatasvir	41572.28156	1056.360701	594.6383436	37.71725391
Elbasvir–grazoprevir	40027.81508	1185.552264	659.6587963	41.8990499
Sofosbuvir–ledipasvir	41067.71641	1077.700886	606.6509947	38.47920311
Simeprevir–sofosbuvir	41321.25708	1064.804802	596.1214544	37.97773475
Daclatasvir–sofosbuvir	41169.43703	1078.643501	603.4126605	38.42803146
Ombitasvir/paritaprevir/ritonavir/ribavirin	40888.72333	1104.465267	617.0107364	39.26761301

individuals who reached sustained virologic response; as in Table 3, within those who did not reach treatment success, DAA treatment illustrated there was a higher percentage of the Medicaid cohort that remained in earlier stage of disease. For DAA-based regimens, the number of individuals in decompensated cirrhosis progressed from ~60 to 260, over the 10-year cohort analysis. In addition, as demonstrated in Table 3, DAA regimens showed that end-stage liver disease outcomes, such as liver transplantation, were low; after 10 years, the number of individuals with liver transplantation in the cohort increased by ~20. Peginterferon–ribavirin regimens showed that cohort progression toward liver transplantation increased by 97 patients, after the 10-year period of time.

Finally, considering the impact on health expenditures due to improved access to DAAs in Medicaid beneficiaries, as shown in Table 4, Sofosbuvir–velpatasvir also resulted in the lowest decompensated cirrhosis and hepatocellular carcinoma-related healthcare cost per person, over the 10-year time frame the cohort was followed. The next treatment option that resulted in lowered negative liver-related outcomes as well as reduced health expenditures is elbasvir–grazoprevir and sofosbuvir–ledipasvir.

Within the Medicaid cohort of HCV patients, sensitivity analysis concerning the retreatment of hepatocellular cancer during the second year of follow-up was conducted, to illustrate the effects of retreatment. The retreatment of all or none of the patients who did not reach treatment success was analyzed. The retreatment of all eligible patients (those who did not reach treatment success), illustrated higher savings/averted medical costs and improved outcomes. Thus, compared to not retreating the cohort, it is evident that there is a pattern of reduced number of negative health outcomes for patients, which arises in retreatment of all eligible cohort patients.

Discussion

This study demonstrates the importance of treatment with DAAs for patients in the early stages of the disease (without cirrhosis) to prevent cirrhosis and the negative outcomes associated with HCV infection. Furthermore, the result of this cohort analysis has many health equity implications for Medicaid beneficiaries with HCV, especially in terms of improved access to DAA medications within Medicaid.

Currently, many Medicaid beneficiaries do not have access to DAAs, as coverage is restricted toward patients with cirrhosis/liver disease. It becomes evident that the primary impact of DAAs on patients with and without cirrhosis is driven by the number of individuals in earlier stages of the disease.[45] The risk of liver-related disease is higher in patients with cirrhosis, as reaching treatment success results

Table 4. Cohort Analysis–Year 10: Healthcare Costs of Medicaid Beneficiaries Without Cirrhosis

Treatment regimen	HCC healthcare costs per 10 years	HCC healthcare costs per person	DCC healthcare costs per 10 years	DCC healthcare costs per person	Liver transplantation (first year/total incident cases) healthcare costs per 10 years	Liver transplantation (first year/total incident cases) healthcare costs per person
No treatment	$435,443,320.89	$6,034.12	$645,476,757.68	$8,944.64	$92,292,676.44	$1,278.94
Peginterferon–ribavirin	$84,830,588.40	$1,175.53	$124,014,066.74	$1,718.51	$18,347,552.27	$254.25
Sofosbuvir–velpatasvir	$28,178,598.18	$390.48	$39,633,801.65	$549.22	$6,346,233.61	$87.94
Elbasvir–grazoprevir	$31,295,432.78	$433.67	$44,448,636.24	$615.94	$7,044,797.83	$97.62
Sofosbuvir–ledipasvir	$28,747,851.20	$398.37	$40,434,468.20	$560.32	$6,474,437.74	$89.72
Simeprevir–sofosbuvir	$28,246,885.35	$391.43	$39,964,659.74	$553.81	$6,391,230.83	$88.57
Daclatasvir–sofosbuvir	$28,596,628.34	$396.28	$40,478,671.63	$560.93	$6,466,297.87	$89.61
Ombitasvir/paritaprevir/ritonavir/ribavirin	$29,248,963.84	$405.32	$41,437,692.90	$574.22	$6,606,249.52	$91.55

in continued disease progression, not normal health status; thus, the liver cancer healthcare costs are higher in patients with cirrhosis, compared to those without cirrhosis. However, this indicates that DAAs are more cost saving in the case of patients without cirrhosis (early stage). Since DAAs are highly effective, and reaching sustained virologic response results in avoidance of disease progression of HCV natural history, the costs associated with a cohort of patients treated with DAAs are low, emphasizing the importance of early treatment.

Essentially, treatment and HCV disparities influence health services. Thus, the results of this study can be placed in the context of conceptual frameworks/theory of the Andersen–Aday model.

The Andersen–Aday model explains health services utilization as a function of population and delivery system characteristics. The Andersen–Aday model illustrates disparities and health equity issues in HCV treatment utilization, where age, gender, race/ethnicity, income, education, occupation, consumer behavior, place of birth/citizenship status, comorbidities predispose certain groups as vulnerable to HCV. Insurance status/coverage, regular source of care, screenings/tests are the major components of the delivery system that enable utilization of services and treatment. Along with predisposing and enabling factors, perceived/medical need affects the realized access—that is, actual use of care, which in turn improves health outcomes.

Health equity then needs to be considered in terms of access to DAAs/health services—for prescription. The implications of this analysis aids in the clarification of prescription drug coverage for Medicaid beneficiaries and current restrictions.[38] Coverage for sofosbuvir–ledipasvir in Medicaid patients is restricted by physician type, for 2/3rds of states.[30] Another manner for denying DAA is to restrict its prescription to specialists, and not by general practitioners or primary care physicians.[30] The 30 states that cover sofosbuvir for treatment of HCV infection have prior authorization criteria that require sofosbuvir to be prescribed by a gastroenterologist, hepatologist, or liver infectious disease specialist.[30,36] Lack of an usual source of care can infringe on access to care and treatments.[46] Difficulties with entry to the healthcare system, as well as accessing specialist care in an available location, often occur to patients with inadequate coverage, or those on Medicaid. In certain states, coverage for DAAs is also restricted by limits on weekly refills, the investigation of prior pharmacy refill records to estimate patient adherence; these restrictions may not be feasible for patients due to transportation limitations.[36]

Furthermore, the achievement of health equity for HCV patients is dependent on not limiting access to treatment based on disease severity.

The Centers for Medicare and Medicaid Services have issued a letter to states on the health disparity issues that arise with prescription coverage; the agency is concerned that managed care plans are more stringent than fee for service Medicaid regarding the coverage of DAAs.[47] The uptake of these medications is low due to the issue of affordability and coverage, especially for Medicaid patients.[37] The Medicare/Medicaid dual eligible populations, who have compounded risk factors for HCV infection due to age and low-income status, are especially at risk for reduced access to medications due to affordability.

Since the use of DAAs provides strong cost savings, states may also want to review policies and consider changing those that otherwise interfere with access, such as lack of network specialists and associated stigma from approval criteria. As shown in a study of HCV screening and treatment in southeast Michigan, Medicaid patients who screened positive for HCV were more likely to have inadequate care coordination and linkage between providers.[48]

The goal of eliminating HCV is precluded by screening, delivery coordination, and disparities in clusters of vulnerable populations. The combination of a scale up strategy with a physician-based promotion of DAA treatment as prevention would address gaps in care.[49,50] The advent of new pangenotypic treatments, such as sofosbuvir–velpatasvir, and coordination among Medicaid stakeholders and multiple payers create a direction toward improved care delivery and a quick scale-up strategy for treatment.[50]

Patients are often facing drug authorization issues through Medicaid[30,46,51,52]; due to issues with authorization and coverage, the public health of the community is at risk, with the avoidance of the medication costs associated with a cure for the viral infection,[38] the public health benefit of addressing health disparity in hepatitis C needs to be balanced.[50] Furthermore, unintended consequences in the entire healthcare system may be a result of changes in pharmacy benefits for Medicaid patients.[46,50] In addition, with changes in approval of coverage, costs of physician paperwork burden for prior authorization, documentations of treatment history, and appeals of medical necessity will change, further affecting delay in treatments and potential public health benefit from reduced transmission and individual health outcome risks.

The results of this study indicate that despite real-world variation in treatment discontinuation, implementation

of coverage for DAAs results in savings for Medicaid. One of the biggest critiques of Medicaid coverage for DAAs is that patients must be adherent to treatment regimens although there is no strong evidence that discontinuation affects outcomes, in HCV interferon-based treatments[46,52–56]; currently, an area for future research is to evaluate whether this is consistent in oral DAA medications.[46,52–56] The sensitivity analysis conducted in this study shows that even when there is 8.3% treatment discontinuation, there is still overall benefit to Medicaid, as the benefit of treatment is averaged out.

The Office of Health Equity has recognized the importance of the disparities that exist within HCV and the contribution of this disease toward advanced liver disease outcomes, with the development of the Hepatitis C–Advanced Liver Disease Disparities Dashboard, using data from the VA system.[57] The dashboard allows for views of vulnerable areas for targeting interventions to improve health disparities within the VA population.[57] Building on this work with additional vulnerable populations, especially Medicaid and dual eligible Medicare/Medicaid beneficiaries, would aid in increasing the coordination among siloed physician groups and payers, as well as the availability of evidence for decision makers. Increasing access to information regarding the impact of disparities in care and treatment would improve targeting of care.

Conclusion

The Medicaid population is at a high risk for HCV infection, due to socioeconomic burdens and lack of financial resources.[30,31] In this study, we have discussed how increased coverage of DAA treatments can improve efforts toward reduced risk of long-term negative health outcomes, especially liver cancer, for patients with HCV. Efforts toward increased DAA coverage and affordability are urgent, as early treatment of individuals with early stages of HCV can aid the burden of disparities. The high prevalence in HCV, especially in vulnerable and disproportionately affected populations such as Medicaid-insured African Americans, Asian Americans and Pacific Islanders, Hispanics and Latinos, and Native Americans, means that this disease is a challenge from both health outcome and cost long-term perspectives (health affairs).

With the looming impact of DAA treatment on Medicaid and health disparities, this study provides a foundation for the coordinated actions of decision makers, providers, and Medicaid analysts to value treatments in the context of long-term prevention, and management of HCV toward the goal of health outcomes and equity.[58]

Author Disclosure Statement

No competing financial interests exist.

References

1. McHutchison JG, Bacon BR, Owens GS. Making it happen: managed care considerations in vanquishing hepatitis C. Am J Manag Care. 2007;13:S327.
2. World Health Organization. [Homepage]. 2016. Available at www.who.int/en/ Accessed May 20, 2016.
3. Klevens RM, Hu DJ, Jiles R, et al. Evolving epidemiology of hepatitis C virus in the United States. Clin Infect Dis. 2012;55(suppl 1):S3–S9.
4. Belousova V, Abd-Rabou AA, Mousa SA. Recent advances and future directions in the management of hepatitis C infections. Pharmacol Ther. 2015;145:92–102.
5. Cox-North PP, Shuhart MC. Hepatitis C online: core concepts. Evaluation and staging of liver fibrosis. 2015. Available at www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/evaluation-staging/core-concept/all Accessed June 15, 2016.
6. Thornton. Core concepts. evaluation and prognosis of patients with cirrhosis. University of Washington. 2015. Available at www.hepatitisc.uw.edu/go/evaluation-staging-monitoring/evaluation-prognosis-cirrhosis/core-concept/all Accessed May 12, 2016.
7. Food and Drug Administration. [Homepage]. 2016. Available at www.fda.gov/ Accessed July 10, 2016.
8. Bezemer G, Van Gool AR, Verheij-Hart E, et al. Long-term effects of treatment and response in patients with chronic hepatitis C on quality of life. An international, multicenter, randomized, controlled study. BMC Gastroenterol. 2012;12:11.
9. Zetterman RK. HCV treatment: where we're at, where we're going. 2013. Available at www.medscape.com/viewarticle/817546 Accessed July 19, 2016.
10. Veterans Affairs. (2016). Homepage. Available at www.va.gov/ Accessed January 5, 2017.
11. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370:1889–1898.
12. Afdhal N, Reddy, KR, Nelson, DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370:1483–1493.
13. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014;370:1879–1888.
14. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144:705–714.
15. Centers for Disease Control and Prevention. [Homepage]. 2016. Available at www.cdc.gov/ Accessed December 15, 2016.
16. Ditah I, Ditah, F, Devaki P, et al. The changing epidemiology of hepatitis C virus infection in the United States: national health and nutrition examination survey 2001 through 2010. J Hepatol. 2014;60:691–698.
17. Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012;156:271–278.
18. Davis GL, Alter MJ, El–Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010;138:513–521.
19. Armstrong GL, Alter MJ, McQuillan GM, et al. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. Hepatology. 2000;31:777–782.
20. U.S. Preventive Services Task Force. Final recommendation statement hepatitis C: screening. 2013. Available at www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-c-screening Accessed July 18, 2016.
21. Menzin J, White LA, Nichols C, et al. The economic burden of advanced liver disease among patients with hepatitis C virus: a large state Medicaid perspective. BMC Health Serv Res. 2012;12:459.
22. Rice JP. Hepatitis C treatment: back to the warehouse. Clin Liver Dis. 2015;6:27–29.
23. Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Ann Intern Med. 2005;142:105–114.
24. Singal AG, Volk ML, Jensen D, et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gasteroenterol Hepatol. 2010;8:280–288.

25. Pharmaceutical Research and Manufacturers of America. Twenty-five years of progress against hepatitis C: setbacks and stepping stones. 2014. Available at www.phrma.org/sites/default/files/pdf/Hep-C-Report-2014-Stepping-Stones.pdf Accessed June 11, 2015.
26. Alter HJ, Liang TJ. Hepatitis C: the end of the beginning and possibly the beginning of the end. Ann Intern Med. 2012;156:317–318.
27. Kiser JJ, Flexner C. Direct-acting antiviral agents for hepatitis C virus infection. Annu Rev Pharmacol Toxicol. 2013;53:427–449.
28. Merck Sharp & Dohme Corp (Merck). Merck voluntarily discontinuing VICTRELIS® (boceprevir) 200 mg Capsules. 2015. Available at www.fda.gov/downloads/drugs/drugsafety/drugshortages/ucm430818.pdf Accessed December 18, 2016.
29. University of Washington. Hepatitis C online. Available at www.hepatitisc.uw.edu/ Accessed December 15, 2016.
30. Barua,S, Greenwald R, Grebely J, et al. Restrictions for Medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States. Ann Intern Med. 2015;163:215–223.
31. Milliman, Inc. Health care reform and hepatitis c: a convergence of risk and opportunity. 2013. Available at http://us.milliman.com/uploadedFiles/insight/2013/convergence-of-risk-and-opportunity.pdf Accessed May 19, 2016.
32. Stepanova M, Kanwal F, El-Serag HB, et al. Insurance status and treatment candidacy of hepatitis C patients: analysis of population-based data from the United States. Hepatology. 2011;53:737–745.
33. Khallafi H, George N, Qureshi K. The prescribers' dilemma: treatment of hepatitis c infection for Medicaid insured patients in United States. Liver Res Open J. 2015;1:26–31.
34. Bankhead C. Payers' perspectives: health economics outcomes in managed care. Am Health Drug Benefits. 2015;8:144–147.
35. Neuman T, Hoadley J, Cubanski J. The cost of a cure: Medicare's role in treating hepatitis C. 2014. Health Affairs Blog. Available at http://healthaffairs.org/blog/2014/06/05/the-cost-of-a-cure-medicares-role-in-treating-hepatitis-c/ Accessed May 15, 2016.
36. Canary LA, Klevens RM, Holmberg SD. Limited access to new hepatitis C virus treatment under state Medicaid programs. Ann Intern Med. 2015;163:226–228.
37. Mantravadi S. Hepatitis C direct acting antivirals and disruptive innovation. Presented at Southwest Academy of Management Annual Meeting: Disruptive Innovation, Little Rock, AR, 2017. Available at www.swamfbd.org/uploads/SWAM_Proceedings_2017.pdf Accessed April 3, 2017.
38. Center for Health Law and Policy Innovation of Harvard Law School. Examining hepatitis C virus treatment access: a review of select state Medicaid fee-for-service and managed care programs. 2013. Available at www.chlpi.org/wp-content/uploads/2013/12/Examining_HCV_Treatment_Access_Report.pdf Accessed March 20, 2015.
39. Healthy People 2020. Access to Health Services. 2017. Available at www.healthypeople.gov/2020/topics-objectives/topic/Access-to-Health-Services Accessed April 20, 2017.
40. Gordon SC, Lamerato LE, Rupp LB, et al. Prevalence of cirrhosis in hepatitis C patients in the Chronic Hepatitis Cohort Study (CHeCS): a retrospective and prospective observational study. Am J Gastroenterol. 2015;110:1169–1177.
41. Medicaid NADAC -National Average Drug Acquisition Cost. Pharmacy drug pricing. Available at www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Pharmacy-Pricing.html Accessed January 18, 2017.
42. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. AASLD—IDSA. HCV Guidance: recommendations for testing, managing, and treating hepatitis C. 2016. Available at www.hcvguidelines.org/full-report-view Accessed July 28, 2016.
43. Chhatwal J, Kanwal F, Roberts MS, et al. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. Ann Intern Med. 2015;162:397–406.
44. Gray AM, Clarke PM, Wolstenholme JL, et al. *Applied Methods of Cost-effectiveness Analysis in Health Care*. Oxford, United Kingdom: Oxford University Press, 2011.
45. Mantravadi S. The oncogenic hepatitis C virus and direct acting antivirals: economic implications for hepatocellular carcinoma in Medicaid beneficiaries with cirrhosis. Am J Manag Care. 2017;23:SP180–SP1844.
46. Clements KM, Clark RE, Lavitas P, et al. Access to new medications for hepatitis C for Medicaid members: a retrospective cohort study. J Manag Care Spec Pharm. 2016;22:714–722b.
47. Center for Medicare & Medicaid Services. Assuring Medicaid beneficiaries access to hepatitis C (HCV) drugs. 2015. Available at www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Downloads/Rx-Releases/State-Releases/state-rel-172.pdf Accessed June 12, 2016.
48. Bourgi K, Brar I, Baker-Genaw K. Health disparities in hepatitis C screening and linkage to care at an integrated health system in southeast Michigan. PLoS One. 2016;11:e0161241.
49. Lo Re V. Nearly half of hepatitis C patients on Medicaid denied coverage for life-saving drugs. Penn Researchers Rep. 2015. Available at www.pennmedicine.org/news/news-releases/2015/november/nearly-half-of-hepatitis-c-pat Accessed April 5, 2017.
50. Roy V, Choskhi D, Kissler S, et al. Making hepatitis C a rare disease in the United States. 2016. Available at http://healthaffairs.org/blog/2016/06/15/making-hepatitis-c-a-rare-disease-in-the-united-states/ Accessed July 1, 2017.
51. Do A, Mittal Y, Liapakis A, et al. Drug authorization for sofosbuvir/ledipasvir (harvoni) for chronic HCV infection in a real-world cohort: a new barrier in the HCV care cascade. PLoS One. 2015;10:e0135645.
52. Graham J. Medicaid, private insurers begin to lift curbs on pricey hepatitis V drugs. 2016. Available at http://khn.org/news/medicaid-private-insurers-begin-to-lift-curbs-on-pricey-hepatitis-c-drugs/ Accessed January 8, 2017.
53. Azar MM, Springer SA, Meyer JP, et al. A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. Drug Alcohol Depend. 2010;112:178–193.
54. Malta M, Strathdee SA, Magnanini MM, et al. Adherence to antiretroviral therapy for human immunodeficiency virus/acquired immune deficiency syndrome among drug users: a systematic review. Addiction. 2008;1;103:1242–1257.
55. Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clin Infect Dis. 2013;57(suppl_2): S80–S89.
56. Higgs P, Sacks-Davis R, Gold J, Hellard M. Barriers to receiving hepatitis C treatment for people who inject drugs: myths and evidence. Hepat Mon. 2011;11:513–518.
57. Data.Gov. Hepatitis C—Advanced Liver Disease Disparities Dashboard. 2017. Available at https://catalog.data.gov/dataset/hepatitis-c-advanced-liver-disease-disparities-dashboard Accessed July 2, 2017.
58. Núñez A, Schilling JL. A space to promote intentional thoughtful action. Health Equity 2017;1:1–1.

Cite this article as: Mantravadi S (2017) Patterns in liver-related health outcomes with hepatitis C virus treatments and health equity implications for decision makers: a cohort analysis of Medicaid patients, *Health Equity* 1:1, 156–164, DOI: 10.1089/heq.2017.0018.

Abbreviations Used

DAA = direct acting antiviral
HCV = hepatitis C virus