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Effectiveness of Ledipasvir/Sofosbuvir and Predictors of Treatment Failure in Members with Hepatitis C Genotype 1: A Retrospective Cohort Study in a Medicaid Population

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Effectiveness of Ledipasvir/Sofosbuvir and Predictors of Treatment Failure in Members with Hepatitis C Genotype 1:

A Retrospective Cohort Study in a Medicaid Population

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INTRODUCTION

- An estimated 2.7 to 3.9 million Americans suffer from chronic HCV infection.[1] The primary goal of therapy in chronic HCV infection is eradication of HCV RNA, which is predicted by achievement of SVR12. Current treatment guidelines recommend treatment with antiviral medications for all patients with chronic HCV infection.[2] Harvoni® (ledipasvir/sofosbuvir) is a combination of DAA agents FDA-approved for the treatment of HCV genotypes 1, 4, 5, and 6 on October 10, 2014.[3]
- Real-world studies of LDV/SOF in the VA system and in academic and community medical centers have shown rates of SVR12 over 90% with 8-week, 12-week, and 24-week courses with and without ribavirin.[4-7] There is an unmet need for real-world effectiveness data in the Medicaid population.
- HCV genotype 1 accounts for 74% of chronic HCV infections in the US.[8] Several durations of treatment with LDV/SOF are FDA-approved, and selection of a treatment regimen is based on clinical factors of the patient's HCV infection, including treatment history, cirrhosis, and baseline HCV RNA.[2,3]
- The Massachusetts Medicaid (MassHealth) DUR program maintains a comprehensive HCV medication management program. The MassHealth PA criteria allow for optimized treatment of chronic HCV infection and do not contain restrictions based on liver fibrosis stage, SUD, or prescriber specialty.

OBJECTIVES

- **Primary Objective:** To evaluate the effectiveness of HCV genotype 1 treatment with LDV/SOF as measured by SVR12 in the MassHealth FFS and PCC plan population
- **Secondary Objectives:** To evaluate the effectiveness of HCV genotype 1 treatment with LDV/SOF within the subgroups of 8, 12, and 24-week regimens, and to identify predictors of treatment failure

METHODS

- This retrospective cohort study utilized clinical and demographic data that is routinely compiled from PA requests by the comprehensive HCV medication management program of the MassHealth DUR program in an internal database, as well as pharmacy claims data from the MassHealth POPS.
- **Inclusion Criteria:**
  - Member is over 18 years of age
  - Diagnosis of HCV genotype 1
  - Completion of at least one 8-week, 12-week, or 24-week course of LDV/SOF with or without ribavirin between October 10, 2014 and November 1, 2016
  - Availability of SVR12 result or detectable viral load any time after treatment completion prior to November 1, 2016
  - Continuous MassHealth FFS or PCC coverage for a minimum of the duration of treatment with LDV/SOF
- **Exclusion Criteria:**
  - Mixed HCV genotype
  - HCV genotype other than genotype 1
- **Study Variables:**
  - Viral load data was collected from the internal database of the comprehensive HCV medication management program.
  - Other clinical variables included HIV co-infection, SUD, cirrhosis, history of failure on a previous HCV treatment, history of failure on a previous DAA agent, baseline HCV RNA ≥6 million IU/mL, and presence of potential drug-drug interaction with LDV/SOF.
  - A member was considered to have a potential drug-drug interaction if there was at least one paid claim for a medication that may affect concentrations of LDV/SOF at any point during the member's treatment with LDV/SOF.
  - Demographic variables included sex and age.
- **Statistical Analysis:**
  - **Primary Objective:**
    - › Viral load data was used to calculate the proportion of all members who completed at least one 8-week, 12-week, or 24-week course of LDV/SOF and achieved SVR12.
  - **Secondary Objectives:**
    - › Viral load data was used to calculate the proportion of members who achieved SVR12 by treatment regimen and by clinical and demographic variables for each treatment regimen.
    - › The number of members with and without each clinical and demographic variable who achieved SVR12 and who did not achieve SVR12 were used to perform bivariate and multivariate analyses and calculate the odds of failure to achieve SVR12.

ABBREVIATIONS

CI = confidence interval, **DAA =** direct-acting antiviral, **DUR =** drug utilization review, **FDA =** Food and Drug Administration, **FFS =** Fee-For-Service, **HCV =** hepatitis C virus, **HIV =** human immunodeficiency virus, **IU =** international units, **LDV/SOF =** ledipasvir/sofosbuvir, **OR =** odds ratio, **PA =** prior authorization, **PCC =** Primary Care Clinician, **POPS =** Pharmacy Online Processing System, **RNA =** ribonucleic acid, **SUD =** substance use disorder, **SVR12 =** sustained virologic response at 12 weeks, **VA =** Veterans Affairs

REFERENCES

[1] Centers for Disease Control and Prevention. Viral Hepatitis – Statistics & Surveillance [webpage on the internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2016 [cited 2017 Feb 15]. Available from: https://www.cdc.gov/hepatitis/statistics/.

[2] American Association for the Study of Liver Diseases, Infectious Diseases Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C [guideline on the internet]. 2016 [cited 2017 Feb 15]. Available from: http://www.hcvguidelines.org.

[3] Harvoni® [package insert]. Foster City (CA): Gilead Sciences; 2016 Jun.

[4] Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-World Effectiveness of Ledipasvir/Sofosbuvir in 4,365 Treatment-Naïve, Genotype 1 Hepatitis C-Infected Patients. Hepatology. 2016;64(2):405-14.

[5] Ioannou GN, Beste LA, Chang MF, Green PK, Lowey E, Tsui JI, et al. Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients with Hepatitis C in the Veterans Affairs National Health Care System. Gastroenterology. 2016;S0016-5085(16):34575-9.

[6] Terrault NA, Zeuzem S, Di Bisceglie AM, Lim JK, Pockros PJ, Frazier LM, et al. for the HCV-TARGET Study Group. Effectiveness of Ledipasvir-Sofosbuvir Combination in Patients With Hepatitis C Virus Infection and Factors Associated of Sustained Virologic Response. Gastroenterology. 2016 Aug 23. pii: S0016-5085(16)34927-7. [Epub ahead of print]

[7] Younossi ZM, Park H, Gordon SC, Ferguson JR, Ahmed A, Dieterich D, Saab S. Real-world outcomes of ledipasvir/sofosbuvir in treatment-naïve patients with hepatitis C. Am J Manag Care. 2016 May;22(6 Spec No.):SP205-11.

[8] Centers for Disease Control and Prevention. Hepatitis C FAQs for Health Professionals [webpage on the internet]. Atlanta (GA): Centers for Disease Control and Prevention; 2017 [cited 2017 Feb 24]. Available from: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm.

RESULTS

Table 1. Proportions of Members by Clinical and Demographic Variables, N (%)

Characteristic	LDV/SOF for 8 weeks N=297	LDV/SOF for 12 weeks with ribavirin N=69	LDV/SOF for 12 weeks without ribavirin N=399	LDV/SOF for 24 weeks with or without ribavirin N=31	LDV/SOF total for all members N=796
Sex					
Male	163 (54.9%)	55 (79.7%)	258 (64.7%)	18 (58.1%)	494 (62.0%)
Female	134 (45.1%)	14 (20.3%)	141 (35.3%)	13 (41.9%)	302 (38.0%)
Age					
Mean age, in years (SD)	49.8 (11.0)	57.4 (5.6)	54.5 (8.9)	57.4 (7.7)	53.1 (9.9)
<65 years	291 (98.0%)	67 (97.1%)	380 (95.2%)	27 (87.1%)	765 (96.1%)
≥65 years	<11 (2.0%)*	<11 (2.9%)*	19 (4.8%)	<11 (12.9%)*	31 (3.9%)
Comorbidities					
HIV	0 (0.0%)	10 (14.5%)	128 (32.1%)	<11 (12.9%)*	142 (17.8%)
SUD	53 (17.9%)	<11 (13.0%)*	50 (12.5%)	<11 (3.2%)*	113 (14.2%)
Cirrhosis	0 (0.0%)	41 (59.4%)	177 (44.4%)	23 (74.2%)	241 (30.3%)
Treatment History					
Treatment-naïve	297 (100.0%)	19 (27.5%)	311 (77.9%)	<11 (6.5%)*	629 (79.0%)
Treatment-experienced, total	0 (0.0%)	49 (71.0%)	88 (22.1%)	29 (93.6%)	166 (20.9%)
Treatment-experienced, DAA	0 (0.0%)	<11 (4.4%)*	<11 (0.5%)*	<11 (22.6%)*	12 (1.5%)
Other					
Baseline HCV RNA ≥6 million IU/mL	0 (0.0%)	<11 (10.1%)*	130 (32.6%)	<11 (12.9%)*	141 (17.7%)
Baseline HCV RNA <6 million IU/mL	297 (100.0%)	62 (89.9%)	268 (67.2%)	26 (83.9%)	653 (82.0%)
DDI	13 (4.4%)	<11 (11.6%)*	27 (6.8%)	<11 (25.8%)*	56 (7.0%)

DAA=direct-acting antiviral, DDI=drug-drug interaction based on claims history, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IU=international units, LDV/SOF=ledipasvir/sofosbuvir, SD=standard deviation, SUD=substance use disorder, RNA=ribonucleic acid
*Not reportable due to cell size <11

Table 2. Proportions of Members Who Achieved SVR12, N(%)

Characteristic	LDV/SOF for 8 weeks N=297	LDV/SOF for 12 weeks with ribavirin N=69	LDV/SOF for 12 weeks without ribavirin N=399	LDV/SOF for 24 weeks with or without ribavirin N=31	LDV/SOF total for all members N=796
Total	285 (96.0%)	62 (89.9%)	382 (95.7%)	27 (87.1%)	756 (95.0%)
Sex					
Male	155 (95.1%)	49 (89.1%)	249 (96.5%)	16 (88.9%)	469 (94.9%)
Female	130 (97.0%)	13 (92.9%)	133 (94.3%)	11 (84.6%)	287 (95.0%)
Age					
<65 years	279 (95.9%)	61 (91.0%)	364 (95.8%)	23 (85.2%)	727 (95.0%)
≥65 years	<11 (100.0%)*	<11 (50.0%)*	18 (94.7%)	<11 (100.0%)*	29 (93.6%)
Comorbidities					
HIV	0 (N/A)	<11 (90.0%)*	124 (96.9%)	<11 (75.0%)*	136 (95.8%)
SUD	51 (96.2%)	<11 (100.0%)*	46 (92.0%)	<11 (100.0%)*	107 (94.7%)
Cirrhosis	0 (N/A)	36 (87.8%)	168 (94.9%)	22 (95.7%)	226 (93.8%)
Treatment History					
Treatment-naïve	285 (96.0%)	17 (89.5%)	298 (95.8%)	0 (0.0%)	600 (95.4%)
Treatment-experienced, total	0 (N/A)	45 (90.0%)	84 (95.5%)	27 (93.1%)	156 (93.4%)
Treatment-experienced, DAA	0 (N/A)	<11 (100.0%)*	<11 (100.0%)*	<11 (85.7%)*	11 (91.7%)
Other					
Baseline HCV RNA ≥6 million IU/mL	0 (N/A)	<11 (100%)*	126 (96.9%)	<11 (100.0%)*	137 (97.2%)
Baseline HCV RNA <6 million IU/mL	285 (96.0%)	55 (88.7%)	256 (95.5%)	22 (84.6%)	618 (94.6%)
DDI	12 (92.3%)	<11 (100%)*	24 (88.9%)	<11 (87.5%)*	51 (91.1%)

DAA=direct-acting antiviral, DDI=drug-drug interaction based on claims history, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IU=international units, LDV/SOF=ledipasvir/sofosbuvir, N/A=not applicable, SD=standard deviation, SUD=substance use disorder, RNA=ribonucleic acid
*Not reportable due to cell size <11

DISCUSSION

- The proportion of members who achieved SVR12 overall is comparable to the proportions of members who achieved SVR12 in other real-world studies of LDV/SOF (Table 2).[4-7]
- LDV/SOF is FDA-approved as an 8-week regimen in treatment-naïve, non-cirrhotic members with a baseline HCV RNA <6 million IU/mL.[3] Current treatment guidelines note that preliminary real-world data for the comparative effectiveness of 8-week and 12-week regimens in this population is inconclusive, and leave the selection of treatment duration to the discretion of the prescriber.[2]
- A high proportion of treatment-naïve, non-cirrhotic, HCV mono-infected members with a baseline HCV RNA <6 million IU/mL that received 8 weeks of LDV/SOF achieved SVR12. These results are comparable to those seen with 8-week regimens in other real-world studies of LDV/SOF (Table 2).[4-7]
- The proportion of members who received 12 weeks of LDV/SOF with ribavirin and achieved SVR12 is comparable to the proportion of members who received 24 weeks of LDV/SOF and achieved SVR12 (Table 2).
- Bivariate and multivariate analyses revealed no statistically significant differences in odds of failure to achieve SVR12 by clinical and demographic variables, with the exception of lower odds of failure with cirrhosis in members receiving 24 weeks of treatment.

DISCLOSURES/ACKNOWLEDGMENTS

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LIMITATIONS

- Members for whom viral load data is not available or who had an undetectable viral load less than 12 weeks after treatment completion were not included (N=228). These members may account for additional cure rate data.
- Pharmacy claims data was only available for claims billed to a MassHealth FFS or PCC plan. Medications billed to other payers or paid in cash are not included, and may account for additional drug-drug interactions.
- Data regarding history of failure on a previous HCV treatment or DAA agent were compiled from the internal database of the MassHealth comprehensive HCV medication management program, and included discontinuation of prior therapies because of adverse events, as well as relapse after completion of a full treatment course.

CONCLUSION

- Treatment of HCV genotype 1 with LDV/SOF is associated with a high rate of SVR12 in one state's Medicaid population, including treatment with 8 weeks of LDV/SOF in non-cirrhotic, HCV mono-infected members with a baseline HCV RNA <6 million IU/mL.
- The clinical and demographic variables included in this study were not found to be predictors of treatment failure, as they were not associated with statistically significant differences in odds of failure to achieve SVR12. However, cirrhosis was associated with lower odds of failure to achieve SVR12 in members receiving 24 weeks of LDV/SOF.