Association Between Baseline Creatinine Clearance and Treatment Failure in Patients With Hepatitis C Virus Treated With Ledipasvir and Sofosbuvir

Jeffrey W. Jansen,1,2 Travis W. Linneman,1 Gillian M. Powderly,3 Ryan P. Moenster,4 and Leela Nayak5

1Department of Research, VA Saint Louis Health Care System, St. Louis, Missouri; 2Department of Pharmacy, SCL St. Vincent Healthcare, Billings, Montana; 3Department of Pharmacy, VA Saint Louis Health Care System, St. Louis, Missouri; 4Department of Pharmacy Practice, Saint Louis College of Pharmacy, St. Louis, Missouri; 5Department of Gastroenterology, Southeastern Louisiana Veterans Healthcare System, New Orleans, Louisiana

Background. Hepatitis C remains a major cause of liver disease globally and is responsible for approximately 500,000 deaths annually. Newer direct-acting antivirals achieve cure rates at or above 90% with excellent tolerability for most patients. The literature focusing on identification of predictors of efficacy and safety with specific hepatitis C therapies has been inconclusive and often conflicting.

Methods. A retrospective, single-center, case–control analysis of all veteran patients aged ≥18 through ≤89 years who completed a treatment course of 8, 12, or 24 weeks with ledipasvir and sofosbuvir (LDV/SOF) combination therapy for hepatitis C infection was conducted. Patients who were identified and met inclusion criteria were assigned to either the case group (SVR12 failure; hepatitis C viral load detectable at least 11 weeks after therapy completion) or the control group (SVR12 success; hepatitis C viral load undetectable at least 11 weeks after therapy completion).

Results. Twenty-nine SVR12 failures and 411 SVR12 successes were included in the analysis. The overall failure rate was consistent with the current literature, at 6.6% (29/440). Bivariate analysis identified only baseline creatinine clearance >80 mL min-1 (Cockcroft-Gault) as a possible predictor of SVR12 failure (P = .026). In the multivariate analysis, pretreatment creatinine clearance >80 mL min-1 remained independently associated with SVR12 failure (odds ratio, 2.95; 95% confidence interval, 1.17–7.46; P = .023).

Conclusions. In hepatitis C patients treated with LDV/SOF, a pretreatment creatinine clearance of >80 mL min-1 was associated with SVR12 failure.

Keywords. clinical pharmacology; direct acting antivirals; hepatitis C virus; ledipasvir; sofosbuvir; treatment failure.
A retrospective, single-center, case–control analysis of veteran patients aged ≥18 through ≤89 years who completed a treatment course of 8, 12, or 24 weeks with LDV/SOF combination therapy for hepatitis C infection from October 10, 2014, through April 8, 2016, was conducted. Patients who discontinued therapy, passed away during therapy, or did not receive medication through the VA St. Louis Veterans Affairs Health Care System Hepatitis C clinic were excluded. All patients were identified through pharmacy medication dispensing records.

Patients who were identified and met inclusion criteria were assigned to either the case group (SVR12 failure; hepatitis C viral load detectable at least 11 weeks after therapy completion) or the control group (SVR12 success; hepatitis C viral load undetectable at least 11 weeks after therapy completion). For patients with multiple viral loads obtained after therapy completion, the viral load closest to week 12 after completion of therapy was utilized for group assignment on the basis that reinfection vs relapse could not be determined in a patient with a detectable viral load after initial SVR12 success. Evaluation at or beyond 11 weeks was utilized, as patients are routinely scheduled for therapy follow-up evaluation at 11–14 weeks after treatment completion, with some patients having laboratory evaluation completed up to 1 week before their visit.

Factors defined a priori for inclusion in bivariate analysis were gender, ethnicity, age, duration of therapy, hepatitis C genotype, previous treatment failure, histamine-2 receptor antagonist (H2RA) use, proton pump inhibitor (PPI) use, ribavirin use, presence of cirrhosis (defined as a Fibroscan score >14.6 kilopascal and/or biopsy demonstrating cirrhosis), pretreatment creatinine clearance (CrCl; Cockcroft-Gault), baseline platelet count, Fibrosis-4 (FIB-4) score, and vitamin D levels.

Descriptive statistics were used to evaluate baseline characteristics between study populations. Bivariate analysis was completed to examine relationships between patient characteristics and SVR12 failure utilizing the chi-square or Fisher exact test for categorical variables and the Student t test or Wilcoxon rank-sum test for continuous variables. Variables with a P value <.2 in the bivariate analysis were included in the initial regression model. Due to the results of recently published literature [5, 6], a secondary analysis with FIB-4 score, ethnicity, and baseline platelet count forced into the model, regardless of bivariate association, was also completed. The Hosmer and Lemeshow test was utilized to evaluate the goodness of fit of the multivariate model, and outcomes are reported as odds ratios with 95% confidence intervals. Significance was determined using a 2-sided alpha of .05, and statistical analysis was conducted using IBM-SPSS, version 22.0 (IBM Corp., Armonk, NY). This study was approved by the VA Saint Louis Health Care System Institutional Review Board.

RESULTS

Six hundred fifty-four patients were identified as having received LDV/SOF combination therapy between October 10, 2014, and April 8, 2016, from the VA Saint Louis Health Care System. A total of 440 patients met inclusion and exclusion criteria: 29 patients with SVR12 failure (case group) and 411 patients with SVR12 success (control group). All patients included in the original pilot analysis [8] were included in the current analysis. Figure 1 displays the trial profile of this study. The overall SVR failure rate was 29/440 (6.6%).

Baseline characteristics were similar between groups, with the only significant difference observed being baseline renal function (Table 1). Bivariate analyses revealed baseline CrCl >80 mL min-1 as the only variable significantly associated with SVR12 failure (P = .026). Proton pump inhibitor use was included in the multivariate model, per protocol (bivariate P < .2). As about 50% of patients had missing data for vitamin D level >30 ng mL-1 or on supplementation, this variable was not included in the multivariate model. Table 2 provides the complete results of the bivariate analyses.

Table 3 provides the results of the primary and secondary regression models. In the primary regression analysis, baseline creatinine clearance >80 mL min-1 was significantly associated with SVR12 failure after controlling for PPI use (odds ratio [OR], 2.95; 95% confidence interval [CI], 1.17–7.46; P = .023). In the secondary analysis with FIB-4 score, ethnicity, and baseline platelet count forced into the model, baseline creatinine clearance >80 mL min-1 remained the only variable
Role of CrCl With LDV/SOF Treatment Failure • OFID • 3

significantly associated with increased rates of SVR12 failure (OR, 3.24; 95% CI, 1.25–8.39; P = .016).

**DISCUSSION**

This analysis further evaluated potential predictors of SVR12 failure of LDV/SOF for the treatment of hepatitis C with LDV/SOF. The findings support an association of pretreatment CrCl of >80 mL min−1, as determined by the Cockcroft-Gault method, with increased rates of SVR12 failure of LDV/SOF. An association between SVR12 failure and baseline platelets <150 000 µL−1, race, or severity of disease, as reflected by pre-treatment FIB4 score or presence of cirrhosis, was not demonstrated in this analysis of HCV patients treated with LDV/SOF, whereas this was reported by earlier studies [5–8]. In contrast to a prior study [7], but consistent with the present authors’ previous findings [8], PPI use fell out of the regression model as an independent predictor of decreased rates of SVR in this study when controlling for other variables.

Other potential predictors of failure not found to have a significant association with LDV/SOF failure in this analysis included presence of cirrhosis, HCV genotype, ribavirin

| Table 1. Baseline Demographics |
|--------------------------------|
| **SVR12 Success** | **SVR12 Failure** | **P**-**Value** |
|---------------------|------------------|-----------------|
| Mean age (SD), y    | 62.0 (5.6)       | 62.0 (4.2)      | .983 |
| Male gender, No. (%)| 401 (97.6)       | 29 (100)        | .395 |
| Ethnicity, No. (%)  |                  |                 | .886 |
| White               | 162 (39.4)       | 11 (39.7)       | |
| Black               | 235 (57.2)       | 17 (58.6)       | |
| Other               | 14 (3.4)         | 1 (3.4)         | |
| Mean CrCl (SD), mL min−1 | 86.5 (23.3) | 96.1 (25.6) | .034 |
| HCV genotype, No. (%) |                |                 | .570 |
| 1                   | 405 (98.5)       | 28 (96.6)       | |
| 1a                  | 296              | 24              | |
| 1b                  | 89               | 3               | |
| 4                   | 4 (1.0)          | 1 (3.4)         | |
| 6                   | 2 (0.5)          | 0 (0.0)         | |
| Planned duration, No. (%) |        |                 | .652 |
| 8 wk                | 122 (29.7)       | 10 (34.5)       | |
| 12 wk               | 261 (63.5)       | 17 (58.6)       | |
| 24 wk               | 28 (6.8)         | 2 (6.9)         | |
| Mean platelets (SD), 103 µL−1 | 179.0 (63.4) | 179.4 (62.0) | .972 |
| Mean FIB4 score (SD) | 3.28 (3.0)     | 3.09 (1.8)      | .732 |
| Mean HCV VL (SD), copies mL−1 | 3.958138 (6 x 106) | 5.215197 (10 x 106) | .355 |
| Mean vitamin D (SD), ng mL−1 | 34.7 (171) | 36.3 (12.8) | .742 |

Abbreviations: CrCl, creatinine clearance (Cockcroft-Gault); H2RA, histamine-2 receptor antagonist; HCV VL, hepatitis C viral load; PPI, proton pump inhibitor; SVR12, sustained viral response at 12 weeks.

| Table 2. Results of Bivariate Analysis |
|---------------------------------------|
| **SVR12 Success** | **SVR12 Failure** | **P**-**Value** |
|---------------------|------------------|-----------------|
| Adherencea          | 395/411 (96.1)   | 29/29 (100)     | .279 |
| Previous treatment failure | 85/411 (20.7) | 7/29 (24.1)    | .658 |
| Cirrhosis           | 98/411 (23.4)    | 6/29 (20.7)     | .474 |
| Ribavirin           | 20/411 (4.9%)    | 1/29 (3.4%)     | .590 |
| PPI                 | 97/411 (23.6)    | 10/29 (34.5)    | .187 |
| H2RA                | 10/411 (2.4)     | 1/29 (3.4)      | .735 |
| CrCl >80 mL min−1   | 240/411 (58.4)   | 23/29 (79.3)    | .026 |
| Vitamin D >30 ng mL−1 OR supplementation | 203/221 (91.9) | 13/17 (76.5)  | .058 |

Abbreviations: CrCl, creatinine clearance (Cockcroft-Gault); H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; SVR12, sustained viral response at 12 weeks.

aAs noted by a clinical pharmacy specialist following each patient and documented in the patients’ follow-up notes.
use, histamine-2 receptor blocker therapy, age, and vitamin D deficiency. For some of these variables, the limited number of patients with data available (ie, vitamin D status) or limited number of cases/controls meeting these criteria (ie, histamine-2 receptor blocker therapy) could have limited the ability of our model to identify significant associations.

There is currently a lack of data available evaluating the potential contribution of pretreatment creatinine clearance as a potential contributor to SVR12 failure rates for DAA use to treat hepatitis C. A prior analysis completed by the present authors reported a 1:4 case–control study of 12 SVR12 failures and 48 randomly selected SVR12 successes [8]. That analysis demonstrated that creatinine clearance \( \geq 90 \text{ mL min}^{-1} \) was associated with a higher rate of SVR12 failure. The current analysis builds upon these data, evaluating the prior 12 failure cases along with 17 additional failures and 411 total treatment successes. Other currently available data regarding attempts to identify predictors of treatment failure for HCV, along with available clinical trials evaluating LDV/SOF, did not specifically evaluate the potential of elevated baseline creatinine clearance with increased SVR12 failure rates or report specifically how many patients were studied with creatinine clearance values \( >80 \text{ mL min}^{-1} \) [5–13].

A potential theory of the association between higher creatinine clearance and increased rates of SVR12 failure could be explained through the excretion mechanisms for LDV/SOF. Although ledipasvir is primarily excreted through the biliary tract, with a more minor contribution of renal clearance [14], sofosbuvir is primarily eliminated through the kidneys [14]. Initial studies of sofosbuvir have demonstrated that decreased exposure to sofosbuvir (<200 mg daily) was associated with higher rates of viral relapse [15]. Thus, patients with higher creatinine clearance could potentially be at risk for higher rates of SVR12 failure resulting from increased SOF clearance and subsequent decreased exposure to SOF. This potential decrease in SOF may result in LDV only–like therapy for at least some portion of the dosing interval. This situation could potentially increase the risk of LDV resistance development [16, 17] and thereby increase rates of LDV/SOF combination treatment failure.

In contrast to our findings, recently published articles have identified patient race, baseline or pretreatment platelet value of \( <150 \text{ 000} \mu L^{-1} \), severity of disease as determined by baseline model for end-stage liver disease (MELD) scoring or Aspartate Aminotransferase to Platelet Ration Index (APRI) or FIB-4 score, PPI use, decompensated liver disease, and BMI \(<25\text{ or }>30\text{ kg/m}^{2}\) as predictors of treatment failure with DAA for hepatitis C [5–7]. Su and colleagues reported that black and Hispanic patients were at an increased risk of treatment failure compared with white patients (adjusted OR, 0.77; 95% CI, 0.69–0.87; and OR, 0.76; 95% CI, 0.62–0.93, respectively) [6]. Another analysis reported by Werner and colleagues identified pretreatment platelet count \( \leq 100 \text{ nL}^{-1} \) and MELD score \( \geq 10 \) as predictive of increased rates of failure (OR, 0.117; 95% CI, 0.037–0.373; and OR, 0.24; 95% CI, 0.072–0.88, respectively) [5]. An evaluation by Backus and colleagues demonstrated an increased rate of SVR12 failure in African American patients (OR, 0.8; 95% CI, 0.7–0.92), patients with a FIB-4 score >3.25 (OR, 0.6; 95% CI, 0.53–0.69), patients utilizing PPIs (OR, 0.81; 95% CI, 0.71–0.92), and presence of decompensated liver disease (OR, 0.58; 95% CI, 0.45–0.74) to be predictive of failure in patients taking LDV/SOF [7]. We were unable to observe a significant association of race, baseline platelet value, PPI use, or disease severity (as reflected by FIB-4 score or presence of cirrhosis as determined by fibroscan and/or biopsy) with increased rates of LDV/SOF SVR12 failure in this patient population. The prior studies by Su et al. and Backus et al. included more patients \((n = 21095 \text{ and } n = 21242, \text{ respectively})\) and studied multiple treatment regimens; thus any associations specific to LDV/SOF therapy are unavailable for comparison.

The current analysis is not without limitations. First, given the retrospective design, the information is dependent on the accuracy and completeness of the medical records. Further, data points were not consistent for all patients; for creatinine clearance (and other similar criteria), the most recent value before the medication start date but within 12 months before therapy was utilized. Not all values were as close to the medication start date as would be ideal. Data regarding baseline resistance for individual strains were not universally available in the population and therefore could not be accounted for. Similarly, post-therapy resistance and changes in resistance profile across treatment courses were not routinely collected during the majority of the studied time frame, thus disallowing for an assessment of whether higher creatinine clearance failures could be associated with development of LDV resistance. Additionally, although this analysis was much larger than our prior evaluation of CrCl and SVR12 failure with LDV/SOF treatment, the relatively low number of case patients may limit the ability to detect associations with variables reported by prior studies such as severity of liver disease, PPI use, baseline platelet

| Table 3. Primary and Secondary Multivariate Analysis |
|-----------------------------------------------|
|                               | OR (95% CI) | P Value |
|-------------------------------|-------------|---------|
| **Primary analysis**          |             |         |
| CrCl >80 mL min-1             | 2.947 (1.165–7.456) | .023    |
| PPI                           | 1.934 (0.859–4.355)    | .111    |
| **Secondary analysis**        |             |         |
| CrCl >80 mL min-1             | 3.236 (1.248–8.388)    | .016    |
| PPI                           | 2.042 (0.898–4.643)    | .089    |
| Ethnicity                     | 1.351 (0.654–2.791)    | .416    |
| FIB4 score                    | 1.057 (0.865–1.290)    | .589    |
| Platelets                     | 1.002 (0.993–1.010)    | .718    |

Abbreviations: CI, confidence interval; CrCl, creatinine clearance (Cockcroft-Gault); PPI, proton pump inhibitor.
value, and race or ethnicity [5–8]. Finally, as an analysis of a single Veterans Affairs Health Care System in the United States, the generalizability to other populations may be limited.

Importantly, in addition to the above limitations, these data do not provide insight on whether patients with higher creatinine clearance have better or worse outcomes with LDV/SOF therapy compared with other available treatment regimens, or if this finding is reproducible in patient populations treated with other sofosbuvir-containing regimens. Additionally, although the failure rate in patients with CrCl >80 mL min⁻¹ was approximately 2.55 times that of those with CrCl <80 mL min⁻¹ (8.75% vs 3.39%, respectively), the success rate in this group was still found to be >90%. However, on a population scale, our results suggest that patients with CrCl >80 mL min⁻¹ have a cost per cure approximately 5.5% higher than patients with CrCl <80 mL min⁻¹.

Despite the limitations of this analysis, the data demonstrate that pretreatment creatinine clearance ≥80 mL min⁻¹ is an independent risk factor of SVR12 failure with use of LDV/SOF for the treatment of hepatitis C. In addition, this data set was unable to corroborate in bivariate or multivariate evaluation prior analyses of race, baseline platelet value, PPI use, or disease severity estimates as being predictive of failure with LDV/SOF for HCV treatment. These findings warrant further investigation into the effect of pretreatment creatinine clearance on the success rates of other sofosbuvir-containing HCV treatment regimens. Further, these results allow for the consideration of careful investigation into the tolerability and effectiveness of alternative or increased dosing of sofosbuvir (combined with ledipasvir) on SVR12 success rates in patients with pretreatment CrCl ≥80 mL min⁻¹. Ultimately, continued evaluation of patient, viral, and medication-specific characteristics associated with HCV treatment failure with DAAAs is prudent to continue to optimize treatment regimen selection and cost-effectiveness.

Acknowledgments

Ethical approval. This protocol was reviewed and approved by the VA Saint Louis Health Care System Institutional Review Board.

Financial support. None.

Informed consent. Due to the retrospective nature of this work, the VA Saint Louis Health Care System Institutional Review Board waived the need for informed consent.

Potential conflicts of interest. None of the authors have any conflicts of interest to disclose. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Gower E, Estes C, Blach S, et al. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014; 61:545–57.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380:2095–128.
3. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed 25 January 2019.
4. Biddell MR, McLaughlin M, Faragon J, et al. Desirable characteristics of hepatitis C treatment regimens: a review of what we have and what we need. Infect Dis Ther 2016; 5:299–312.
5. Werner CR, Schwarz JM, Egetemy DP, et al. Second-generation direct-acting antiviral hepatitis C virus treatment: efficacy, safety, and predictors of SVR12. World J Gastroenterol 2016; 22:8509–9.
6. Su E, Green PK, Berry K, Ioannou GN. The association between race/ethnicity and the effectiveness of direct antiviral agents for hepatitis C virus infection. Hepatology 2017; 65:426–38.
7. Backus LI, Belperio PS, Shahoumian TA, et al. Real-world effectiveness and predictors of sustained virological response with all-oral therapy in 21,242 hepatitis c genotype-1 patients. Antivir Ther 2017; 22:481–93.
8. Jansen JW, Powederly GM, Linneman TW. Identification of predictors for treatment failure in hepatitis C virus patients treated with ledipasvir and sofosbuvir. Ann Pharmacother 2017; 51:543–7.
9. Lawitz E, Poodad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet 2014; 383:515–23.
10. Aldhah N, Reddy KR, Nelson DR, et al. ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014; 370:1483–93.
11. Kowdley KV, Gordon SC, Reddy KR, et al. ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014; 370:1879–88.
12. Aldhah N, Zeaem S, Kwo P, et al; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014; 370:1889–98.
13. Naggie S, Cooper C, Saag M, et al; ION-4 Investigators. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med 2015; 373:705–13.
14. Ledipasvir/Sofosbuvir (Harvoni) [package insert]. Foster City, CA: Gilead Sciences, Inc; 2016.
15. Rodriguez-Torres M, Lawitz E, Kowdley KV, et al. Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naive patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial. J Hepatol 2013; 58:663–8.
16. Lawitz EJ, Gruener D, Hill JM, et al. A phase 1, randomized, placebo-controlled, 3-day, dose-ranging study of GS-5885, an NNSA inhibitor, in patients with genotype 1 hepatitis C. J Hepatol 2012; 57:24–31.
17. Wong KA, Worth A, Martin R, et al. Characterization of hepatitis C virus resistance from a multiple-dose clinical trial of the novel NNSA inhibitor GS-5885. Antimicrob Agents Chemother 2013; 57:8333–40.