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BRIEF REPORT

Incidence and Impact of Persistent Viremia on SVR Rates in Patients Receiving Direct-Acting Antiviral Therapy

Alicia B. Carver,[1] Autumn D. Zuckerman,[1] Joshua DeClercq,[2] Leena Choi,[2] and Cody A. Chastain[3]

[1]Specialty Pharmacy Services, Vanderbilt University Medical Center, Nashville, Tennessee, USA, [2]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA, and [3]Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Rates of persistent viremia (PV) while on direct-acting antiviral therapy were low (5.7%) in a real-world cohort of 983 patients. High sustained virologic response rates were achieved both in patients with PV (92.9%) and those with rapid virologic response (96.5%), without significant differences.

Keywords. antiviral agents; hepatitis C virus; rapid virologic response; sustained virologic response; viral load.

Treatment of hepatitis C virus (HCV) infection with direct-acting antivirals (DAAs) typically results in rapid virologic response (RVR) and subsquent sustained virologic response (SVR) rates nearing 100% [1]. Few patients, however, do not achieve RVR and instead continue to have an HCV viral load that remains positive while on DAA treatment, otherwise known as persistent viremia (PV). The American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD/IDSA) HCV Guidance previously recommended viral load testing on therapy but provided limited guidance on the management of PV, recommending rechecking a viral load 2 weeks following a detectable week 4 viral load and discontinuation of treatment at week 6 if the subsequent viral load has increased by >10-fold. Current guidance does not recommend routine viral load testing during treatment unless alanine transaminase levels fail to decline (when elevated at baseline) or there are concerns regarding patient adherence. The clinical significance of PV during therapy remains uncertain [2].

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Correspondence: Alicia B. Carver, PharmD, BCPS, CSP, Specialty Pharmacy Services, Vanderbilt University Medical Center, 726 Melrose Ave, Nashville, TN 37211 (alicia.b.carver@vumc.org).

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Although the incidence of PV with DAA treatment was <2% in various DAA registrational trials, more recent real-world reports have demonstrated higher rates of up to 29% [1, 3–5]. The clinical impact of PV on SVR rates has not been consistently demonstrated in trials [3, 5–7]. Given the limited data available to guide management of patients with PV, we sought to describe the incidence of PV, determine its impact on SVR rates, and describe the types of interventions performed for patients with PV in a real-world setting.

METHODS

This was a single-center prospective cohort study of HCV-infected patients receiving DAA therapy at Vanderbilt University Medical Center (VUMC). The choice and length of HCV regimen, timing of follow-up visits, laboratory testing, and interventions were at the discretion of the provider. All treating providers attempted to obtain HCV RNA at week 4 of HCV treatment as a standard of care. Data were prospectively collected and stored in Research Electronic Data Capture (REDCap), which is hosted at VUMC [8]. This study was approved by the VUMC Institutional Review Board (#151671).

Eligible patients initiated DAA treatment at VUMC between October 1, 2014, and September 30, 2017. Exclusion criteria included lack of an HCV RNA drawn between day 21 and day 62, previous DAA treatment, and early DAA discontinuation.

PV was defined as an HCV RNA ≥15 IU/mL (≥lower limit of quantification [LLOQ]) at any time between day 21 and day 62 of treatment. RVR was defined as an HCV RNA <15 IU/mL (<LLOQ) at any time between day 21 and day 62 of treatment. Provider management of PV was categorized as no intervention, diagnostic intervention (eg, repeat testing of HCV RNA), or therapeutic intervention (eg, change in prescribed DAA treatment regimen or duration). Patients receiving both diagnostic and therapeutic interventions were classified as having received therapeutic interventions. SVR was defined as an undetectable HCV RNA at least 12 weeks after treatment completion. Patients were categorized as not achieving SVR if they had a detectable viral load at any time following end of treatment (EOT). Patients were categorized as lost to follow-up if they completed DAA treatment but did not complete SVR labs. Baseline HCV RNA was measured and defined as the most recent HCV RNA before the start of DAA treatment. For those patients experiencing PV, the log reduction of HCV RNA was measured, as well as adherence and use of proton pump inhibitors (PPIs). Patients were defined as adherent if <7 DAA doses were missed at any point during their treatment. Approximately 90% of HCV RNA analyses were performed at VUMC, using

the Roche Cobas AmpliPrep-Taqman HCV test with LLOQ ≤15 IU/mL.

Descriptive statistics were reported as medians, interquartile ranges, means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Logistic regression was used to determine the effect of PV on SVR rates. Due to the disparity in sample size between the 2 groups, along with the high SVR rate, traditional covariate adjustment in a logistic regression was infeasible and had many potential confounders. Therefore, we utilized the propensity score (PS) method to adjust for as many potential confounding variables as possible (ie, a total of 26 variables) without testing the significance of these variables in predicting the likelihood of group membership (ie, RVR vs PV). As the number of variables included in the PS model was large compared with the number of patients in the PV group, the PS was generated using a regularized regression [9]. Finally, we used a PS adjustment with a restricted cubic spline with 3 knots in the final logistic regression model with SVR as the outcome.

RESULTS

A total of 1572 patients initiated DAA treatment during the study period (Supplementary Figure 1). Patients were excluded for the following: no HCV RNA results between days 21 and 62 (n = 322), previous DAA treatment (n = 116), or early DAA discontinuation (n = 58). Ninety-two patients were lost to follow-up, and 1 patient was re-infected before SVR assessment. To compare SVR rates between those with RVR and PV, we constrained our analysis to the subset of patients with known SVR status (n = 983). Of those 983 patients, 56 (5.7%) had PV. Baseline characteristics were similar between the groups (Table 1). Most patients were noncirrhotic white males with genotype 1 infection, naïve to previous treatment, and treated with ledipasvir/sofosbuvir.

SVR rates were similar in those with RVR (96.5%) and PV (92.9%). After adjusting for potential differences between the groups, we found insufficient evidence to support the hypothesis of a difference in SVR rates (odds ratio, 0.62; 95% CI, 0.23–2.20; $P = .40$).

Of 56 patients with PV, most (n = 49; 87.5%) were adherent, while 6 (10.7%) missed 7 or more doses while on treatment, and 1 (1.8%) was unable to be assessed. Between baseline HCV RNA and the first on-treatment monitoring, most patients with PV experienced a reduction of HCV RNA of >4 log (n = 28; 50%) or >5 log (n = 21; 37.5%), while fewer patients experienced a reduction of >6 log (n = 3; 5.4%), >3 log (n = 3; 5.4%), or >2 log (n = 1; 1.8%).

Forty-one (73.2%) patients experiencing PV had some type of intervention; 27 (65.9%) diagnostic and 14 (34.1%) therapeutic. Of those patients undergoing diagnostic intervention alone (n = 27), 18 (66.7%) had a subsequent undetectable HCV RNA, 6 (22.2%) had a subsequent HCV RNA <15 IU/mL, and 3 (11.1%) continued to experience PV requiring subsequent diagnostic interventions. Therapeutic interventions consisted of treatment extension to 24 weeks (n = 5), addition of ribavirin (RBV; n = 4), addition of RBV and treatment extension to 24 weeks (n = 3), PPI held and treatment extension to 24 weeks (n = 1), and increased RBV dose (n = 1). Six (10.7%) patients with PV were on a PPI at baseline, all of which were on doses of omeprazole 20 mg daily or its equivalent.

Of PV patients not receiving an intervention, 80% (12/15) achieved SVR, compared with 98% (40/41) of those receiving an intervention. Diagnostic interventions were associated with SVR rates of 96.3% (26/27), whereas therapeutic interventions were associated with SVR rates of 100% (14/14). Given the low frequency of PV, a subgroup analysis of intervention effects on SVR rates could not be performed.

DISCUSSION

This study provides insight into the incidence of PV, clinician response to PV, and treatment outcomes in patients experiencing PV on DAA therapy. The frequency at which PV occurs in the DAA era has not been consistently reported. Pooled data from 12 registrational trials of interferon-free DAA regimens demonstrated low rates (<2%) of HCV RNA ≥LLOQ at week 4 of treatment [1]. In contrast, several real-world studies using similar regimens have reported higher rates of HCV RNA ≥LLOQ at treatment-week 4, varying from 14% to 29% [3–5]. PV occurred in 5.6% of patients within our real-world population of 983 DAA-treated patients. All patients with PV experienced a viral load reduction of at least >2 log after initiation of DAA treatment. A higher incidence of cirrhosis was observed in the PV group; however, given the disparity between sample sizes of patients with RVR or PV, we were unable to determine if this was a predictor of PV.

Conflicting data exist regarding the impact of PV on SVR, which raises the question of the utility of viral load monitoring in patients on DAA therapy. One large Veterans Affairs registry study (n = 21 095) found that patients with a detectable viral load at week 4 of DAA therapy had a lower likelihood of achieving SVR, although SVR rates remained high (86.2%–91.8%) in those patients [4]. A smaller study of 123 patients also found that patients achieving RVR are more likely to achieve SVR; however, this finding was limited to cirrhotic, genotype 3 patients [10]. In contrast, other small studies have failed to show a correlation between PV and treatment failure, including a recent pooled study of 950 patients with SVR rates of 97%–100% in patients with (n = 36) and without PV (n = 223) at week 4, respectively [3, 7, 11]. Our study provides further insight by demonstrating no difference in SVR between these groups. Taken together, these data suggest that on-treatment HCV RNA monitoring may be unnecessary, and instead suggest its utility may lie in patients at risk for nonadherence. These data support the recent AASLD/IDSA guidance update, which

Table 1. Patient Demographics and Baseline Characteristics

	Combined (n = 983)	Rapid Virologic Response (n = 927)	Persistent Viremia (n = 56)
Gender, % (No.)			
Male	64 (632)	63 (588)	79 (44)
Female	36 (351)	37 (339)	21 (12)
Age, y	51.0 56.0 61.0 (54.6 ± 10.6)	51.0 56.0 61.0 (54.7 ± 10.6)	50.0 55.0 59.2 (53.1 ± 9.9)
BMI, kg/m^2	24.1 27.4 31.6 (28.3 ± 6.5)	24.0 27.4 31.7 (28.3 ± 6.5)	25.4 27.2 30.3 (28.7 ± 6.5)
Race, % (No.)			
White	73.6 (723)	73.6 (682)	73.2 (41)
Black	22.4 (220)	22.1 (205)	26.8 (15)
Hispanic	0.9 (9)	1.0 (9)	0.0 (0)
Asian	0.8 (8)	0.9 (8)	0.0 (0)
Egyptian	1.3 (13)	1.4 (13)	0.0 (0)
Other[a]	0.7 (7)	0.8 (7)	0.0 (0)
Unknown	0.3 (3)	0.3 (3)	0.0 (0)
Previous treatment, % (No.)			
Naïve	82 (807)	82 (763)	79 (44)
Experienced[b]	18 (176)	18 (164)	21 (12)
Genotype, % (No.)			
1a	60.8 (598)	60.1 (557)	73.2 (41)
1b	17.2 (169)	17.9 (166)	5.4 (3)
1	2.0 (20)	2.2 (20)	0.0 (0)
2	7.7 (76)	7.9 (73)	5.4 (3)
3	8.9 (87)	8.5 (79)	14.3 (8)
4	2.3 (23)	2.4 (22)	1.8 (1)
6	0.6 (6)	0.6 (6)	0.0 (0)
Multiple[c]	0.3 (3)	0.3 (3)	0.0 (0)
Unknown	0.1 (1)	0.1 (1)	0.0 (0)
Fibrosis stage, % (No.)			
F0	11.0 (108)	10.9 (101)	12.5 (7)
F1	7.9 (78)	8.0 (74)	7.1 (4)
F0–F1	7.9 (78)	8.1 (75)	5.4 (3)
F1–F2	0.5 (5)	0.5 (5)	0.0 (0)
F2	6.5 (64)	6.6 (61)	5.4 (3)
F2–F3	17.5 (172)	17.5 (162)	17.9 (10)
F3	5.1 (50)	5.1 (47)	5.4 (3)
F3–F4	4.3 (42)	4.4 (41)	1.8 (1)
F4	29.7 (292)	28.8 (267)	44.6 (25)
Unknown	9.6 (94)	10.1 (94)	0.0 (0)
Cirrhosis, % (No.)			
Yes	34 (335)	33 (309)	46 (26)
No	66 (648)	67 (618)	54 (30)
CTP score, % (No.)			
A (5–6)	69.9 (234)	70.6 (218)	61.5 (16)
B (7–9)	24.8 (83)	23.9 (74)	34.6 (9)
C (>10)	5.4 (18)	5.5 (17)	3.8 (1)
Medication regimen, % (No.)			
DCV + SOF	4.4 (43)	4.6 (43)	0.0 (0)
DCV + SOF + RBV	0.6 (6)	0.6 (6)	0.0 (0)
SOF/VEL	10.1 (99)	10.2 (95)	7.1 (4)
SOF/VEL + RBV	2.0 (20)	1.5 (14)	10.7 (6)
EBR/GZR	2.0 (20)	2.2 (20)	0.0 (0)
EBR/GZR + RBV	0.3 (3)	0.3 (3)	0.0 (0)
LDV/SOF	62.9 (619)	63.2 (586)	57.1 (32)
LDV/SOF + RBV	8.0 (79)	7.6 (70)	16.1 (9)
G/P	0.1 (1)	0.1 (1)	0.0 (0)
SOF + SIM	0.7 (7)	0.8 (7)	0.0 (0)

Table 1. Continued

	Combined (n = 983)	Rapid Virologic Response (n = 927)	Persistent Viremia (n = 56)
SOF + SIM + RBV	0.1 (1)	0.1 (1)	0.0 (0)
SOF + RBV	4.6 (45)	4.5 (42)	5.4 (3)
PrO + RBV	0.2 (2)	0.2 (2)	0.0 (0)
PrOD	0.6 (6)	0.6 (6)	0.0 (0)
PrOD + RBV	3.4 (33)	3.3 (31)	3.6 (2)
HIV, % (No.)			
Yes	16 (161)	16 (147)	25 (14)
No	84 (822)	84 (780)	75 (42)
Liver transplant, % (No.)			
Yes	2.1 (21)	2.2 (20)	1.8 (1)
No	97.9 (962)	84 (780)	98.2 (55)
SVR achieved, % (No.)			
Yes	96.3 (947)	96.5 (895)	92.9 (52)
No	3.7 (36)	3.5 (32)	7.1 (4)

a b c represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables. $x \pm s$ represents X ± 1 SD. Numbers after proportions are frequencies.

Abbreviations: CTP, Child Turcotte Pugh; DCV, daclatasvir; EBR/GZR, elbasvir/grazoprevir; G/P, glecaprevir/pibrentasvir; LDV/SOF, ledipasvir/sofosbuvir; PrO, paritaprevir/ritonavir/ombitasvir; PrOD, paritaprevir/ritonavir/ombitasvir/dasabuvir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SOF/VEL, sofosbuvir/velpatasvir; SVR, sustained virologic response.

[a]Other races included Native American, Ethiopian, Rowandan, Burmese, Russian, Arabic.

[b]Treatment experienced included patients previously treated with interferon +/- ribavirin.

[c]Multiple genotypes included combinations of the following: 1a + 2a, 1a + 2b, 1a + 3, 1 + 3, and 1a + 4.

recommends against on-treatment viral load monitoring except in select circumstances [2].

We found that the majority (87.5%) of patients experiencing PV were adherent, and for the small number of patients on PPIs, which can decrease the absorption of some DAAs, no patients were on doses exceeding the maximum recommended dose. For patients at risk for nonadherence, provider engagement is likely to improve adherence and treatment completion rates [12]. Forty-one (73.2%) of the 56 patients experiencing PV had some sort of intervention, which demonstrates provider engagement. Patient evaluation at week 4, which may include virologic monitoring, may improve engagement by providing an opportunity to assess treatment adherence and side effects and navigate care barriers.

The impact of provider intervention in PV on SVR is not well studied. Extending ledipasvir/sofosbuvir and glecaprevir/pibrentasvir from 8 to 12 weeks in patients with PV did not demonstrate SVR differences in previous studies, though studies may not have been powered for that end point [4, 11]. In the current study, we observed higher SVR rates in PV patients receiving any intervention; however, we are unable to quantify the impact of intervention in patients with PV due to limited sample size. Based on our results of PV patients not receiving an intervention achieving an SVR of 80% (12/15), compared with 98% (40/41) in those receiving an intervention, there may be utility in HCV viral load monitoring and subsequent interventions in specific clinical scenarios.

Prospective randomized studies would be ideal to assess the impact of interventions on patients with PV; however, low rates of PV make these study designs unlikely. The small number of PV cases limited our ability to identify significant predictors of PV or clinical outcomes. Given the time period of this study, some regimens were used that are no longer considered first-line therapy. Additionally, a single assay was not consistently utilized among all patients, resulting in variability in the limit of detection.

In conclusion, low rates of PV while on DAA therapy were seen in this large, real-world cohort. Patients with PV and RVR had similarly high rates of SVR. These findings support current management and treatment recommendations and contribute to the current literature by describing the rate of PV, the frequency and type of interventions in response to PV, and the impact of PV on SVR rates in a large real-world cohort.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. Written informed consent was not required, as the data used were collected as part of standard clinical practice on human subjects. The Vanderbilt University Medical Center Institutional Review Board approved this study (#151671).

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