Clinical Infectious Diseases

MAJOR ARTICLE

Effect of Paritaprevir/Ritonavir/Ombitasvir/Dasabuvir and Ledipasvir/Sofosbuvir Regimens on Survival Compared With Untreated Hepatitis C Virus–Infected Persons: Results From ERCHIVES

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Background. Interferon-based regimens are associated with a substantial survival benefit for persons infected with hepatitis C virus (HCV). Survival data with direct-acting antiviral agents are not available. We conducted this study to quantify the effect of paritaprevir/ritonavir, ombitasvir, dasabuvir (PrOD) and ledipasvir/sofosbuvir (LDV/SOF) regimens upon mortality.

Methods. In the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES), a well-established national cohort of HCV-infected Veterans, we identified HCV-infected persons initiated on PrOD or LDV/SOF, excluding those with human immunodeficiency virus, hepatitis B surface antigen positivity, hepatocellular carcinoma, or missing HCV RNA or FIB-4 scores. For each case, we identified a propensity score–matched control never initiated on treatment. Primary outcome was survival. Outcomes were assessed using frequency of events, Kaplan-Meier curves, and Cox proportional hazards regression analyses.

Results. We identified 1473 persons on PrOD, 5497 on LDV/SOF, and 6970 propensity score–matched untreated persons. Treated persons were more likely to be obese and have cirrhosis, but less likely to have stage 3–5 chronic kidney disease (CKD), alcohol or drug abuse or dependence diagnosis, and anemia. The proportion of persons who died was higher in the untreated group compared with either treatment group (PrOD, 0.3%; LDV/SOF, 1.4%; untreated controls, 2.5%; $P < .001$). A significantly larger percentage of treated patients survived to 18 months of follow-up, compared with untreated controls ($P < .001$). In multivariable Cox regression analysis, treatment with either regimen (hazard ratio [HR], 0.43; 95% confidence interval [CI], .33–.57) and attainment of sustained virologic response (SVR) were associated with significantly lower mortality (HR, 0.57; 95% CI, .33–.99).

Conclusions. Treatment with PrOD or LDV/SOF and SVR are associated with a significant mortality benefit, apparent within the first 18 months of treatment.

Keywords. HCV; survival; sofosbuvir/ledipasvir; PrOD; ERCHIVES.

Newer oral direct-acting antiviral agents (DAAs) against hepatitis C virus (HCV) infection have revolutionized the management of patients with chronic HCV infection [1]. Numerous agents are now approved for use in various combinations and reliably achieve sustained virologic response (SVR) rates of >90% [2]. While viral eradication is understandably the primary endpoint in clinical trials and the primary goal in clinical care, an important benefit would be improvement in survival and a reduction in complications of chronic HCV infection. Numerous studies in the interferon/ribavirin era demonstrated such benefit in reducing mortality and complications [3–5]. Emerging data in the era of DAA therapy suggest that these agents are associated with lower fibrosis progression, but potentially a paradoxically higher incidence of hepatocellular carcinoma [6, 7]. Large studies demonstrating a survival benefit from these agents are lacking. We conducted this study to determine the effect of 2 different DAA regimens (paritaprevir/ritonavir, ombitasvir, dasabuvir [PrOD]) and sofosbuvir/ledipasvir [LDV/SOF] upon all-cause mortality, within a large, population-based national cohort of adults with HCV.

METHODS

Data Sources and Study Subjects

We used the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) for this study. ERCHIVES is a well-established national cohort of HCV-infected persons and age-matched (5-year blocks), sex-matched, and race-matched controls, who received care within any of the Veterans Health Administration (VA) healthcare facilities. Numerous previous publications

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have described the creation and update of the ERCHIVES database [8–11]. In brief, all HCV-infected Veterans are identified through the electronic medical records based on a positive HCV antibody test. Age-matched (5-year blocks), race-matched, and sex-matched HCV-uninfected controls are also identified based on a negative HCV antibody test in the same year as the corresponding HCV positive case. Demographic, clinical, laboratory, pharmacy, utilization, and vital status data are retrieved from VA's Corporate Data Warehouse. Data are retrieved using scrambled social security numbers and merged to yield a comprehensive database of HCV-infected and -uninfected persons after cleaning and validation according to our established algorithms. The cohort is updated yearly to include newly diagnosed cases.

For the current study, we identified HCV-infected persons within ERCHIVES who were started on a PrOD or LDV/SOF regimen. We excluded those with human immunodeficiency virus (HIV) coinfection, positive hepatitis B surface antigen test, hepatocellular carcinoma, missing laboratory test results, or missing HCV RNA or FIB-4 score at baseline and ≥12 weeks after completion of treatment. For each person identified in the PrOD and LDV/SOF groups, we identified a HCV-infected control never initiated on any HCV treatment, matched by propensity scores by age in 5-year blocks, race, sex, HCV genotype, diabetes, estimated glomerular filtration rate, low-density lipoprotein cholesterol level, and FIB-4 score.

Definitions

We used FIB-4 and Child-Turcotte-Pugh (CTP) scores to estimate the severity of liver disease. FIB-4 and CTP scores were calculated based on clinical and laboratory variables recorded closest to, but prior to baseline. FIB-4 was calculated as follows:

$$\mathrm{FIB}-4=\mathrm{age}[\mathrm{years}]\times\mathrm{AST}[\mathrm{IU/L}]/\mathrm{platelet\ count}\left[\times10^{9}/\mathrm{L}\right]\times\left(\mathrm{ALT}^{1/2}[\mathrm{IU/L}]\right).$$

Child-Turcotte-Pugh score was calculated using a point scoring system for total bilirubin, serum albumin, international normalized ratio, and presence and severity of ascites and hepatic encephalopathy using a validated algorithm published by Kaplan et al [12]. Based on the points accrued, patients were assigned CTP class A (5–6 points), B (7–9 points), or C (10–15 points). To account for extreme outliers, we excluded those with values >99.99th percentile for alanine and aspartate aminotransferases. Cirrhosis was defined as a FIB-4 score of >3.5 as per our previous publications. Diabetes was defined using a previously published algorithm of blood glucose measurement, use of insulin or oral hypoglycemic agents, and *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes [13, 14]. Chronic kidney disease (CKD) was defined by estimating glomerular filtration rate using the *Chronic Kidney Disease* Epidemiology Collaboration (CKD-EPI) equation [15]. Anemia was defined as hemoglobin values of <13 g/dL for men and <12 g/dL for women. Alcohol and drug abuse and dependence were defined by presence of at least 1 inpatient or 2 outpatient *ICD-9*, *Clinical Modification* codes [16].

Primary Outcome

The primary outcome was survival. For time-to-event analyses, time at risk was measured from treatment initiation to last observation date in ERCHIVES. Mortality data and date of death were obtained from the VA Corporate Data Warehouse, which collects mortality information on Veterans in care from multiple sources.

Statistical Analyses

We compared the demographic, clinical, and laboratory characteristics of persons in the PrOD and LDV/SOF groups with corresponding untreated and matched controls. Mean or median values were compared using the χ^2 or Wilcoxon signed-rank test, as appropriate. We created Kaplan-Meier curves to illustrate the time to death for each group (PrOD, LDV/SOF, and untreated). We determined the factors associated with mortality using a multivariable Cox regression model. Assumptions for proportionality were tested using Schoenfeld residuals. We used SAS software version 9.4 (SAS Institute, Cary, North Carolina) and Stata software version 11 (StataCorp, College Station, Texas) for analyses.

Ethical Approval

The study was approved by the institutional review board at the VA Pittsburgh Healthcare System (Pittsburgh, Pennsylvania).

RESULTS

Within ERCHIVES, we identified 1473 persons in the PrOD group, 5497 in the LDV/SOF group, and 6970 untreated persons who met the study criteria (Figure 1). Baseline demographic, clinical, and laboratory characteristics are provided in Table 1. Median age was 62 years in the PrOD group and 61 years in the LDV/SOF group, and 95%–97% were men. Persons who were treated with either regimen had higher median body mass index and were more likely to have cirrhosis (PrOD, 24.9%; LDV/SOF, 29.4%; untreated controls, 19.4%), but less likely to have stage 3–5 CKD (PrOD, 22.7%; LDV/SOF, 27.3%; untreated controls, 31.8%), alcohol abuse or dependence diagnosis (PrOD, 17.2%; LDV/SOF, 19.5%; untreated controls, 28.0%), drug abuse or dependence diagnosis (PrOD, 18.5%; LDV/SOF, 21.5%; untreated controls, 30.0%), and anemia (PrOD, 8.7%; LDV/SOF, 14.7%; untreated controls, 20.3%). The proportion of persons who died was higher in the untreated group compared with either treatment group (PrOD, 0.3%; LDV/SOF, 1.4%; untreated controls, 2.5%; $P < .001$ for either regimen vs untreated controls). (Baseline characteristics comparing both treatment groups with their respective propensity-score matched controls are provided in Supplementary Table 1).

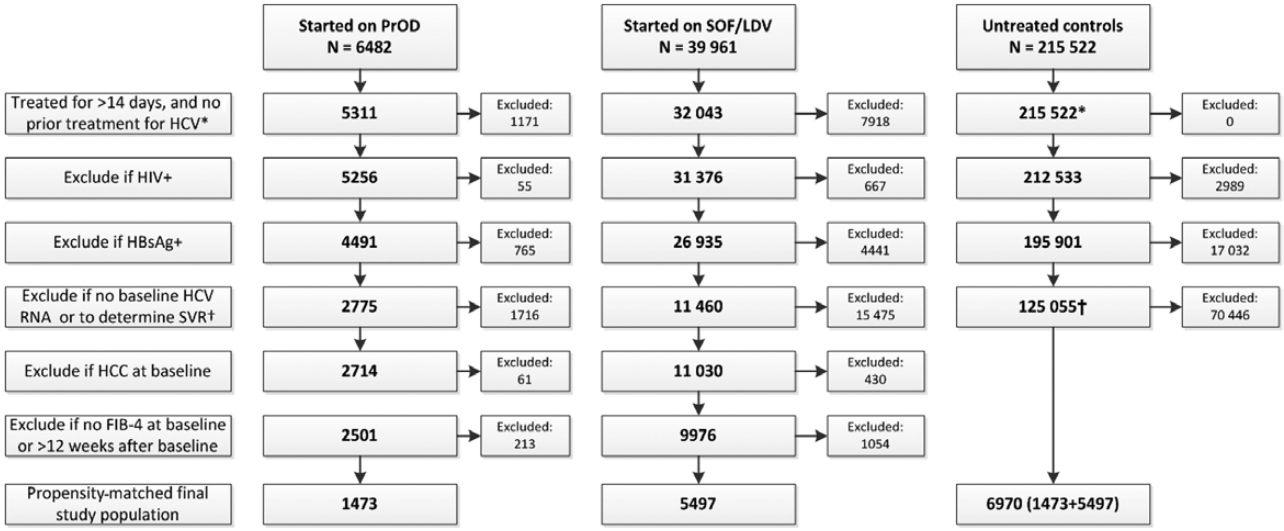


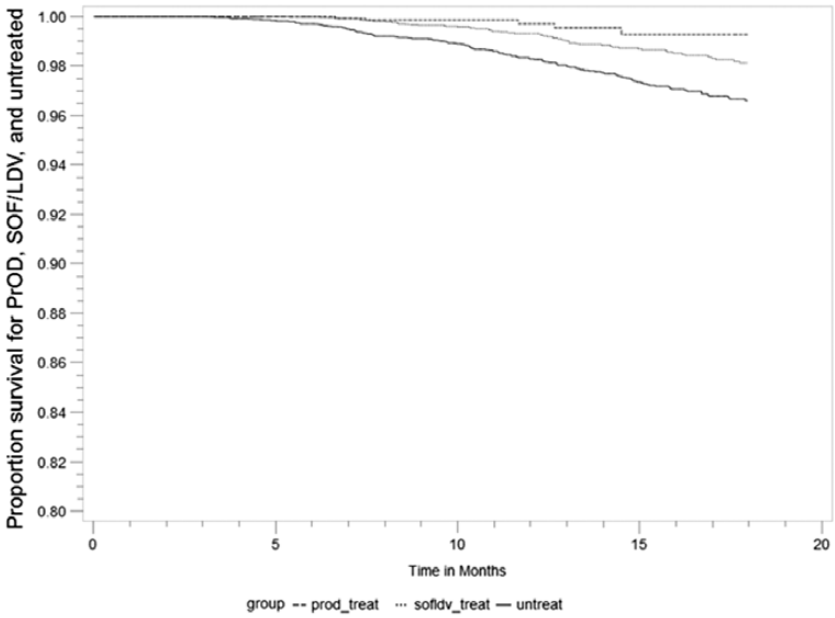
Figure 1. Study flowchart. *For the untreated controls, the persons retained were those who never received any treatment for hepatitis C virus (HCV). †For untreated controls, those with missing or undetectable HCV RNA were excluded at this stage. Abbreviations: HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PrOD, paritaprevir/ritonavir, ombitasvir, dasabuvir; SOF/LDV, sofosbuvir/ledipasvir; SVR, sustained virologic response.

Kaplan-Meier curves comparing PrOD and LDV/SOF regimens with untreated controls showed significantly larger proportion of treated persons surviving at 18 months of follow-up compared with untreated controls (Figure 2). When each treatment regimen was compared only with their own untreated control group, treated groups showed similar improvement in

Table 1. Baseline Characteristics Among Patients Treated With Ledipasvir/Sofosbuvir or Paritaprevir/Ritonavir, Ombitasvir, Dasabuvir, and Untreated, Propensity Score–Matched Controls

	PrOD	LDV/SOF	Untreated	*P* Value		
Characteristic	(n = 1473)	(n = 5497)	(n = 6970)	A vs B	A vs C	B vs C
Age, y, median (IQR)	62 (58–65)	61 (57–65)	61 (57–65)	<.001	<.001	.1
Sex, male, %	96.7	96.2	95.3	.3	.01	.01
Race/ethnicity, %						
White	46.9	55.4	54.4	<.001	<.001	.03
Black	32.0	25.7	28.0			
Hispanic	1.6	1.7	1.6			
Other	19.5	17.2	16.0			
BMI, kg/m^2, median (IQR)	27.8 (24.7–31.0)	28.1 (25.0–31.7)	27.1 (23.9–31.1)	.01	.001	<.001
BMI >30 kg/m^2, %	31.4	35.6	30.9	.003	.71	<.001
Cirrhosis (FIB-4 score >3.5), %	24.9	29.4	19.4	.001	<.001	<.001
Diabetes, %	13.2	15.0	13.9	.08	.43	.09
CKD stage 3–5, %	22.7	27.3	31.8	<.001	<.001	<.001
Alcohol abuse or dependence, %	17.2	19.5	28.0	.04	<.001	<.001
Drug abuse or dependence, %	18.5	21.5	30.0	.01	<.001	<.001
HCV RNA, $\log_{10}$ IU/mL, median (IQR)	6.6 (6.1–8.5)	6.4 (5.8–7.2)	6.4 (5.7–7.1)	<.001	<.001	.01
Genotype, %						
1a (incl. 1ab and 1NS)	61.2	63.8	62.6	<.001	<.001	<.001
1b	38.2	17.2	23.0			
Not specified/mixed	0.6	19.0	14.4			
Anemia, %	8.7	14.7	20.3	<.001	<.001	<.001
Child-Turcotte-Pugh class, %						
A (score 5–6)	93.5	89.6	86.7	<.001	<.001	<.001
B (score 7–9)	6.4	9.8	12.6			
C (score 10–15)	0.1	0.5	0.7			
Achieved SVR, %	94.0	90.7	NA	<.001		
Died, %	0.3	1.4	2.5	.001	<.001	<.001

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; HCV, hepatitis C virus; IQR, interquartile range; LDV/SOF, ledipasvir/sofosbuvir; NA, not applicable; NS, not specified; PrOD, paritaprevir/ritonavir, ombitasvir, dasabuvir; SVR, sustained virologic response.



Number at risk	1 month	5 months	10 months	15 months	18 months
LDV/SOF	5497	5477	4322	2562	1392
PrOD	1473	1471	1018	304	17
Untreated	6962	6883	5546	2961	1468

Figure 2. Kaplan-Meier curves for survival for paritaprevir/ritonavir, ombitasvir, dasabuvir (PrOD), ledipasvir/sofosbuvir (LDV/SOF), and untreated controls. ($P < .001$).

proportion surviving at 18 months (Supplementary Figure 1). In a multivariable logistic regression model, factors associated with a higher mortality included increasing age and presence of cirrhosis, diabetes, CKD, or anemia at baseline. Factors associated with lower mortality included black race, increasing HCV RNA, and treatment with either regimen (hazard ratio [HR], 0.43; 95% confidence interval [CI], .33–.57; Table 2). In a model limited to those who received treatment, attainment of SVR was associated with a significantly lower mortality (HR, 0.57; 95% CI, .33–.99; Table 3).

We conducted additional analyses comparing survival in treatment groups stratified by cirrhosis at baseline (Supplementary Figure 2) and after excluding those with CKD stage 3–5 and a diagnosis of alcohol or drug abuse or dependence (Supplementary Figure 3) to understand the influence of these factors upon survival. We also estimated the hazards of death in a multivariable Cox proportional hazards model in this subpopulation (Supplementary Table 2). Treatment remained associated with a significant survival benefit in these analyses.

DISCUSSION

To our knowledge, this is the first large-scale study to demonstrate the effect of newer DAA regimens upon survival. Treatment with 2 commonly used DAA regimens, PrOD and LDV/SOF, was associated with significant improvements in survival within the first 18 months of treatment, compared with demographically and clinically similar untreated HCV-infected controls. Treatment with either PrOD or LDV/SOF

Table 2. Factors Associated With Mortality in the Full Study Population (Multivariable Cox Regression Analysis)

Factor	Hazard Ratio	95% CI
Age, y, per 10-y increase	1.24	(1.04–1.49)
Male sex	1.46	(.64–3.31)
Race/ethnicity		
White (comparator)	1	
Black	0.6	(.43–.83)
Hispanic	0.79	(.32–1.93)
Other	0.87	(.6–1.26)
Body mass index ≥30 kg/m^2 (vs <30)	0.98	(.75–1.28)
Cirrhosis, FIB-4 score >3.5 (vs ≤3.5)	3.13	(2.43–4.05)
Diabetes	1.36	(1–1.85)
CKD stage 3–5	1.44	(1.09–1.9)
Alcohol abuse or dependence	1.07	(.79–1.47)
Drug abuse or dependence	0.96	(.7–1.32)
HCV RNA, per 1 $\log_{10}$ IU/mL	0.93	(.87–.99)
Genotype		
1a (comparator) (includes 1ab, 1NS)	1	
1b	1.21	(.9–1.64)
Non-1 (all other groups combined)	1.21	(.87–1.67)
Treated with either LDV/SOF or PrOD (vs untreated)	0.43	(.33–.57)
Anemia	2.3	(1.75–3.02)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; HCV, hepatitis C virus; LDV/SOF, ledipasvir/sofosbuvir; PrOD, paritaprevir/ritonavir, ombitasvir, dasabuvir.

Table 3. Factors Associated With Mortality in the Treated Population to Demonstrate the Impact of Sustained Virologic Response (Multivariable Cox Regression Analysis)

Factor	Hazard Ratio	(95% CI)
Age, y, per 10-y increase	1.23	(.86–1.77)
Male sex[a]	…	NA
Race/ethnicity		
White (comparator)	1	
Black	0.46	(.24–.88)
Hispanic	1.29	(.4–4.2)
Other	0.63	(.3–1.33)
BMI ≥30 kg/m^2 (vs <30 kg/m^2)	1.16	(.74–1.83)
Cirrhosis, FIB-4 score >3.5 (vs ≤3.5)	2.23	(1.4–3.56)
Diabetes	1.46	(.84–2.52)
Chronic kidney disease, stage 3–5	1.19	(.72–1.96)
Alcohol abuse or dependence	1.52	(.89–2.6)
Drug abuse or dependence	1.05	(.59–1.88)
HCV RNA, per 1 $\log_{10}$ IU/mL	1	(.88–1.13)
Genotype		
1a (comparator)	1	
1b	1.28	(.72–2.25)
Non-1 (all other groups combined)	1.27	(.73–2.2)
Anemia	2.17	(1.31–3.59)
Attaining sustained virologic response	0.57	(.33–.99)

Abbreviations: BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; NA, not applicable.

[a]No females achieved the stated endpoint.

was associated with a 57% reduction in mortality, and attainment of SVR was associated with a 43% reduction in mortality.

Several previous studies demonstrated the effect of older, interferon-based regimens upon survival [3–5]. In contrast, such data are lacking for the newer, all-oral DAA regimens. While it is intuitive that newer therapies will improve survival, quantification of such benefit is important to determine the population-level benefits of the newer therapies. Our study provides strong evidence and quantification of the impact of PrOD and LDV/SOF regimens upon overall survival. Similar to the pre-DAA studies, we observed a significant survival benefit with treatment and with attainment of SVR. As 94% of PrOD-treated and 91% of LDV/SOF-treated persons attained SVR, the population-level benefit of successful HCV eradication is expected to be significant. Although we studied only PrOD and LDV/SOF regimens, similar benefit can be expected with other DAA-based regimens.

Presence of comorbidities was associated with higher mortality. Whether such mortality was associated with the comorbidity itself or HCV is unclear. With the newer DAAs, there is a clear increase in treatment rates of patients with comorbidities, and presence of such comorbidities alone should not be a contributing factor in the decision to initiate treatment. Of note, diagnoses of alcohol or drug abuse or dependence were not associated with increased mortality. These factors were previously considered a contraindication, or at least a significant barrier to treatment. Our results suggest that a history of these conditions should not deter providers from initiating treatment.

A curious finding was a significantly reduced mortality among African-American patients who received therapy with PrOD or LDV/SOF. Disparities in clinical outcomes usually negatively affect black individuals, as has been demonstrated for heart disease and cancer [17, 18]. In the pre-DAA era, black individuals were less likely to be initiated on anti-HCV treatment [19]. More recently, an analysis of National Health and Nutrition Examination Survey (NHANES) data found that the racial group with highest HCV-related mortality was Mexican Americans, followed by non-Hispanic whites. In that analysis, non-Hispanic blacks had a lower all-cause mortality compared with other racial/ethnic groups, although that mortality was higher than among HCV-uninfected persons [20]. Lower mortality has also been observed in black HCV-infected individuals on hemodialysis, compared with whites on hemodialysis [21]. Whether the lower mortality is due to differences in clinical characteristics, disease severity, or other factors is not known.

Major strengths of our study include a large, geographically and racially diverse population treated for HCV. Additionally, there are no financial incentives or disincentives in treating Veterans with the newer DAAs, which serves to reduce treatment bias based on financial and insurance status. Our study was conducted in the ERCHIVES database, which is a well-characterized, national cohort of HCV-infected Veterans. Patient selection, data collection, and outcome measures have been carefully developed over years, and have been subjected to rigorous peer review through the numerous publications to its credit.

Certain limitations must be noted to interpret the results of our study. Selection of patients for treatment and assignment of treatment group were not randomized. There are differences in some baseline clinical characteristics between the PrOD and LDV/SOF groups. Therefore, direct comparisons between these 2 groups cannot be made. However, we identified controls for each group based on propensity score matching, which would mitigate the imbalance in such characteristics. Our study population was predominantly male, and there were no deaths observed in the small number of women who received treatment. Hence, this study cannot be generalized to the entire population.

In conclusion, treatment for HCV with either PrOD or LDV/SOF and attainment of SVR are associated with a significant reduction in mortality, a benefit that is seen within the first 18 months of treatment. Benefits of treatment at a population level are expected to be substantial.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

Author contributions. A. A. B. had complete access to data at all times and accepts the responsibility of the integrity of this article.

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