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RESEARCH ARTICLE

Efficacy and Safety of Direct Acting Antivirals (DAAs) in an Urban Clinical Setting

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Abstract

Background: Development of novel direct acting antivirals (DAAs) has led to > 95% sustained virological response rates (SVR12) in patients with hepatitis C virus (HCV) in controlled clinical trials.

Objective: The purpose of this study was to evaluate the safety and efficacy of DAAs in a non-controlled setting.

Methods: This retrospective cohort included patients who initiated on DAAs between May 2014 and May 2018. The primary endpoint was SVR12. Descriptive statistics were used to analyze the results. Bivariate associations between patients achieving treatment success and demographic and clinical variables were conducted using chi-square, Fisher's exact test, and independent samples t-test with a two-sided alpha value of 0.05.

Results: Of the 50 patients with HCV who were initiated on DAAs, 3 were lost to follow-up and 1 died during treatment. SVR12 was achieved in 42 of 50 (84%) patients by ITT analysis and in 42 of 45 (93%) patients by the per-protocol analysis. Two patients died and 3 were lost to follow-up (LTFU). All 3 patients LTFU had a history of heroin use; this was the only demographic factor significantly associated with treatment failure (Fisher's exact p = 0.02).

Conclusion and relevance: Findings from our cohort indicate that SVR12 rates based on ITT analysis are lower than the > 95% rates seen in large controlled clinical trials, mainly due to patients being lost to follow-up. These findings suggest that a gap remains in the HCV treatment cascade, especially in the underserved populations and persons with a history of drug use.

Keywords

Hepatitis C, Antivirals

Introduction

Interferon-free oral regimens with direct-acting antivirals (DAAs) are now the standard of care for treatment of chronic hepatitis C virus (HCV) infection [1,2]. In registrational clinical trials, these regimens result in sustained virologic response at post-treatment week 12 (SVR12) rates of > 95% in most patient populations with HCV, including those co-infected with HIV [1,2]. Recent analyses of efficacy and safety of DAAs in real-world setting have shown similarly high SVR12 rates [3-5].

Several studies, however, have shown lower SVR12 rates in males, patients with advanced fibrosis/cirrhosis, and those with a history of prior HCV therapy [6-8]. Additionally, demographics such as African American race, psychiatric comorbidities, and lower education level have shown to be associated with lower medication adherence rates [9,10]. Some community practices have also reported suboptimal SVR12 rates based on intention-to-treat (ITT analyses), mainly due to high lost to follow-up (LTFU) rates [6,11,12] and associations between illicit drug use, LTFU, and lower SVR12 rates [13-15]. These smaller real-world studies provide complementary data to registrational trials by highlighting additional efficacy and safety information of new regimens in a broader population.

Our urban family medicine clinic is located in a large city in the southeastern United States, and currently provides care to approximately 2,400 individuals,

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including 485 with HIV and 89 with HCV. The majority of our patients are enrolled in government health care assistance programs (Medicaid, Ryan White) and therefore have limited access to specialists, such as hepatologists/gastroenterologists.

Since the FDA approval of sofosbuvir/ledipasvir (SOF/LDV) in 2014, we sought to treat as many of our patients infected with HCV as possible. Due to the initial formulary restrictions, patients with advanced fibrosis (F3) and compensated cirrhosis (F4) were generally the first ones to be treated, with a subsequent expansion of access to all patients, regardless of fibrosis status. Patients with decompensated cirrhosis were referred to a hepatology/gastroenterology specialist. Of the 89 patients with HCV, we included 50 in this analysis. The other 49 patients were not included due to various reasons, such as being treated by a hepatology/gastroenterology specialist, lack of consistent follow-up at the clinic, and lack of adequate HIV virologic suppression (if HIV/HCV co-infected).

The goal of this retrospective analysis is to describe the safety and efficacy of DAAs in our practice, where the majority of patients with HCV are co-infected with HIV.

Methods

Study population

All patients initiated on DAAs between March 2014 and May 2018 were included in this analysis.

Study design

This was a single-center, retrospective study performed at a family medicine clinic in Charlotte, North Carolina. Data were retrospectively collected from an electronic medical records database.

Measurements

All the standard laboratory measurements (HCV RNA, HCV genotype, liver function tests, chemistry, CBC) were recorded throughout the duration of HCV treatment and until the SVR12 follow-up appointment. Baseline HCV Fibrosure® (LabCorp) results were also recorded; this is currently the preferred non-invasive biomarker to assess patients' liver fibrosis status at our practice.

Effectiveness and safety assessments

HCV RNA measurements were documented throughout the treatment period, through 12 weeks post-treatment. Treatment success was defined as undetectable HCV RNA 12 weeks after completion of therapy (i.e., SVR12). Treatment failure was defined as lack of SVR12 in any patient who was initiated on DAA therapy. Virologic failure was considered as one of the causes of treatment failure. Virologic failure included either on-treatment failure [(defined as HCV RNA > 15 IU/mL at the end of treatment (EOT)] or post-treatment relapse (defined as undetectable HCV RNA at EOT but > 15 IU/mL at 12 weeks after EOT). Treatment failure could also include failure due to other reasons, including death and LTFU after EOT.

Documented adverse events (AEs) were recorded for each patient's treatment period. Common Terminology Criteria for Adverse Events (CTCAE) version 5 was utilized to retrospectively grade AEs. Adverse events in the CTCAE classification are graded 1 through 5 (1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening; 5 = death). Additionally, specific clinical descriptions are provided for the severity of each AE [16]. Any early treatment discontinuations due to AEs or other factors were also extracted from the medical records.

Statistical analysis

The primary objective, proportion of patients achieving SVR12 based on ITT analysis, was assessed with descriptive statistics. SVR12 rates using per-protocol (PP) analysis and safety/tolerability were also assessed. Bivariate associations between SVR12 rates and demographic and clinical variables were conducted using chi-square, Fisher's exact test, and independent samples t-tests. Analyses were conducted using SAS version 9.4. Tests were two-sided, with a p value set at less than 0.05 to indicate statistical significance.

Ethical aspects

The research review board at Wingate University approved this study.

Results

Patients

HCV DAAs were initiated in 50 patients; SOF/LDV was the most frequently prescribed DAA combination (31/50 patients; 62%). SOF/LDF was prescribed for 12 weeks in 30 patients and for 8 weeks in 1 patient. Elbasvir/grazoprevir (EBR/GZR) and sofosbuvir/velpatasvir (SOF/VEL) were prescribed for 12 weeks in 8 and 7 patients, respectively. Ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) with dasabuvir (DSV) was prescribed for 12 weeks in 2 non-cirrhotic patients with genotype 1b and in combination with ribavirin (RBV) for 1 non-cirrhotic patient with genotype 1a; 1 patient with cirrhosis and genotype 1a received OBV/PTV/r with DSV and RBV for 24 weeks. Additional baseline demographics are described in (Table 1).

Our study population consisted of mainly African American men with advanced fibrosis/cirrhosis, who were naïve to HCV therapy and co-infected with HIV. Only 3 patients (6%) had previously been treated for HCV; all 3 failed prior peginterferon (peg IFN) with RBV therapy. In addition to HIV, other common comorbidities were hypertension (n = 26, 52%), diabetes (n = 12, 24%), depression/anxiety (n = 8, 16%), dyslipidemia (n = 8, 16%), GERD (n = 7, 14%), and bipolar/schizophrenia (n = 6, 12%). Two patients had chronic kidney disease

Table 1: Baseline Characteristics.

Characteristic	Total cohort, n = 50
Age, years [mean (SD)]	57 (10)
Males, n (%)	39 (78%)
Black/African American, n (%)	42 (84%)
Caucasians, n (%)	4 (8%)
Hispanic, n (%)	4 (8%)
Genotype, n (%)	
1	43 (86%)
1a	30 (60%)
1b	13 (26%)
2	3 (6%)
3	3 (6%)
4	1 (2%)
Advanced fibrosis/cirrhosis (F3-4), n (%)	28 (56%)
Baseline HCV RNA (IU/ml), median (range)	2,769,930 (33,270-16,400,000)
HCV RNA > 800,000 (IU/ml), n (%)	39 (78%)
DAA Therapy	
SOF/LDV	31 (62%)
EBR/GZR	8 (16%)
SOF/VEL	7 (14%)
OBV/PTV/r + DSV +/- RBV	4 (8%)
Previous HCV treatment status	
Naïve, n (%)	47 (94%)
Experienced, n (%) [pegIFN + RBV]	3 (6%)
History of prior heroin use	3 (6%)
HIV co-infection, n (%)	33 (66%)
CD4+ cell count (cells/mm^3), median (range)	588 (95-2200)
HIV-1 RNA ≤ 50 copies/ml, n (%)	28/33 (85%)
Receiving HAART, n (%)	32/33 (97%)
Payer, n (%)	
Medicare	19 (38%)
Medicaid	8 (16%)
Private insurance	10 (20%)
Pharmaceutical Patient Assistance Program	13 (26%)

DAA: Direct acting antiviral therapy; DSV: Dasabuvir; EBR/GZR: Elbasvir/grazoprevir; HCV: Hepatitis C virus; HAART: Highly active antiretroviral therapy; HIV: Human immunodeficiency virus; OBV/PTV/r: Ombitasvir/paritaprevir/ritonavir; pegIFN: Pegylated interferon; RBV: Ribavirin; SOF/LDV: Sofosbuvir/ledipasvir; SOF/VEL: Sofosbuvir/velpatasvir.

(CKD) with an estimated creatinine clearance (CrCL) less than 30 ml/min and were treated with agents that are approved for use in this population; one patient was treated with EBR/GZR and the other patient was treated with OBV/PTV/r with DSV.

Three of the patients (6%) had a history of prior heroin abuse. All 3 patients reported the timing of last heroin use being greater than 3 months ago, and lack of current heroin use was confirmed on the urine drug screen (UDS) prior to HCV therapy initiation. Of the 50 patients that initiated HCV therapy, 3 were lost to follow-up after achieving undetectable HCV RNA at the end of treatment and all 3 had a history of heroin use. Two patients died during therapy; 1 died due to newly diagnosed hepatocellular carcinoma (HCC) and 1 from sepsis unrelated to HCV.

Effectiveness

SVR12 was achieved in 42 of 50 (84%) patients by ITT analysis and in 42 of 45 (93%) patients by the per-protocol analysis. Among the four DAA combinations studied, there was some variability in SVR12 rates among patients with the different HCV genotypes, most likely due to the small sample size in each treatment group (Table 2). Patients with advanced fibrosis/cirrhosis (F3-F4) experienced similar SVR12 rates as patients without significant liver fibrosis (F0-F2) (Table 2).

Based on the ITT analysis, 8 patients experienced treatment failure. Virologic failure occurred in 4 patients; 3 patients experienced post-treatment relapse and 1 patient experienced on-treatment failure (this patient also died from HCC). Treatment failure due to other reasons was noted in 5 patients, including 3 patients who were LFTU after achieving HCV RNA < 15 IU/mL at the EOT and 2 patients who died. The only factor statistically significantly associated with treatment failure was a history of prior heroin use (Fisher's exact p = 0.02). There were no cases of HCV reinfection.

Safety

HCV therapy with DAAs was well tolerated; one patient reported insomnia and another patient reported dyspepsia during treatment. Grade 1-2 laboratory abnormalities were noted in 23 (46%) patients and included elevations in alkaline phosphatase (n = 3, 6%); bilirubin (n = 2, 4%), glucose (n = 12, 24%); serum creatinine (n = 5, 10%); AST/ALT (n = 2, 4%); anemia (n = 2, 4%); neutropenia (n = 1, 2%), and hypertriglyceridemia (n = 3, 6%).

Discussion

Similar to previous reports from other community practices [6,11-13]. we saw a lower ITT SVR12 rate compared to the large registrational trials, mainly due to 3 (6%) patients being LTFU. A recent report from the Grady Liver Clinic in Atlanta, GA showed that out of the 439 patients initiated on HCV therapy in 2017, only 286 (65%) achieved SVR12 by ITT analysis due 130 (30%) patients failing to follow up for their SVR12 check. Of these 130 patients, 80 (62%) eventually completed SVR12 testing and 30 (38%) did not re-engage in care [11]. In a South Australian cohort of 1921 patients receiving DAA treatment 2016-2017, 80% and 96% experienced SVR12

Table 2: Treatment Outcomes in the Intention-to-Treat Population.

Outcome	All, n = 50	SOF/LDV, n = 31	SOF/VEL, n = 7	EBR/GZR, n = 8	OBV/PTV/r + DSV +/- RBV, n = 4
SVR12	42 (84)	26 (84)	6 (86)	6 (75)	4 (100)
SVR12 according to GT					
GT1	36/43 (84)	25/30 (83)	1/1 (100)	6/8 (75)	4/4 (100)
GT1a	26/30 (87)	17/21 (81)	-	7/7 (100)	2/2 (100)
GT1b	11/13 (85)	8/9 (89)	1/1 (100)	0/1 (0)	2/2 (100)
GT2	3/3 (100)	-	3/3 (100)	-	-
GT3	2/3 (67)	-	2/3 (67)	-	-
GT4	1/1 (100)	1/1 (100)	-	-	-
SVR12 according to liver fibrosis status					
F0-F2	18/22 (82)	12/14 (86)	3/4 (75)	2/3 (67)	1/1 (100)
F3-F4	24/28 (86)	14/17 (82)	3/3 (100)	4/5 (80)	3/3 (100)
Virologic failure					
On-treatment failure	1 (2)*	1 (3)*			
Post-treatment relapse	3 (6)	2 (6)	1 (14)	0	0
Failure due to other reasons					
LTFU after EOT	3 (6)	2 (6)	0	1 (13)	0
Death	2 (4)*	1 (3)*	0	1 (13)	0

DSV: Dasabuvir; EBR/GZR: Elbasvir/grazoprevir; EOT: End of treatment; F0-F2: Fibrosis stage 0 to 2; F3-F4: Fibrosis stage 3 (advanced fibrosis) to 4 (cirrhosis); GT: Genotype; OBV/PTV/r: Ombitasvir/paritaprevir/ritonavir; LTFU: Lost to follow up; RBV: Ribavirin; SOF/LDV: Sofosbuvir/ledipasvir; SOF/VEL: Sof osbuvir/velpatasvir.

*One patient is counted twice; this patient experienced on-treatment failure and died.

rate by ITT and per-protocol, respectively, due to 14% of patients being LTFU [6]. A community practice in Austin, Texas reported a greater than 50% LTFU rate in their cohort of 247 patients treated with DAAs 2014-2016, translating to SVR12 rates of 46% and 95% by ITT and per-protocol analyses, respectively [12].

Of all the baseline demographics, only prior heroin use was significantly associated with DAA treatment failure in our study. In addition, the 3 patients with a history of heroin use were the same 3 patients who were lost to follow-up. Historically, concerns regarding poor medication adherence as well as psychiatric comorbid conditions and intolerable adverse effects with peg IFN/RBV therapy were some of the factors that led to the exclusion of substance users from HCV treatment consideration [17]. These perceptions continue to play a role in today's era of DAAs, with many physicians unwilling to treat patients with active illicit drug use [17-20].

Similar to our small study, other studies have reported that current or former drug abuse results in higher LTFU rates and a lower odds of SVR with DAAs [13-15]. A combined analysis of two large Spanish cohorts that included HIV/HCV-coinfected and HCV-monoinfected patients reported a significantly lower SVR12 rate for ongoing drug users compared to non-drug users (79% vs. 95%; $p < 0.001$), mainly due to a high LTFU rate of 17% [15]. Data from the ANCHOR trial suggest that initiating buprenorphine during HCV therapy improves adherence and treatment success rates [21].

In contrast, many other studies as well as post-hoc analyses of registrational trials have reported high SVR12 rates in persons with a history of injection drug use [22-26]. The phase IV SIMPLIFY Study reported a SVR12 rate of 94% in patients who received SOF/VEL and had ongoing injection drug use during HCV treatment [22]. A phase II trial in 38 patients with a history of injection drug use who were on stable opioid substitution therapy (OST) reported a SVR12 rate of 97.5% after 12 weeks of OBV/PTV/r with DSV and RBV [23]. The C-EDGE CO-STAR study evaluated EBR/GZR in 301 patients who were on OST and reported a SVR12 rate of 90%, despite 50% of patients having documented positive UDS for a drug of abuse other than methadone or buprenorphine. This study also reported > 95% of patients having > 95% medication adherence rates, documented by patients in their electronic medication diary [24]. Post-hoc analyses from the phase III ION and ASTRAL studies have shown similarly high SVR12 and medication adherence rates in patients on OST despite ongoing drug use [25,26]. These data sets have led to the current recommendations that emphasize that HCV treatment is not contraindicated in people who inject drugs (PWID) (active or recent use) and successful HCV therapy benefits public health by reducing HCV transmission [1,2].

The findings from our study and several other cohorts suggested that a significant gap remains in the HCV treatment cascade, especially in the underserved

populations and PWID. Creative strategies and additional resources are needed to continue to engage and to re-engage difficult-to-reach patients. Our practice recently allocated funds to employ a full-time case manager who is responsible for additional outreach support for our patients infected with HCV and HIV. The case manager works closely with the PWID population to get them engaged with inpatient and outpatient drug rehabilitation programs. We are now also performing careful screening of patients to identify candidates for opioid substitution therapy. At the initial treatment counseling visit, additional emphasis is being placed on the importance of monthly follow-up during DAA treatment as well as SVR12 follow-up visit, with all of the appointments being scheduled at initiation of therapy.

Limitations

The small sample size and retrospective study design are the main limitations of our analysis; therefore, results may not be applicable to other patient cohorts. Although we found heroin use to be associated with treatment failure, other demographic factors, such as advanced fibrosis/cirrhosis, mental illness, and sex cannot be ruled out as contributors to treatment failure due to our sample size being too small to detect such correlations.

Only 7 (14%) patients in our cohort presented with HCV genotype 2-4; therefore, concrete conclusions regarding SVR12 results in this specific patient population cannot be made from our study. The small sample size also disallowed us to analyze the potential effects of different DAA regimens on outcomes. LTFU was noted in 3 patients, and although definitive inferences are difficult to make from such a small number, it is interesting that all 3 patients had a history of heroin use. This LTFU rate also impacted treatment success by ITT, leading to a SVR12 rate that is ~10% lower than seen in registrational trials. Our observations suggest that a larger patient cohort should be studied, with a similar demographic profile, to more accurately ascertain SVR12 rates in this population.

Conclusions

Results from our small study indicate that patients being lost to follow-up leads to SVR12 rates that are lower than the > 95% rates seen in large controlled clinical trials, based on ITT analysis, and heroin use is associated with treatment failure. Whereas large controlled trials provide robust efficacy and safety data in large patient populations, additional data from “real-world” practices that are treating underserved populations are needed to provide complementary data and further insight on how to optimize SVR12 rates in these patients.

In the underserved populations with HCV, creative strategies and additional resources may be needed to continue to engage and to re-engage difficult-to-reach patients.

Author Contributions

All authors contributed to this study, data collection and analysis, as well as drafting of the manuscript.

Conflict of Interest/Funding

None of the authors report any conflicts of interest pertaining to this manuscript. No funding was obtained for this study.

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