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High rates of hepatitis C virus (HCV) cure using direct-acting antivirals in HIV/HCV-coinfected patients: a real-world perspective

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Objectives: There are few data on the real-world experience of FDA-approved oral hepatitis C virus (HCV) direct-acting antiviral (DAA) drug combinations in HIV/HCV-coinfected patients. We evaluated the safety and efficacy of DAA therapies in a cohort of HIV/HCV patients in a large urban clinic in Chicago.

Methods: HIV/HCV-coinfected adults (≥18 years) enrolled in the Northwestern University Viral Hepatitis Registry between January 2013 and June 2015 were analysed. Treated patients received one of the following DAA combinations: sofosbuvir/ledipasvir, sofosbuvir/ribavirin, sofosbuvir/simeprevir or paritaprevir/ritonavir/ombitasvir/dasabuvir ± ribavirin. The primary outcome was sustained virological response at 12 weeks after DAA completion (SVR12).

Results: Seventy-seven HIV/HCV patients were evaluated for DAA therapy. Most patients were male (62/77, 81%) and infected with HCV genotype 1 (67/77, 87%). Some 32/77 (42%) were cirrhotic and 29/77 (38%) had received prior treatment with an IFN-containing regimen. DAA therapy was more likely to be started in Caucasians than persons of other ethnicities ($P=0.01$). The overall SVR12 rate was 92% in 52 patients who completed therapy and had follow-up by the end of the study: sofosbuvir/simeprevir, 32/33 (97%); sofosbuvir/ribavirin, 4/7 (57%); sofosbuvir/ledipasvir, 11/11 (100%); and paritaprevir/ritonavir/ombitasvir/dasabuvir, 1/1 (100%). Four patients relapsed after therapy with sofosbuvir/simeprevir ($n=1$) or sofosbuvir/ribavirin ($n=3$). Adverse events were uncommon and did not result in DAA treatment interruption or discontinuation.

Conclusions: The HCV DAA combinations of sofosbuvir/ledipasvir and sofosbuvir/simeprevir were highly effective and well tolerated in this diverse population of HIV/HCV-coinfected patients, many of whom had advanced liver disease. HIV coinfection should not be considered a barrier to successful HCV treatment with DAAs.

Introduction

The development of new oral direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C virus (HCV) infection has been met with unprecedented success. Cure rates with three DAA combinations used for HCV genotype (GT) 1 infection (sofosbuvir/ledipasvir, paritaprevir/ritonavir/ombitasvir/dasabuvir ± ribavirin and sofosbuvir/simeprevir ± ribavirin) range from 92% to 100%.[1,2] High rates of cure have also been observed in 'difficult to treat' groups including patients with cirrhosis and HIV coinfection.[3–6]

Currently, there are few published data on the 'real world' experience with HCV DAAs in HIV/HCV-coinfected patients. The objective of this current study was to assess the safety and efficacy of selected HCV DAA combinations in a prospective cohort of HIV/HCV-coinfected patients with predominantly advanced disease characteristics.

Methods

Study population

HIV-infected subjects ≥18 years old with chronic HCV infection [HCV antibody positive with detectable serum HCV RNA (≥15 IU/mL)] enrolled in the Northwestern University Viral Hepatitis Registry between January 2013 and June 2015 and followed through February 2016 were analysed. Liver transplant recipients were excluded.

Ethics

The Institutional Review Board of Northwestern University approved this study and all patients provided written informed consent.

Clinical and laboratory protocols

A multidisciplinary team provided clinical care to all patients. HCV DAA treatment choice and duration were based on DAA availability, insurance

criteria and current guidelines.[7] Available DAA treatment regimens for HCV at the start of the study included sofosbuvir (SOVALDI®) plus simeprevir (OLYSIO®) for the treatment of patients with GT1 and sofosbuvir plus ribavirin for the treatment of GTs 2 and 3, followed by sofosbuvir plus ledipasvir (HARVONI®) for GT1 after October 2014 and paritaprevir/ritonavir/ombitasvir/dasabuvir (VIEKIRA PAK®) ± ribavirin after December 2014. Prior to HCV DAA initiation, ART was modified as indicated to avoid drug–drug interactions with DAAs. Liver disease was assessed by liver biopsy or non-invasive serological markers [AST/platelet ratio index, Fibrosis-4 (FIB-4), FibroSURE™ and FibroScan®].[8,9] Plasma HCV RNA levels were quantified at baseline, monthly, at the end of DAA treatment (EOT) and 12 weeks after DAA therapy (Roche Diagnostics, Indianapolis, IN, USA; lower limit of detection of 15 IU/mL).

Data collection

Clinical and laboratory data were abstracted from medical records including patient demographics, underlying liver disease, prior HCV treatment, comorbid medical conditions, ART and adverse effects.

Outcomes and statistical analysis

The primary outcome was sustained HCV viral response (HCV RNA ≤15 IU/mL) 12 weeks after treatment completion (SVR12). Secondary outcomes were: (i) treatment-related adverse events; and (ii) sustained HIV viral non-suppression (HIV RNA ≥20 copies/mL present on at least two consecutive samples). Continuous variables were compared using Student's *t*-test and the Mann–Whitney test. Categorical variables were compared using the χ^2 test and Fisher's exact test (SPSS version 22.0; IBM, Armonk, NY, USA).

Results

Baseline characteristics

Seventy-seven HIV/HCV-coinfected patients were evaluated in the clinic for HCV therapy. Fifty-four (70%) patients completed HCV therapy by the end of the study. The majority of patients were male (62/77, 81%) and infected with HCV GT1 (67/77, 87%). A higher proportion of Caucasians received therapy compared with other ethnicities ($P=0.01$). The most common reason for not starting DAAs in 23 (30%) patients was an estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 (26%). No patients were denied DAA therapy for insurance reasons. See Table 1.

HCV treatment outcomes

Treatment combinations included sofosbuvir/simeprevir (without ribavirin) ($n=35$), sofosbuvir/ribavirin ($n=7$), sofosbuvir/ledipasvir ($n=11$) and paritaprevir/ritonavir/ombitasvir/dasabuvir ($n=1$). After excluding 1 patient who was lost to follow-up after achieving an EOT response and 1 person who expired during therapy, overall SVR12 was 92%: 32/33 (97%) for persons receiving sofosbuvir/simeprevir; 4/7 (57%) for sofosbuvir/ribavirin; 11/11 (100%) for sofosbuvir/ledipasvir; and 1/1 (100%) for paritaprevir/ritonavir/ombitasvir/dasabuvir (Figure 1). Four patients experienced HCV recurrence after therapy: sofosbuvir/simeprevir ($n=1$) or sofosbuvir/ribavirin ($n=3$). Two of three patients who failed sofosbuvir/ribavirin were infected with GT1a, were cirrhotic and had a prior null response to pegylated IFN/ribavirin±boceprevir. The third recurrence occurred in a patient who was infected with GT2a, cirrhotic and treatment experienced and who received only 12 weeks of sofosbuvir/ribavirin. One recurrence occurred after 12 weeks of sofosbuvir/simeprevir in a GT1a patient with cirrhosis and prior treatment with pegylated IFN/ribavirin+telaprevir, which was discontinued after 2 weeks due to side effects. All four patients who experienced HCV recurrence had achieved HCV RNA ≤15 IU/mL after 4 weeks of therapy. While we could not absolutely distinguish relapse from reinfection in these patients, there were no GT switches at the time of recurrence to suggest reinfection.

Table 1. Baseline characteristics of the study cohort (all patients)

Patient characteristic	DAA treatment ($N=54$)	No treatment[a] ($N=23$)	*P*
Age (years), mean (SD)	53.2 (9.5)	55.1 (7.9)	0.410
Male, *n* (%)	44 (82)	18 (78)	0.744
Race/ethnicity, *n* (%)			0.013
Caucasian	27 (50)	4 (17)	
African American	17 (32)	15 (65)	
Hispanic	10 (19)	4 (17)	
BMI (kg/m^2), mean (SD)	26.7 (6.0)	24.7 (4.8)	0.334
Active substance use, *n* (%)	21 (39)	7 (30)	0.607
HCV GT, *n* (%)			0.344
1a/1	36 (67)	16 (84)	
1b	13 (24)	2 (11)	
2 or 3	5 (9)	1 (5)	
Prior HCV treatment, *n* (%)			0.413
pegylated IFN/ribavirin	16 (30)	6 (26)	
pegylated IFN/ribavirin+PI[b]	5 (9)	0 (0)	
pegylated IFN only	1 (2)	1 (4)	
naive	32 (59)	16 (70)	
On antiretrovirals, *n* (%)	53 (98)	23 (100)	0.511
Cirrhosis, *n* (%)	26 (48)	6 (26)	0.083
HCV RNA ($\log_{10}$ IU/mL), mean (SD)	6.2 (0.6)	6.4 (0.7)	0.273
CD4 T cells (cells/mm^3), mean (SD)	516 (279)	516 (358)	0.747
HIV RNA <20 copies/mL, *n* (%)	49 (91)	18 (78)	0.136
ALT (U/L), mean (SD)	73.4 (64)	36.7 (16)	0.004
Total bilirubin (mg/dL), mean (SD)	1.2 (1.4)	0.7 (0.9)	0.004
Albumin (g/dL), mean (SD)	4.1 (0.5)	3.9 (0.7)	0.098
Platelet count (×10^3/μL), mean (SD)	176 (94)	211 (95)	0.136

[a]Reasons for not initiating DAAs: lost to follow-up after first evaluation (4, 17%); eGFR ≤30 mL/min/1.73 m^2 (6, 26%); transferred care elsewhere (3, 13%); awaiting clinical evaluation or HCV DAA treatment approval (1, 4%); provider reluctance to treat because of concerns about non-adherence or substance abuse (5, 22%); death (1, 4%); shortened life expectancy (1, 4%); and patient preference to delay therapy (2, 9%).
[b]Telaprevir, $n=1$; boceprevir, $n=4$.

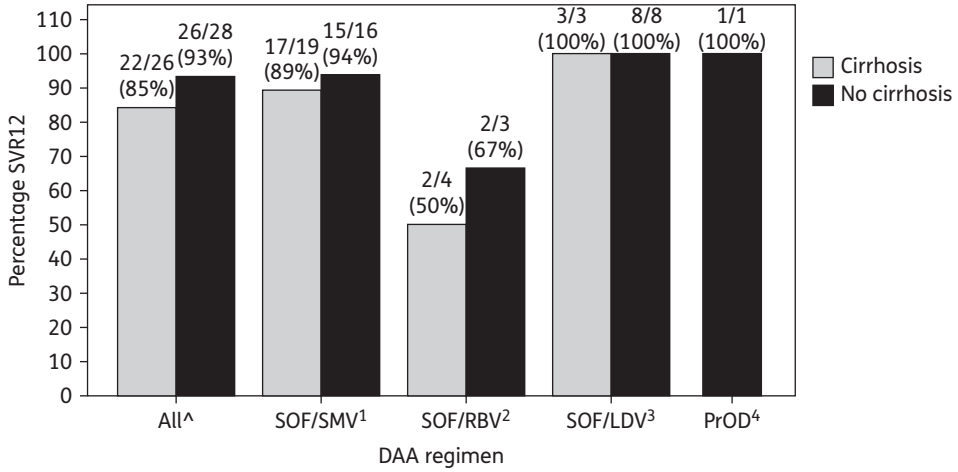

Figure 1. Virological treatment outcome by DAA regimen ($N=54$). SOF/SMV, sofosbuvir/simeprevir; SOF/RBV, sofosbuvir/ribavirin; SOF/LDV, sofosbuvir/ledipasvir; PrOD, paritaprevir/ritonavir/ombitasvir/dasabuvir. ^Four relapses; one death (SOF/SMV); one with EOT then lost to follow-up (SOF/SMV). [1]Twelve weeks GT1a/1b ($n=34$) and 24 weeks GT1b ($n=1$). [2]Twelve weeks GT2a ($n=1$), 16 weeks GT2a/b ($n=3$), 24 weeks GT1a ($n=2$) and 24 weeks GT3 ($n=1$). [3]Eight weeks GT1a ($n=2$), 12 weeks GT1a/1b ($n=8$) and 24 weeks GT1a ($n=1$). [4]Twelve weeks GT1a ($n=1$).

Adverse events

Twenty-six out of 54 (48%) patients experienced at least one adverse event, which were minor, including fatigue, pruritis and headache. Four patients on sofosbuvir/simeprevir had grade III–IV creatinine or total bilirubin elevations, which did not result in DAA treatment interruption or discontinuation. Three patients initiated on sofosbuvir/ledipasvir received concurrent ART with both tenofovir disoproxil fumarate and a boosted PI (bPI); none experienced an increase in serum creatinine >0.4 mg/dL. One death was reported in a patient receiving sofosbuvir/simeprevir after 2 weeks of HCV therapy due to decompensated cirrhosis, which was present prior to initiating therapy.

Antiretroviral modifications

ART switches were required in 31/54 (57%) initiating DAAs. Switches were most commonly made in patients initiating sofosbuvir/simeprevir (81%) and included switching from efavirenz or a bPI to either raltegravir or dolutegravir. None experienced any sustained HIV virological breakthrough as a result of ART change. Two out of five patients on an ART regimen containing both tenofovir and a bPI and initiating sofosbuvir/ledipasvir had their bPI switched to raltegravir prior to starting this regimen.

Discussion

In this 'real world' cohort of HIV/HCV-coinfected patients, excellent responses to therapy were observed, with an overall SVR12 rate of 92% in 'as treated' analyses consistent with other published observational and clinical trial data.[3,4,10–13]

High rates of cure were observed despite almost half the patients having cirrhosis and a history of prior treatment experience, factors that have traditionally been associated with reduced rates of cure in clinical trials. None of the patients on the combination of sofosbuvir/simeprevir required the addition of ribavirin and, notably, 14/15 (93%) cirrhotic patients, who had received only 12 weeks of sofosbuvir/simeprevir prior to the recommendation to extend therapy to 24 weeks, achieved SVR12. The high rates of treatment success with DAA therapy achieved in our cohort likely reflect the established pattern of good adherence with outpatient clinic visits and prescribed medication prior to initiating HCV therapy, as well as the multidisciplinary approach to HCV management in our clinic.

The four HCV virological recurrences that occurred after DAA therapy can be attributed to individual patient and DAA treatment characteristics. Two recurrences occurred after completion of sofosbuvir/ribavirin combination therapy for HCV GT1a infection in cirrhotic patients who had prior null responses to pegylated IFN/ribavirin and pegylated IFN/ribavirin+boceprevir regimens, respectively. Sofosbuvir/ribavirin is no longer recommended for treatment of GT1 infection based on low SVR12 rates (10%–52%) reported in other studies.[12,14] The two other recurrences occurred in cirrhotic patients infected with GTs 1a and 2a who received sofosbuvir/simeprevir and sofosbuvir/ribavirin, respectively, and were likely the result of suboptimal treatment durations. Both had completed therapy before recommendations to extend therapy in these patients were published.[10,15]

Thirty-one out of 54 (57%) patients required modifications to their ART regimen prior to HCV treatment initiation, mostly switches from a bPI to an integrase inhibitor prior to initiating sofosbuvir/simeprevir. Notably, a straightforward switch could be made in all of the patients, without concern for inactivity from resistance mutations, and the high rates of ART switch did not impact HIV treatment efficacy. This is in contrast to recent data from Pittsburgh where a switch in ART was viable in only 46% of HIV/HCV-coinfected patients initiating sofosbuvir/simeprevir.[16] Coadministration of a bPI, tenofovir and ledipasvir did not result in any elevation of creatinine levels in three patients, although larger studies are needed to verify our experience. It should be noted that specific measurements of renal tubular function, tenofovir levels or routine urinalysis were not performed.

Similar to other published data involving DAA therapy, the overall prevalence of side effects and laboratory toxicities was

low and no DAA treatment interruptions or discontinuations occurred as a result. One death occurred in a patient with decompensated liver disease after receiving 2 weeks of sofosbuvir/simeprevir. Although rare, hepatic decompensation and fatal hepatic failure have been reported post-marketing in patients treated with simeprevir with Child–Pugh class B or C and simeprevir is no longer recommended in these patients.[17]

An unexpected finding was the racial disparity in the likelihood of eligible HIV/HCV-coinfected patients receiving DAA therapy. A higher proportion of Caucasians evaluated for treatment received DAA therapy than persons of other racial groups and only 53% of African Americans initiated DAAs. Past studies of pegylated IFN/ribavirin regimens reported racial differences in access to HCV care and treatment among African Americans and Hispanics compared with Caucasians, even after adjusting for clinical or socio-demographic differences.[18] The persistence of racial discrepancies in accessing treatment, in this era of more tolerable, highly curative HCV therapies, is worthy of further study.

Limitations of this study include the small number of patients, single-centre experience and observational design of the study. Additionally, no comparator group of HCV-monoinfected patients was included.

In conclusion, excellent treatment outcomes among our cohort of HIV/HCV-coinfected patients were achieved with the currently approved DAA combinations for HCV. The combination of sofosbuvir/simeprevir remains a viable option for the treatment of patients infected with HCV GT1, especially among those on compatible ART.

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Transparency declarations

F. P. receives compensation to serve as a consultant for and on the speakers' bureaus of Gilead Sciences, Janssen Pharmaceuticals, Bristol-Myers Squibb and Merck. All other authors: none to declare.

Author contributions

C. H. contributed to protocol design and development, data collection and analysis and writing of the first draft of the manuscript. J. G. contributed to protocol design and development, data collection and analysis and writing of the manuscript. L. R. A. contributed to data collection and analysis and review of the manuscript. F. P. contributed to protocol design and development and review of the manuscript. M. M. contributed to protocol design and development and review of the manuscript. R. G. contributed to review of the manuscript. D. M. contributed to review of the manuscript. V. S. contributed to protocol design and development, oversight of the study and writing of the manuscript.

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