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ORIGINAL ARTICLE

Real World Response to Direct Acting Antivirals DAA in African Americans Treated in a Non-Gastroenterology Setting

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ABSTRACT

INTRODUCTION: The approval of highly effective direct acting antiviral agents such as sofosbuvir/ledipasvir (Harvoni) for the treatment of hepatitis C, provided an oral, tolerable and effective regimen with fixed dosing and treatment period. Given the large numbers of patients to be treated, it is anticipated that non-GI physicians will be treating more patients than in previous years. The goal of this study was to compare the response to Harvoni of patients treated in a Gastroenterology (GI) clinic to that of an Infectious Disease (ID) clinic.

METHODS: The study collected and analyzed data for HCV patients treated with Harvoni between June 2015 and December 2016 using a university physicians' practice EMR. There were 389 patients

with 294 treated by GI and 95 treated by ID.

RESULTS: The protocol viral clearance responses were similar for hepatitis C virus infection (HCV) patients treated in GI (93%) and ID (94%) as well as for HIV co-infected patients treated in ID (100%). The responses were similar for naïve (92%) and experienced (95%) and for both AA (93%) and non-AA (96%). Significant numbers of patients did not complete therapy (8%) or did not show up for their SVR visit (13%), thus lowering the intent to treat response compared to the protocol adherence response (97% vs 79%). The primary factor for not achieving an SVR was cirrhosis (99% vs 92%).

CONCLUSIONS: ID treated significant numbers of both HIV and non-HIV HCV patients and response to treatment with Harvoni was similar to the SVR rate in the GI clinics. Our data also reflects the real-world results of Harvoni treatment where, intent to treat and per protocol are significantly different. We conclude from our study that treatment of hepatitis C with Harvoni has a high SVR without regard to physician specialty, race, HIV co-infection or previous treatment status.

Key words: Hepatitis C, viral hepatitis, direct acting anti-virals, African Americans

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INTRODUCTION

Chronic Hepatitis C (CHC) affects 2.4 million people in the United States and is one of the leading causes of cirrhosis, hepatocellular carcinoma and liver transplantation^[1-4]. African Americans (AA) who are more likely to be infected with hepatitis C than Caucasians, comprise 23% of infected population, are more likely to develop hepatocellular carcinoma than non-AA populations in the United States, and are more likely to be infected with hepatitis C genotype^[5-10]. Ribavirin/Interferon based regimens were less effective

in the African American population which helped to contribute to the increased numbers of AA patients with CHC^[11-16]. The utilization of dual direct acting antiviral agent (DAA) combinations such as sofosbuvir/ledipasvir (Harvoni®) has provided a shift into an oral, tolerable and effective regimen with fixed dosing and treatment period^[17]. (Comment: Harvoni is no longer a ‘recent’ approval) The licensing trials (ION series of clinical trials) proved high efficacy and safety of Harvoni on the treated population which included 38% African American. Subsequent real-world studies demonstrated that these high rates of efficacy with minimal side effects were also achievable in large scale treatments of AA patients treated in GI clinic settings^[18-24]. Given the ease of treatment protocol, the high effectiveness, the safety profile in special populations such as HIV co-infected patients, the decline in cost and the large numbers of patients to be treated, it is likely that treatment by non-GI physicians will be required. Our aim was to evaluate the “real world” effect of Harvoni® in treating primarily African Americans infected with hepatitis C in both a Gastroenterology and non-Gastroenterology setting.

METHOD

We conducted a single-center retrospective cohort study to collect and analyze data for HCV patients treated with Harvoni® by physicians in the Wayne State University Physicians Group. Patients were treated by two distinct groups of physicians, Gastroenterologists or Infectious Disease specialists, during a two-year period (January 2015-December 2016). The primary medical record search criteria were patients who were scripted and started treatment with Harvoni® during this time frame. HARVONI dosage recommendations are the same for HCV mono-infected and HCV/HIV-1 co-infected patients. All patients in this study were treated as per guidelines: 8 weeks for patients without cirrhosis and with pre-treatment HCV RNA < 6 million IU/mL, 12 weeks for patients without cirrhosis or with compensated cirrhosis and treatment-experienced GT 1 patients without cirrhosis, 24 weeks for treatment-experienced patients with compensated cirrhosis (ChildPugh A). Of note was the fact that ID physicians treated both HIV -HCV coinfecting and mono infected HCV patients whereas GI treated primarily only patients with HCV. Chart review and data collection was performed according to Wayne State Institutional Review Board (IRB)-approved protocol. The Wayne State University Institutional Review Board operates under United States Department and Human Services Federal Wide Assurance. Demographic data such as age, sex, and race were collected for each patient included in the study. Baseline and subsequent virologic data of HCV PCR level were collected for all the patients as the primary criteria of successful treatment. While the traditional definition of SVR is a negative HCV PCR at 12 weeks after the end of treatment, the regular visits of HIV patients often resulted in the confirmation of a negative HCV at the 10 week visit rather than 12 weeks. Thus, the main endpoint of data collection was SVR_(>10) which was defined as undetectable plasma HCV PCR at a visit at least 10 weeks after the end of treatment. Other assessments included end of treatment response, treatment failure and lost to follow up. A distinction was made between patients who were lost to follow up prior to the end of treatment and those who did not come back for a subsequent viral assessment after the end of treatment. Data analysis was performed using the JMP statistical program with student’s t-test for continuous variables and Pearson chi-square for character variables. Statistical significance was defined as $p < 0.05$.

RESULTS

We identified a total of 389 patients treated with Harvoni® by the Wayne State University Gastroenterology (GI) and Infectious Disease (ID) practices. There were 354 (90%) African American and 35 Non-AA patients in the study (Figure 1). Most of the patients ($n = 294$) were treated by GI. Patients were mainly males (73%) with a median age of 62. Co-infection with HIV was identified in 15% of the patients and they were mainly treated by the ID practice with only two patients co-infected with HIV treated by the Gastroenterology practice. The primary reason for this is that patients infected with HIV follow up regularly with the ID practice and unlike previous therapies, co-infected patients can be safely given the anti-viral therapy. Non-HIV infected CHC patients were also treated in the ID practice during this time as a result of staffing, patient volumes, and insurance authorization issues in GI. SVR_(>10) per protocol was 92% and 94% for HIV negative patients treated in GI and ID practices respectively and 100% in HIV positive patients treated by ID physicians (Figure 2). Only two co-infected patients were treated in GI so their response rate (1 out of 2) is not plotted. Although the per protocol SVR_(>10) was greater than 90%, the SVR_(>10) with intent to treat was only 79% due to patients who were lost to follow up after they achieved an end of treatment response (ETR) (10%) or lost to follow up before the ETR visit (6.4%) (Table 1). All patients who were not lost to follow-up prior to ETR assessment, were virus

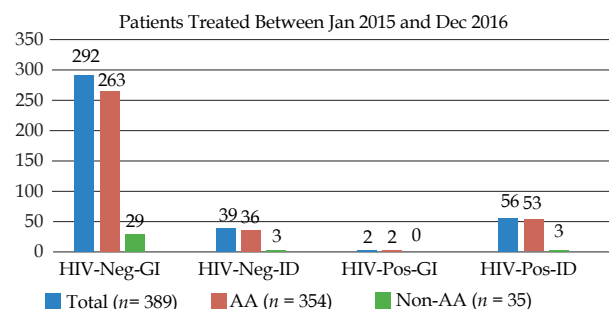


Figure 1 Race, HIV status and treatment specialty for patients treated with ledipasvir/sofosbuvir. The numbers are posted above the bars. Majority of patients were AA (94%) and HIV-negative. They were male (73%) and had a median age of 62. The majority of patients scripted for Harvoni were treated (87%) with 9% denied due to continuing insurance issues. The x-axis indicates the HCV patient population (ie HIV-negative vs HIV positive) and the physician group treating the patients (GI=gastroenterology; ID=Infectious Diseases).

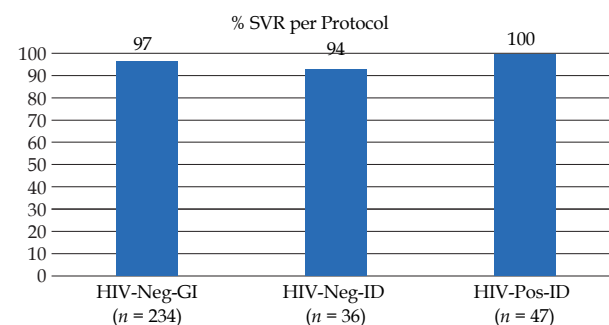


Figure 2 Sustained Virus Response weeks Post Treatment using Protocol Based Assessment. Protocol compliant patients received all of their medication and had HCV RNA measured by PCR at end of treatment (EOT) and at 10-12 weeks after treatment. The x-axis indicates the HCV patient population (ie HIV-negative vs HIV positive) and the physician group treating the patients (GI=Gastroenterology; ID=Infectious Diseases). The response was not significantly different between GI and ID based treatment and between HIV positive and HIV-negative patients treated in ID.

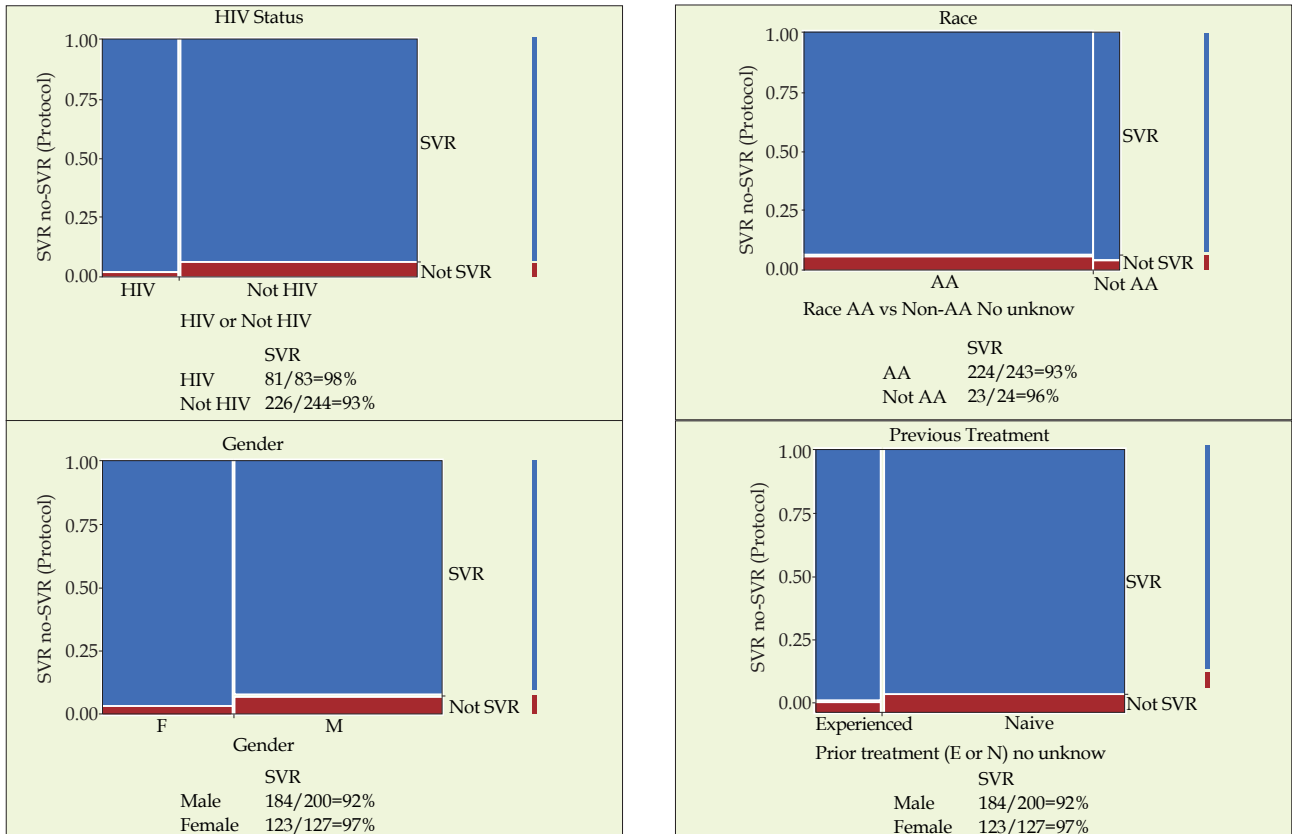


Figure 3a Categorical variables which might influence SVR protocol results. SVR(>10) vs Non-SVR(>10) for categorical variables is represented on the y-axis. The relative size of the groups represented by the width of the “bars”. The number of patients and the % are listed under the figures. All values were not significant as defined by chi-square Pearson evaluation.

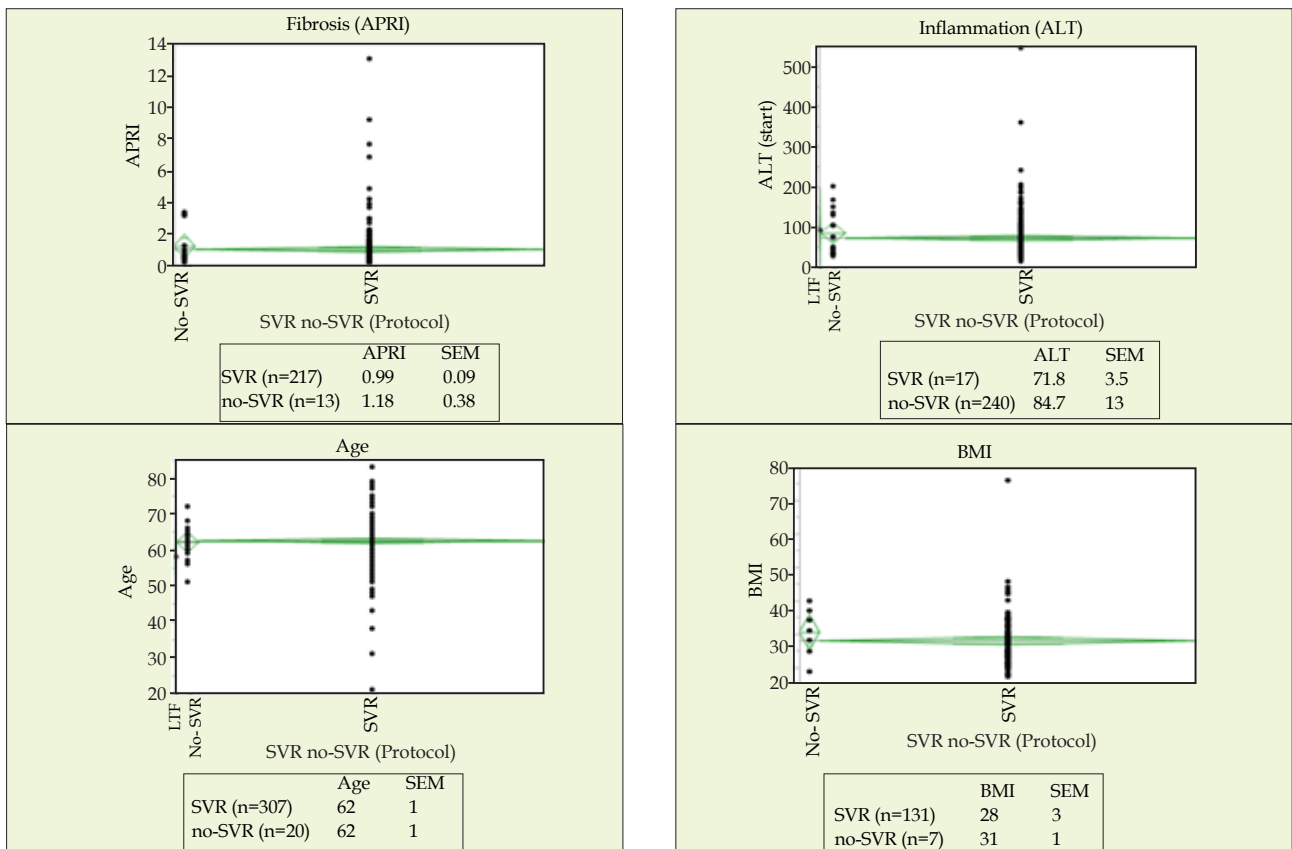


Figure 3b Numerical values which might influence SVR protocol results. SVR(>10) vs Non-SVR(>10) for numerical variables are plotted on the y-axis. The number of patients and the mean and standard error of the mean (SEM) are listed under the figures. All values were not significantly different as defined by student-t test.

negative at ETR, suggesting no viral resistance prior to treatment. Of the 11 patients who relapsed after ETR, 6 had cirrhosis (3 also had previously treated HCC and 1 had HIV), 4 did not have cirrhosis and were naïve to treatment and 1 stopped drug after 4 weeks but had an ETR. When comparing patients with and without cirrhosis, the per protocol response was lower for cirrhotic patients (92% vs 99%). When subjected to multi-variate analysis (Nominal Logistic Fit) to evaluate potential interactions, only cirrhosis achieved statistical significance. Conversely, it was rare for naïve patients who completed treatment without cirrhosis to relapse after ETR regardless of the treatment venue. Significant numbers of patients failed to return for their ETR or SVR_{>10} evaluation, Thus the intent to treat values are significantly lower in the real world as compared to clinical trials.

Data analysis did not show statistically significant difference in achieving SVR_{>10} between African American (93%) and non-African American (96%) treated by GI or ID. Females were able to achieve higher SVR_{>10} with 97% compared to 92% males but it was not significantly different by Pearson chi-Square analysis. Treatment-experienced patients who failed previous treatment (mainly with interferon based therapy) did not have a significantly different response rate than naïve patients (95% vs 92%). Patients co-infected with HIV (98% response) were not significantly different from non-HIV patients (93%).

DISCUSSION

Hepatitis C patients' response to treatment with Harvoni® managed by ID was compared to the response of patients treated by GI. The patient population in this study was majority African American race (94%), and they completed treatment with SVR_{>10} rates that was not different from our non-African American patients. This was true regardless of whether or not the patients were co-infected with HIV. Our data represent real world results of Harvoni® treatment. Response rate calculations are complicated by the high percentage of patients who were lost to follow up both during treatment (8-18%) and after their ETR visit (6-16%). While this was not surprising for non-HIV patients, the same issue was seen in the HIV co-infected patients which was unexpected.

Many of the patients were co-infected with HIV (10%), and the majority reported compliance with different regimens of anti-HIV medications and had a regular follow up with ID. HIV co-infection and treatment did not have impact on SVR_{>10}. Our results are similar to a retrospective study on HCV eradication in patients co-infected with HIV in Florida where treatment results did not differ in both groups, but in that study, occasional HIV virology relapse was reported either due to missed HIV treatment for a period from 5 days-2 weeks or increased HIV viral load secondary to an unspecified cause. We did not evaluate that issue in our **patient population**^[3].

Another finding in our study was the high Harvoni® SVR_{>10} rate in treatment experienced patients. There were only 55 previously treated patients out of 243 patients with an SVR_{>10} protocol response assessed, and the response rate was similar to treatment naïve patients. Most were previously treated with interferon containing regimens and either did not achieve SVR or had a relapse after treatment with those regimens. Since the SVR_{>10} rate was similar between treatment experienced and treatment naïve, our study supports aggressively identifying and treating experienced patients who may have had the disease for a longer period of time and may be at higher risk for liver damage. This is especially important since even patients with cirrhosis are eligible for treatment with DAA therapies. The Phase 3 ION trial demonstrated similar results with >

Table 1 Comparing Protocol to Intent to Treat

	Protocol	Intent to Treat			
	SVR*	SVR (ITT)**	LFT-ETR***	LFT***	Relapse****
GI-HIV negative	227/234 = 97%	227/292 = 78%	34 (11%)	23 (8%)	8 (3%)
ID-HIV negative	34/36 = 94%	34/39 = 87%	2 (5%)	1 (3%)	2 (5%)
GI HIV positive	1/2 = 50%	1/2 = 50%	0 (0%)	0 (0%)	1 (50%)
ID-HIV positive	47/47 = 100%	47/56 = 84%	3 (5%)	6 (11%)	0 (0%)
Overall	309/319 = 97%	309/389 (79%)	39 (10%)	30 (8%)	11 (3%)

*SVR: virus undetectable at least 10 weeks after end of treatment (ETR). **ITT: intent to treat based on all patients. *** LFT-ETR means lost to follow up after ETR visit (all patients negative at ETR visit). **** LTF means lost to follow up prior to ETR visit. **** Relapsed after negative ETR (1 patient did not take all medication but was ETR).

90% SVR rate in treatment naïve and treatment experienced patients and our real world data is consistent with the clinical trials^[19].

We conclude from our study that treatment of hepatitis C with Harvoni® results in a high SVR_{>10} without regard to race, HIV co-infection, previous treatment status or whether the patient is treated in a gastroenterology or infectious disease clinic setting.

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