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Effectiveness of Sofosbuvir Combined with Direct Acting Antivirals in Hepatitis C Patients in a Tertiary Teaching Hospital in Qatar: A Retrospective Observational Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors RMAA, ZJ, DEE and RI conceived, planned and carried out the study. Authors RMAA, ZJ, DEE and RI analyzed the data and contributed to the interpretation of the results. Authors RMAA, ZJ, DEE, RI and MIMI drafted and critically revised the manuscript. All authors provided the final approval of the version to be published.

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is associated with significant morbidity and mortality. The effectiveness of sofosbuvir, as a new direct-acting antiviral (DAA) for chronic HCV infection, needs to be assessed and evaluated among patients with or without cirrhosis with all HCV genotypes.
Aims: This study was conducted to determine the effectiveness of chronic HCV treatment as part of a combination therapy for all HCV genotypes in patients with or without cirrhosis.
Study Design: A retrospective observational study.
Methodology: All patients who received sofosbuvir treatment from the Pharmacy Department of Hamad General Hospital during a 12-month period (between 2014 and 2015) were included.

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Patients were observed up to 12 weeks after treatment course completion. Data were analyzed descriptively and compared using a paired t-test (alpha=0.05).
Results: A total of 95 patients received sofosbuvir. All of these patients received sofosbuvir in combination with other antiviral medications. All HCV genotypes were included; 1a and 4 were the most dominant genotypes (37% and 30.5%, respectively). Half of the patients were treatment naïve. All patients achieved undetectable virus ribonucleic acid (RNA) starting from week 4 of the treatment. A sustained virological response at 12 weeks (SVR12) after completion of the treatment period was maintained in 95% of patients. Relapse was mostly observed in patients with genotype 1a (40%); no patients with HCV genotype 3 exhibited relapse.
Conclusion: The SVR12 after sofosbuvir treatment was maintained in most patients, regardless of genotype, HCV complications HCV or co-administered drugs.

Keywords: Antiviral agents; cirrhosis; genotypes; hepatitis c; sofosbuvir; viruses; Qatar.

ABBREVIATIONS

CDC : Centers for Disease Control and Prevention
DAA : Direct-acting antiviral
EMA : European Medicines Agency
eMR : Electronic medical record
HCC : Hepatocellular carcinoma
HCV : Hepatitis C virus
HGH : Hamad General Hospital
PEG : Pegylated interferon
RNA : Ribonucleic acid
SVR12 : Sustained virological response at 12 weeks
USA : United States of America

1. INTRODUCTION

Hepatitis C virus (HCV) is a slowly progressive infection that affects the liver and can cause both chronic and acute hepatitis, hepatic cirrhosis, and hepatocellular carcinoma (HCC) and is the leading cause of liver transplant [1].

In 2015, a study reported that among a total of 13,704 people in Qatar who were screened for hepatitis C, 272 (2%, 95% confidence interval [CI] (1.8–2.2%) had positive antibodies. During the same period, 237 non-screened patients (NSP) with hepatitis C were referred for treatment [2]. Another study reported that the national-level HCV prevalence in the Arabian Gulf region is comparable to global levels. A higher prevalence is found in specific expatriate populations, reflecting the prevalence in their countries of origin [3]. According to a recent report, over 4,200 people in Qatar have been diagnosed with viral Hepatitis C, with over 1,700 currently receiving treatment. Qatar has been listed by the World Health Organization (WHO) as one of the top ten countries in the world that is on track for the elimination of HCV [4]. The Qatar National plan for HCV control was launched in December 2014 to prioritize and proactively manage HCV with the ultimate aim of eliminating viral hepatitis [5].

The estimated prevalence of HCV in the United States of America (USA) in 2014 was approximately 2.7 to 5.2 million patients. The Centers for Disease Control and Prevention (CDC) stated that approximately 17,000 patients are newly diagnosed with HCV annually, and 12,000 patients die annually from hepatitis C-related liver complications [6]. Additionally, according to the WHO, HCV has contributed to 86,000 deaths in Europe [1]. HCV is distributed worldwide, mostly in central and east Asia and North Africa. There are many genotypes of the virus (1–6), which are distributed by region. HCV genotype 1 is considered as the most prevalent genotype worldwide, and genotype 3 is the most difficult to treat [7].

HCV infection greatly affects both patients and society. It decreases the life expectancy of the affected patients by 8 to 12 years, decreases quality of life, and causes potential disability and dependency. It is considered as the main reason for liver transplant. In addition to the direct economic burden, including hospitalization and medication expenses, HCV decreased patients' fitness for work, causing them to lose their income [8]. A study that evaluated the future complications of chronic hepatitis in the USA in 2003 revealed that the expected percentage of cirrhotic patients will increase from 16% to 32% by 2020 among untreated patients [9]; this raises an alert about the potential of doubling the expected disease burden in the upcoming years.

The goals of HCV therapy are to achieve a sustained virological response (SVR12, defined as reaching undetectable serum virus RNA at least 12 weeks after therapy), which is monitored

for up to 6 months, decrease disease progression to liver cirrhosis, HCC and decompensated liver disease, and minimize the number of cases that require transplantation [10,11].

The emerging data from clinical trials have suggested the superiority of direct-acting antiviral (DAA) regimens over pegylated interferon (PEG)/ribavirin regimens in terms of adverse drug reactions and the disconsolation rate of therapy [12,13]. Notably, when compared to the PEG regimens, the DAA regimens maintained the SVR for a longer duration [14].

Accordingly, the AASLD/IDSA (American Association for the Study of Liver Diseases/Infectious Diseases Society of America) HCV Guidance Panel and WHO have developed standardized guidelines for the treatment of chronic HCV infections (AASLD/IDSA HCV Guidance Panel, 2014; AASLD/IDSA HCV Guidance Panel, 2015; WHO, 2018 [15,16]). They recommended initiating treatment for all chronic HCV-affected patients (except pregnant women and patients with a short life expectancy). Moreover, they also recommended treatment with DAA regimens over regimens containing PEG/ribavirin for all patients with special situations including patients with genotype 3 and with cirrhosis or those with genotypes 5 and 6 with and without cirrhosis. This was further supported by an update from the Canadian Association for the Study of the Liver on the management of chronic hepatitis C (2018) that advocated against the treatment with PEG-containing regimens [17].

Sofosbuvir is indicated for treatment of all HCV genotypes. It is a fixed-dose, once daily, 400 mg tablet administered with or without food and is part of combination therapy either with other DAAs (velpatasvir, daclatasvir or ledipasvir), ribavirin alone or ribavirin and PEG. The duration of therapy and use of PEG depend on the viral genotype and the presence of contraindications to PEG use [18].

Hepatitis has become a worldwide concern. It is widely prevalent and causes extensive direct and indirect burdens. The conventional HCV treatments (ribavirin and PEG) have many limitations and complications that limit their beneficial use. According to Sulkowski et al. (2011), both ribavirin and PEG can cause hematologic, dermatologic, neurologic, immunologic, gastrointestinal, pulmonary, cardiovascular, and ocular effects [19,20]. However, a new emerging generation of DAAs is very promising for HCV management, and these drugs are an effective and well-tolerated group of medications given in a single daily dose.

Sofosbuvir is a DAA that has been approved by the Hamad Medical Corporation for the treatment of chronic HCV since August 2014. Thus, this study was conducted to retrospectively measure the effectiveness of sofosbuvir as part of combination therapy for treatment of patients with all HCV genotypes with or without cirrhosis.

2. MATERIALS AND METHODS

2.1 Study Design

This is a retrospective observational study conducted between 2014 and 2015. The study included all patients who received sofosbuvir treatment from the Pharmacy Department of Hamad General Hospital (HGH). This cohort of patients was followed-up and observed up to 12 weeks after the treatment course was completed. A patient list was generated from the computerized pharmacy system to identify patients who received sofosbuvir from HGH pharmacy. An authorized research team accessed the electronic medical records (eMR viewer) for each patient after obtaining the ethical approval to retrieve demographic information and laboratory results. The data collected included the patient's demographic profile (i.e., sex, age and nationality), the HCV genotype (i.e., 1a, 1b, 2, 3, 4, 5, or 6), HCV-related complications (cirrhosis, HIV, liver transplant, HCC), the treatment history of HCV (DAAs, or ribavirin/PEG), virus RNA level (IU/mL) (baseline and follow-up), calculated renal function using the Modification of Diet in Renal Disease (MDRD) equation (baseline and follow up), recent DAA treatment including sofosbuvir, and the treatment duration. The treatment period was determined starting from the first prescription dispensed from the pharmacy. The observation period ended 12 weeks after completion of the treatment course.

Patients were coded using a unique study number on the data collection sheet. The code was destroyed after data analysis. The data collection sheets were stored on password protected computers and locker folder cabinets, with limited access by the research team.

2.2 Study Population and Sampling

This study included all patients infected with HCV and dispensed sofosbuvir by the Pharmacy Department at HGH. The patients were identified through the computerized pharmacy dispensing system. Due to the small number of patients who received sofosbuvir, all adult patients treated with sofosbuvir were included in the study. Patients aged less than 18 years old were excluded.

2.3 Outcome Measures

The primary outcome of the study was SVR at 12 weeks after the completion of the treatment course with sofosbuvir. In addition, the study also determined the rate of relapses within the 12 weeks after treatment and determined the characteristics of patients who relapsed as follows: (i) the rate of relapse was determined for different HCV genotypes; (ii) the SVR rate in cirrhotic and non-cirrhotic patients was determined; and (iii) the difference in SVR between treatment-naïve and previously treated patients was determined.

2.4 Data Analysis

Data were analyzed using SPSS version 24 (IBM Corp. released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Continuous data are represented as the mean (SD) and 95% CI, and the virus RNA level was determined at baseline and at 12 weeks after completion of the treatment. Categorical data are represented as the frequency and percentage. A paired two-tailed t-test was used to compare the mean virus RNA level at baseline and at 12 weeks after treatment. The significance level was 0.05.

3. RESULTS AND DISCUSSION

Ninety-five patients received the study medications, i.e., sofosbuvir combined with other antiviral medications. The patient demographics, baseline characteristics and co-administered agents are shown in Tables 1 and 2.

During the treatment course, 25% (n=26) of the patients receiving sofosbuvir-containing regimens achieved an undetectable virus RNA level within 2 weeks of the treatment course, reaching 100% starting from the 8th week until the end of the treatment course, which was 12 weeks (Table 3). Of note, 62% (n=59) of the patients received a treatment course of 12 weeks.

Post-treatment monitoring revealed that all patients (n=95) maintained a 100% SVR until the 4^{th} week; however, 5.2% of the patients (5 of 95) relapsed by week 12 after completion of the treatment course (Table 3). The relapse rate was significantly higher for genotype 1a (40%) than for the other genotypes ($p<0.05$). However, none of the patients with genotype 3 relapsed. The characteristics of the relapsed patients are presented in Table 4. Eighty percent (n=76) of the relapsed patients were treated previously.

An SVR12 was observed to be 91.5% of previously treated patients; the treatment-naïve patients achieved a higher SVR12 rate (98%). Additionally, the non-cirrhotic patients showed a higher SVR12 rate than the cirrhotic patients (97% vs. 91.5%, respectively).

Sofosbuvir is a new antiviral drug used to treat chronic HCV and was approved by both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2013 [13]. In this retrospective observational study, conducted at HGH, 95 patients received the study medication sofosbuvir. Among them, 93% received combination therapy consisting of sofosbuvir and other antiviral medications. All HCV genotypes were included; however, genotypes 5 and 6 were not detected during the study period. Four weeks after completing the treatment course, all patients maintained an undetectable virus RNA level. However, at week 12 after treatment, the percentage of patients who maintained an SVR decreased to 95% in the total population (98% of the treatment-naïve patients and 91.5% of the previously treated patients). Relapse was mostly observed in patients with genotype 1a (40%); none of the patients with HCV genotype 3 relapsed.

The study results emphasized that, among all detected genotypes, treatment-naïve patients showed a higher SVR12 rate than previously treated patients (98% vs. 91.5%). Likewise, evidence from genotype 3-infected patients supported our results. The ALY-3 study compared the responses of treatment-naïve and previously treated patients (90% and 86%, respectively) [21].

The efficacy of the sofosbuvir-containing regimens was demonstrated in several studies, supporting its use over other non-sofosbuvir-containing antiviral regimens. The FISSION trial is a non-inferiority trial that evaluated a 12-week treatment course of sofosbuvir plus ribavirin

versus a 24-week course of ribavirin plus PEG among treatment-naïve patients. Compared to ribavirin/PEG, sofosbuvir/ribavirin achieved an SVR in a shorter time period ($p<0.001$), satisfying the non-inferiority requirements. [10]. Additionally, the FUSION trial in 2013 showed that a sofosbuvir/ribavirin combination significantly ($p<0.001$) induced and maintained an SVR12 compared to ribavirin/PEG [22].

Furthermore, the NEUTRINO trial is an open-label clinical study that evaluated the efficacy of sofosbuvir combined with ribavirin and PEG for 12 weeks. The results revealed that 90% (95% CI, 87 to 93) of patients achieved virologic response [21]. Another phase 3, double-blind placebo-controlled trial evaluated the efficacy (i.e., SVR) of sofosbuvir and velpatasvir compared to placebo among all genotypes and revealed that 99% of the treatment group achieved an SVR12 vs. 0% in the placebo group [23]. Finally, a meta-analysis of 8 phase III clinical studies demonstrated the efficacy of a sofosbuvir-containing regimen in terms of the SVR over the standard treatment regimens in terms of maintaining the SVR12 with an odd ratio of 3.66 [24].

The SVR12 rate in our study was higher than that in previous studies. An open-labeled randomized uncontrolled phase 2 study evaluated 49 patients who were treated for 12 weeks and had HCV genotypes 2 and 3, with and without cirrhosis. The SVR12 rate was 89% [25]. Moreover, another phase 3 study, ALLY-3, included patients with and without cirrhosis who were treated with daclatasvir (60 mg) plus sofosbuvir (400 mg) once daily. The SVR12 rate was 90% in treatment-naïve group and 86% in the previously treated patients. Additionally, 96% of patients with genotype 2 infection without cirrhosis tolerated treatment for 12 weeks [25].

Table 1. Patient demographic and clinical information (N=95)

Demographics		**n (%)**
Sex	Male	46 (48.4)
	Female	49 (51.6)
Age (mean±SD)	56.0 ±13.4 years	
Nationality	Qatari	75 (78.9)
	Non-Qatari	20 (21.1)
Genotype	Genotype 1a	35 (36.9)
	Genotype 1b	15 (15.8)
	Genotype 2	3 (3.2)
	Genotype 3	12 (12.6)
	Genotype 4	29 (30.5)
	Genotype 5	0 (0)
	Genotype 6	0 (0)
Previous treatment	Previously treated	46 (48.9)
	Treatment naïve	48 (51.1)
Complications	Cirrhosis	18 (18.9)
	Hepatocellular carcinoma (HCC	1 (1.1)
	Post liver transplant	9 (9.5)
Treatment duration (mean±SD)	12±6 weeks	
Baseline serum creatinine (mean±SD)	63±16 µmol/L	
Baseline virus RNA (mean±SD)	1792270 ± 8005424	

Table 2. Direct-acting antiviral medications co-administered with sofosbuvir (N=95)

DAA used in combination with sofosbuvir	**n (%)**
Simeprevir	39 (42)
Ribavirin	35 (25)
Daclatasvir	23 (25)
Ledipasvir	1 (2)
PEG	6 (7.4)

Table 3. Status of patients during and after the treatment (N=95)

Percentage of patients who achieved undetectable virus RNA levels during treatment		Percentage of patients who maintained the SVR12 after the treatment course	
Treatment period	**Percentage of patients (n)**	**Post-treatment week**	**Percentage of patients (n)**
Week 2	24.70% (26)	2 weeks	100% (95)
Week 4	62.20% (59)	4 weeks	100% (95)
Week 6	94.30% (90)	6 weeks	98.60% (94)
Week 8	100% (95)	8 weeks	98.60% (94)
Week 10	100% (95)	10 weeks	98.60% (94)
Week 12	100% (95)	12 weeks	97.50% (93)

Table 4. The characteristics of the relapsed patients (N=95)

	Age	Sex	Genotype	% of genotype	Previous treatment	Co-morbidities	Treatment duration	Start of relapse (week)	Treatment combination
Case 1	62	F	1a	20	Yes	None	24	12	Sofosbuvir + Simeprevir
Case 2	63	F	1a	20	Yes	Cirrhosis	20	8	Sofosbuvir + Ledipasvir
Case 3	46	M	1b	20	Yes	Cirrhosis	12	6	Sofosbuvir + Simeprevir
Case 4	62	F	4	20	Yes	None	12	10	Sofosbuvir + Simeprevir
Case 5	62	M	2	20	Naïve	Post liver transpl	12	12	Sofosbuvir + Ribavirin

In our study, all patients with HCV genotype 3 maintained an SVR12, and the most predominant genotype that exhibited relapse was genotype 1. This is in contrast with the findings of other studies. A phase-2 trial, ALY-1, examined the use of sofosbuvir/PEG in non-cirrhotic patients with HCV genotype 2 and 3. The authors claimed that the SVR12 rate was highest for genotype 4 (100%) compared to genotypes 1, 2, and 3, in which the reported SVR rates were 82%, 80% and 83%, respectively [26] Moreover, another open-labeled study reported that the SVR12 rate of patients treated with a sofosbuvir-containing regimen (plus PEG plus ribavirin) was higher in genotype 2 than in genotype 3 patients [27].

According to Bhatia et al. (2014), sofosbuvir is effective against all HCV genotypes. Furthermore, it has a good safety profile [28]. Finally, our study revealed that non-cirrhotic patients would benefit from sofosbuvir-containing regimens more than the cirrhotic patients. This finding was supported by the finding of the ALY-3 trial, a phase III trial in which 63% of cirrhotic patients maintained an SVR12 compared to 96% of cirrhotic patients [25].

The main limitation of this study is its design. Despite the feasibility of retrieving the outcome of interest from the already existing database, it has the inherent limitations of a retrospective design. The missing data, patient adherence and poor reporting of the adverse drug reactions cannot be controlled. Additionally, the small sample size and convenience sampling contributed to the limitations associated with the generalizability of the study findings. Thus, a cohort study with a larger sample size should be conducted in Qatar.

4. CONCLUSION

In summary, the study indicated that a twelve-week treatment course with sofosbuvir-containing regimens produced an SVR12 in 97.5% of the patients. Among the patients who relapsed, no patients with genotype 3 relapsed, and 80% of patients were previously treated.

ETHICAL APPROVAL AND CONSENT

This study was reviewed and approved by the Institutional Review Board - the Medical Research Committee of Hamad Medical Corporation (Research ID number: 14426/14). Patient consent was waived by the medical research center due to the retrospective nature of the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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