Research Article

Efficacy of DAAs in the Treatment of Chronic HCV: Real-World Data from the Private Health-Care Sector of the Kingdom of Saudi Arabia

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ABSTRACT

Background and Aim: The hepatitis C virus (HCV) is considered a global health challenge that requires urgent interventions for prevention and control. In this study, we aimed to evaluate the effectiveness of direct-acting antiviral agents (DAAs) for HCV-infected patients in the Kingdom of Saudi Arabia (KSA).

Patients and Methods: In this retrospective cohort study, we ascertained data of patients treated with DAA-based regimens for chronic HCV in the private health-care sector hospitals of KSA between April 2015 and December 2017. Data regarding presence or absence of liver cirrhosis, virus genotype, quantitative HCV RNA test, fibrosis stage, and history of liver disease were included. The primary end point of the study was the overall cure rate, defined as the number of patients achieving sustained viral response (SVR) rate at least 12 weeks following completion of treatment, divided by the total number of patients included in the study.

Results: A total of 262 patients fulfilled the study inclusion criteria. Adult patients were enrolled, of which 114 (44%) were females and 148 (56%) were males. About 105 of the patients (40%) were cirrhotic and 156 were treatment-naïve patients (60%), 84 patients were interferon (INF) experienced, and 22 patients had previously received new DAAs but failed to achieve SVR. The majority of patients received ledipasvir–sofosbuvir±RBV (57%) with SVR rate of approximately 97%.

Conclusions: Our local real-world data indicate an overall HCV cure rate of 97% following treatment with DDA's when prescribed in the private sector. This estimate is acquiescence with previously reported global cure rates.

1. INTRODUCTION

The hepatitis C virus (HCV) is a considerable global health problem that requires urgent public health interventions for its prevention and control. HCV is one of the leading causes of liver cirrhosis, hepatic failure, and hepatocellular carcinoma (HCC). According to World Health Organization, approximately 71 million people worldwide have chronic hepatitis C infection and approximately 400,000 people die each year from HCV, mostly from cirrhosis or HCC [1].

High prevalence rates of HCV (>3.5%) have been reported in Central Asia, East Asia, and North Africa/Middle East. Additionally, a few countries in the region are heavily affected by HCV, including Egypt with a prevalence of 14.7% and Pakistan with a prevalence

of 4.8% [1–3]. The reason behind the scale of the infection burden in Arabian Gulf countries remains poorly understood [1,2,4]. The prevalence of HCV in Saudi Arabia is uncertain because no recent studies have been conducted. According to recent literature, the estimated prevalence of HCV in injection and non-injection drug users is around 35.6%, and the RNA prevalence is estimated to be around 29.9% [1].

There are six major HCV genotypes (GTs) with several subtypes known. These GTs are however structurally different and differ in their clinical behavior. Globally, GT1 is believed to account for the majority of HCV cases. The majority of patients infected with GT2 and GT6 reside in East Asia. GT4 infections on the other hand are most likely to be reported in North Africa and the Middle East; a surge of GT4 infections have been reported in Egypt and thought to be due to mass anti-schistosomal treatments as part of a national program that left many millions of Egyptians infected with HCV. GT5 infections are primarily reported in South Africa [3].

The effectiveness of pegylated interferon (IFN)-γ therapy against HCV infection was first reported in the early 1990s leading to expedited recommendations for it to be part of the first-line treatment regimen against HCV. This composed of a 24- or 48-week course of IFN-γ, depending on GT. Eligible patients required weekly injection but treatment outcomes proved to be poor with ≤10% response rate. However, the addition of ribavirin to IFN-γ therapy considerably improved outcomes and increased sustained viral response (SVR) rates to approximately 30–40% [5]. Nevertheless, this treatment regimen was associated with significant adverse events and lower than desired response, which drove the need for newer and more effective treatments for HCV infection.

Boceprevir and telaprevir were the first-generation direct-acting antiviral agents (DAAs) approved for HCV treatment in 2011 but these treatments were discontinued in practice upon the approval the arrival of sofosbuvir to the market. Sofosbuvir in combination with ribavirin, the first IFN-free all-oral regimen for the treatment of patients with HCV GTs 2 and 3, was approved by the Food and drug administration (FDA) in December 2013. In addition, sofosbuvir in combination with IFN-γ and ribavirin has also been approved for the treatment of patients with HCV GTs 1 and 4 [6]. This not only marked a sea of change in how HCV infection was treated but it also rendered earlier generations of anti-HCV medications obsolete. Following fast on sofosbuvir heels was the introduction of six additional drug formulations able to treat ever-widening range of HCV GTs. DAAs not only offered less side effects, they also reduced the duration of therapy [7]. As such, DAAs are now the standard-of-care for HCV treatment in Saudi Arabia and are recommended by the Saudi Association for the Study of Liver Diseases and Transplantation (SASLT) [8]. The introduction of DAAs for the treatment of HCV is considered a major advancement in HCV treatment in terms of SVR rates and adverse effect profiles.

In this study, we present real-world data of the effectiveness of DAAs for HCV-infected patients in the Kingdom of Saudi Arabia (KSA).

2. MATERIALS AND METHODS

In this retrospective cohort study, we assessed patients treated with DAA-based regimens for chronic HCV in the private health-care sector hospitals of KSA between April 2015 and December 2017. Eligible patients were identified using an electronic database of a major health insurance company.

Patients were included independent of their ethnicity, race, or socioeconomic status. Data regarding presence or absence of liver cirrhosis (based on Fibroscan and ultrasound), virus GT, polymerase chain reaction, fibrosis stage, and history of liver disease were included. Treatment regimens selected by providers were recorded, as were previous HCV treatments. Demographic and other baseline variables were documented at the time of initiating therapy. All patients were closely followed up until their treatment was completed. All patients were tested for treatment response 12 and 24 weeks' post completion of treatment. All discontinuations, treatment modifications, and deaths were documented.

2.1. Outcomes and Definitions

The primary end point of the study was the overall cure rate, defined as the number of patients achieving SVR rate at least 12 weeks following the end of treatment, divided by the total number of patients included in the study. SVR was defined as the absence of HCV RNA from serum 12 and 24 weeks after discontinuation of treatment [9,10]. The main secondary outcome was to identify predictors of SVR.

2.2. Statistical Analysis

We summarized study sample characteristics using means and standard deviation (SD) for continuous variables and frequencies and proportions for categorical variables. We performed bivariate analysis to compare those who were cured (i.e., achieved SVR) and those who were not cured using Student's t-test for age and Fisher's exact test for categorical variables. Fisher's exact test is used when expected frequencies were below 5, as was the case in our sample. We used logistic regression models to calculate odds ratio (OR) with 95% confidence interval (CI) estimating the crude and adjusted association between potential predictors and detection (i.e., not achieving SVR). We performed the analysis for the overall study sample and for the subgroup of patients who used ledipasvir–sofosbuvir±ribavirin. The following variables were assessed as potential predictors of SVR: age in years as a continuous variable, sex (male, female), nationality (Saudi, Egyptian, others), GT (1–4, or 1 and 4), previous HCV treatment (experienced, naïve), and presence of liver cirrhosis (yes, no).

3. RESULTS

3.1. Baseline Characteristics

A total of 262 patients who were seen by gastroenterologists/ hepatologists in nine primary health-care provider clinics were included in the study. Patient's enrolled were aged 18–90 years (mean = 49.9 ± 12.9 years), of which 114 (44%) were females and 148 (56%) were males. About 105 of the patients (40%) were cirrhotic and 156 were treatment-naïve patients (60%), 84 patients were interferon (INF) experienced, and 22 patients had previously received new DAAs but failed to achieve SVR. The major GT detected was GT 4 (78%, n = 205), followed by GT 1 (15%, n = 40); 11 patients had HCV GT 3 (4.20%). The majority of patients received ledipasvir–sofosbuvir±ribavirin (57%), followed by ombitasvir–paritaprevir–ritonavir+ribavirin (28%; Table 1).

3.2. Outcomes

Overall SVR rate was approximately 97%. Ledipasvir–sofosbuvir± ribavirin had an SVR rate of approximately 97% (95% in cirrhotics and 98% in non-cirrhotics), while the sustained virological response rate of ombitasvir–paritaprevir–ritonavir+ribavirin was 99%; The only treatment that was used for GT 3 patients was sofosbuvir combined with daclatasvir or sofosbuvir+IFN, and SVR

Table 1 | Baseline characteristics of 262 patients treated for HCV with DAA's

Characteristics	Total (N = 262)	Cured (N = 255)	Not cured (N = 7)	p-value
Mean age in years (SD)	49.9 (12.9)	49.6 (12.8)	60.7 (7.5)	0.02
Sex				0.14
Male	148 (56%)	142 (56%)	6 (86%)	
Female	114 (44%)	113 (44%)	1 (14%)	
Nationality				0.66
Egyptian	129 (49%)	124 (49%)	5 (71%)	
Saudi	96 (37%)	94 (37%)	2 (29%)	
Others	37 (16%)	37 (15%)	0 (0%)	
Genotype final				0.18
1	40 (15%)	39 (15%)	1 (14%)	
2	2 (1%)	2 (1%)	0 (0%)	
3	11 (4%)	11 (4%)	0 (0%)	
4	206 (79%)	201 (79%)	5 (71%)	
1&4	3 (1%)	2 (1%)	1 (14%)	
Treatment history				1.00
Naïve	156 (60%)	152 (60%)	4 (57%)	
Experienced	106 (40%)	103 (40%)	3 (43%)	
Cirrhosis status				0.12
Non-cirrhotic	157 (60%)	155 (61%)	2 (29%)	
Cirrhotic	105 (40%)	100 (39%)	5 (71%)	
Active ingredient				0.65
Ledipasvir–sofosbuvir	148 (56%)	143 (56%)	5 (71%)	
Ombitasvir–paritaprevir–ritonavir	73 (28%)	72 (28%)	1 (14%)	
Sofosbuvir+daclatasvir	12 (5%)	11 (4%)	1 (14%)	
Sofosbuvir+simeprevir	12 (5%)	12 (5%)	0 (0%)	
Elbasvir–grazoprevir	6 (2%)	6 (2%)	0 (0%)	
Sofosbuvir+ribavirin	5 (2%)	5 (2%)	0 (0%)	
Sofosbuvir+interferon	2 (1%)	2 (1%)	0 (0%)	
Ombitasvir–paritaprevir–ritonavir+sofosbuvir	2 (1%)	2 (1%)	0 (0%)	
Ombitasvir–paritaprevir–ritonavir–dasabuvir	2 (1%)	2 (1%)	0 (0%)	

was 100% achieved in all patients. For GT 4, the overall SVR was 98% (97% with ledipasvir–sofosbuvir±ribavirin and 99% with ombitasvir–paritaprevir–ritonavir+ribavirin) (Table 2).

3.3. Predictors of SVR

Age, gender, nationalities, GT, cirrhosis, treatment naïve versus treatment experienced, and type of medication were assessed as potential predictors of SVR. Results from the unadjusted logistic regression models estimating the association between potential predictors and not achieving SVR in the overall sample and subgroup of patients who received ledipasvir–sofosbuvir±ribavirin show that our data are consistent with an increased odds of not achieving SVR for patients who are males, Egyptian, of GTs 1 and 4 (combined), and those who have confirmed cirrhosis. Result from the multivariable model shows similar results with age approaching statistical significance in the overall sample (Tables 3–6).

4. DISCUSSION

Up to now, several studies both globally and locally have discussed the effectiveness of the newly developed HCV medications. Treatment of HCV continues to evolve rapidly; DAA medications represent a true breakthrough in the treatment of chronic

HCV infection. In this study, we report on data from several primary care private hospitals describing their experience with a comprehensive HCV treatment program. HCV therapy in KSA generally follows recommendations made by European association of the study of liver (EASL) and American association for the study of liver disease (AASLD) Guidelines [9,10]. Data from 262 patients treated with new DAAs were analyzed. Of these patients, 79% were identified as having GT4. The most commonly prescribed regimen was ledipasvir/sofosbuvir±ribavirin.

The treatment approach to HCV infection has changed dramatically over the years, mainly following changes and updates made by EASL and AASLD. Success of treatment with DAAs according to randomized controlled trials exceeds 90% for most HCV-infected patient populations [6,11]. Moreover, cure rates for individual regimens were found to be comparable according to clinical studies [6]. We found that the rate of treatment success of DAAs for HCV in our study cohort was comparable to those reported by other real-world outcome studies. The rate of SVRs among patients who completed therapy was 97% (255/262).

It is clinically relevant to be accustomed with predictors of drug response, especially when medications that are expensive or are associated with adverse events are being used. Our analysis identified male gender, Egyptian nationality, GTs 1 and 4 (combined), and confirmed cirrhosis as statistically significant negative predictors of SVR. However, it is important to take into consideration

Table 2 | SVR rates stratified by prescribed drug

Characteristics	Ledipasvir–sofosbuvir (N = 148) (%)	Ombitasvir–paritaprevir–ritonavir (N = 73) (%)	Sofosbuvir+simeprevir (N = 12) (%)	Sofosbuvir+daclatasvir (N = 12) (%)	Elbasvir–grazoprevir (N = 6) (%)	Sofosbuvir (N = 5) (%)	Sofosbuvir+INF (N = 2) (%)	Ombitasvir–paritaprevir–ritonavir–dasabuvir (N = 2) (%)	Sofosbuvir+ombitasvir–paritaprevir–ritonavir (N = 2) (%)	Total number of cured patients (N = 255) (%)
All patients	143 (97)	72 (99)	12 (100)	11 (92)	6 (100)	5 (100)	2 (100)	2 (100)	2 (100)	255 (97)
Sex										
Female	69 (99)	29 (100)	2 (100)	1 (100)	6 (100)	4 (100)	1 (100)	1 (100)	0 (0)	113 (99)
Male	74 (95)	43 (98)	10 (100)	10 (91)	0 (0)	1 (100)	1 (100)	1 (100)	2 (100)	142 (96)
Cirrhosis status										
Cirrhotic	56 (95)	28 (97)	5 (100)	5 (83)	2 (100)	2 (100)	0 (0)	0 (0)	2 (100)	100 (95)
Non-cirrhotic	87 (98)	44 (100)	7 (100)	6 (100)	4 (100)	3 (100)	2 (100)	2 (100)	0 (0)	155 (99)
Treatment history										
Experienced	60 (97)	29 (100)	7 (100)	2 (67)	0 (0)	3 (100)	0 (0)	0 (0)	2 (100)	103 (97)
Naïve	83 (97)	43 (98)	5 (100)	9 (100)	6 (100)	2 (100)	2 (100)	2 (100)	0 (0)	152 (97)
GT										
1	35 (97)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	2 (100)	0 (0)	39 (98)
2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	2 (100)
3	0 (0)	0 (0)	0 (0)	9 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	11 (100)
4	106 (97)	72 (99)	11 (100)	2 (67)	5 (100)	3 (100)	0 (0)	0 (0)	2 (100)	201 (98)
1&4	2 (67)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (67)

Table 3 | Crude ORs (with 95% CI) estimating the association between patient predictors and detection (i.e., not achieving SVR) in the overall sample using unadjusted regression models (n = 262)

Predictor	Unadjusted OR (95% CI)
Age	1.07 (1.0–1.4)*
Sex	
Female	Ref
Male	4.8 (0.6–40)
Nationality	
Saudi	Ref
Egyptian	1.9 (0.3–10)
Others	1
Genotype	
1	Ref
2	1
3	1
4	0.97 (0.1–8.5)
1&4	19 (0.9–439)
History	
Experienced	Ref
Naïve	0.9 (0.2–4.1)
Cirrhosis	
No	Ref
Yes	3.8 (0.7–20)

*p-value < 0.05.

Table 4 | Adjusted* ORs (with 95% CI) estimating the association between patient predictors and detection (i.e., not achieving SVR) in the overall sample using a multivariable regression model (n = 221)

Predictor	Adjusted OR	95% CI		p-value
Age (years)	1.09	0.99	1.2	0.05
Sex				
Female	Ref	—	—	—
Male	6.4	0.3	122	0.22
Nationality				
Saudi	Ref	—	—	—
Egyptian	1.9	0.2	18	0.58
Others	1	—	—	—
Genotype				
1	Ref	—	—	—
2	1	—	—	—
3	1	—	—	—
4	0.3	0.02	3.4	0.32
1&4	13	0.4	438	0.15
History				
Experienced	Ref	—	—	—
Naïve	1.4	0.3	7.9	0.70
Cirrhosis				
No	Ref	—	—	—
Yes	2.8	0.4	21	0.31

*Multivariable model assessing the association of each of the factors included in the table, while adjusting for others.

while interpreting these results that the CIs are wide and only age shows a statistically significant association, that is, for every year increase in age, there is a 7% increase in odds of not achieving SVR across all medication types and a 10% increase in odds for ledipasvir–sofosbuvir±ribavirin. The ORs for nationality

Table 5 | Crude ORs (with 95% CI) estimating the association between patient predictors and detection among patients using ledipasvir–sofosbuvir±ribavirin using unadjusted regression models ($n = 148$)

Predictor	Unadjusted OR (95% CI)
Age	1.1 (1.0–1.2)*
Sex	
Female	Ref
Male	3.7 (0.4–34)
Nationality	
Saudi	Ref
Egyptian	1.8 (0.3–11)
Others	1
Genotype	
1	Ref
4	0.99 (0.1–9.8)
1&4	17 (0.77–394)
History	
Experienced	Ref
Naïve	1.08 (0.2–6.7)
Cirrhosis	
No	Ref
Yes	2.3 (0.38–14.7)

*p-value < 0.05.

Table 6 | Adjusted ORs (with 95% CI) estimating the association between patient predictors and detection among patients using ledipasvir–sofosbuvir±ribavirin using a multivariable regression model ($n = 148$)

Predictor	Adjusted OR	95% CI		p-value
Age (years)	1.1	0.99	1.2	0.073
Sex				
Female	Ref	—	—	—
Male	7.5	0.5	111	0.145
Genotype				
1	Ref	—	—	—
4	0.5	0.04	6.4	0.607
1 & 4	18	0.6	538	0.096
History				
Experienced	Ref	—	—	—
Naïve	1.2	0.2	9.6	0.873
Cirrhosis				
No	Ref	—	—	—
Yes	2.0	0.2	17	0.519

*Multivariable model assessing the association of each of the factors included in the table, while adjusting for others.

(others) and GTs 2 and 3 were equal to 1 because detection status does not vary in those groups (i.e., all achieved SVR) and their observations were therefore dropped from the model.

We acknowledge that our study holds several key limitations. First, it is a retrospective, observational, nonrandomized study without a control group that could be underpowered to fully examine the relative benefits and drawbacks of different DAA regimens. Patients for whom viral load data are not available or who had an undetectable viral load <12 weeks after treatment completion were not included. These members may account for additional cure rate data. It is noteworthy however that only 5% of the study population were lost to follow-up, which is only marginally higher than the

2.5–3.8% reported in non-indigent real-world studies reflecting external validity of our results.

5. CONCLUSIONS

Local real-world data for Saudi Arabia indicate an overall HCV cure rate of 97% following treatment with DDA's when prescribed in the private sector. This estimate is acquiescence with previously reported global cure rates.

CONFLICTS OF INTEREST

Bupa Arabia provided the data used in this manuscript; statistical analysis was however performed by a third party. Fadia Almahdi, Ohoud Barkia, Reem Alkasam, Asmaa Almahmoud, Ahmed Nabil, and Ayman Alsulaimani are employees of Bupa Arabia.

AUTHORS' CONTRIBUTION

AH, FA, A. Alsulaimani and MM were involved in concept development. AH, FA, EAA, OB, RA, A. Almahmoud and AN completed data collection. AH, FA, EAA, OB, RA, A. Almahmoud, AN, A. Alsulaimani and MM completed analysis and interpretation. AH, FA and MM completed manuscript writing (original drafting and critical revision of the article). MM is the guarantor of the article.

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ETHICAL APPROVAL

Approval for this paper was obtained from the internal review board of Jeddah University, Jeddah.

ABBREVIATIONS

HCV, hepatitis C virus; MENA, Middle East and North Africa; DAAs, direct-acting antiviral agents; KSA, Kingdom of Saudi Arabia; SVR, sustained viral response; HCC, hepatocellular carcinoma; SASLT, Saudi Association for the Study of Liver Diseases and Transplantation; SD, standard deviation; OR, odds ratio; CI, confidence interval.

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