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Observational Study

Effectiveness and safety of generic and brand direct acting antivirals for the treatment of chronic hepatitis C

Abdulla M *et al*. Antivirals for chronic hepatitis C

Maheeba Abdulla, Aysha Mohamed Al Ghareeb, Hamed Ali Hasan Yusuf Husain, Nafeesa Mohammed, Jehad Al Qamish

Abstract

BACKGROUND

Direct Acting Antivirals (DAAs) are a very effective treatment for Hepatitis C virus (HCV). However, brand DAAs are expensive. The licensing of cheaper generic DAAs may address this issue, but there is a lack of clinical studies comparing the efficacy of generic *vs* brand DAA formulations This study aims to compare the efficacy and safety of generic DAAs against brand DAAs for chronic hepatitis C treatment in Bahrain.

AIM

This was a retrospective observational study, conducted between 2016 and 2018, involving 289 patients with chronic HCV infection. Of those patients, 149 were treated with brand-name DAAs, whereas the other 140 patients were treated with generic DAAs. Commonly used DAAs were Ombitasvir/Paritaprevir/Ritonavir ± Dasabuvir ± Ribavirin, and Sofosbuvir/Daclatasvir ± Ribavirin. Sustained Virologic Response (SVR) after 12 wk post treatment was the main outcome variable.

METHODS

This was a retrospective observational study involving 289 patients with chronic HCV infection during 2016 to 2018. There were 149 patients who were treated with brand-name DAAs, while 140 patients were treated with generic DAAs. Commonly used DAAs were Ombitasvir/Paritaprevir/Ritonavir ± Dasabuvir ± Ribavirin, and Sofosbuvir/Daclatasvir ± Ribavirin. SVR after 12 wk post treatment was the main outcome variable.

RESULTS

Overall, 87 patients (30.1%) had cirrhosis and 68.2% had genotype 1 HCV. At 12 wk post treatment, SVR was achieved by 271 (93.8%) of the patients. In patients who were treated with generic medications, 134 (95.7%) achieved SVR at 12 wk post treatment, compared to 137 (91.9%) among those treated with brand medications (P = 0.19). Having cirrhosis (OR: 9.41, 95%CI: 2.47–35.84) and having HCV genotype 3 (OR: 3.56, 95%CI: 1.03–12.38) were significant independent predictors for not achieving SVR. Alanine transaminase, gamma-glutamyl transpeptidase, and total bilirubin levels decreased significantly following therapy with both generic and brand DAAs.

CONCLUSION

Generic and brand DAAs demonstrate comparable effectiveness in the treatment of chronic hepatitis C patients. Both are safe and equally effective in improving biochemical markers of hepatic inflammation.

Key Words: Hepatitis C virus, Direct acting antivirals, Generic, Brand, Sofosbuvir, Ombitasvir, Ledipasvir, Daclatasvir, Paritaprevir, Ritonavir, Dasabuvir, Ribavirin, Sustained virologic response

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Core Tip: The World Health Organization aims to eliminate Hepatitis C virus (HCV) infection by 2030. Its guidelines recommend treatment for all individuals diagnosed with HCV infection >12 years. Management of HCV in low- and middle-income countries is hampered by high costs of medication. This is the first study to compare efficacy and safety of generic compared to original brand Direct Acting Antivirals (DAAs) for hepatitis C treatment in Bahrain, where the prevalence of HCV infection is estimated to be 1.7% (1.39 – 2.21%). Overall, our study adds to the literature on the similarity in effectiveness in patients receiving both brand and generic formulations of DAAs for chronic hepatitis C.

INTRODUCTION

Over 71 million individuals live with Hepatitis C Virus (HCV) globally, equivalent to 1% of the worlds' population[1]. Furthermore, approximately 5 million new cases of HCV were diagnosed in 2015[2]. HCV can present as an acute or a chronic infection. Acute HCV infection does not present with symptoms and up to 30% (15%–45%) of affected persons spontaneously eliminate the virus within 6 mo without medication[3]. However, roughly 70% of HCV infected persons develop chronic infection, and up to 30% of those will develop cirrhosis and hepatocellular carcinoma within 20 years – eventually leading to almost 1 million deaths annually[3,4]. Achieving a Sustained Virologic Response (SVR), where the HCV Ribonucleic Acid (RNA) levels remain undetectably low, has been associated with a reduction in liver-associated complications, improvement in health-related quality of life and reduction in the need for liver transplantation among individuals with chronic hepatitis C[4-6].

Direct-Acting Antivirals (DAAs) have revolutionized the treatment landscape for patients with chronic hepatitis C because they have been shown to demonstrate high

SVR rates[7,8]. In response to this, the World Health Organization (WHO) proposed strategies for the elimination of HCV infection by 2030[9]. Achieving the HCV elimination strategy requires the diagnosis of 90% of those infected with hepatitis C, followed by treatment of 80% of those diagnosed – this will ultimately lead to an 80% reduction in new HCV infections, and a 65% reduction in HCV-associated mortality[8,9]. Furthermore, the WHO updated its chronic hepatitis C guidelines recommending treatment for all individuals diagnosed with HCV infection who are 12 years of age or older, irrespective of disease stage[9].

The uptake of DAAs in the management of HCV infection in several countries, especially in low- and middle-income countries (LMICs), has been hampered by the high cost of medications[10]. Moreover, the increase in the rate of new HCV infections, the low rate of testing for HCV infection globally, and patent ownership rights and restrictions by brand name companies producing the DAAs, have hampered the production of their generic versions; and low rates of treatment in LMICs (harboring 72% of HCV burden) continue to threaten the attainment of the WHO HCV elimination strategies[7]. With the increasing voluntary license permission being granted to companies producing generic DAAs by brand name manufacturers, the use of generic DAAs has substantially improved access to hepatitis C treatment in developing countries[11,12]. However, there are increasing concerns regarding the safety and efficacy of generic DAA formulations. A pharmacokinetic study has revealed similar bioequivalence between the generic and brand DAA formulations[13], and several real-world studies of generic DAAs and their systematic review have reported high SVR rates of 92% – 98% in HCV patients irrespective of their genotype[7,14-15]. Despite these findings, comparative studies assessing the effectiveness and safety of generic *vs* brand DAA formulations for hepatitis C treatment are needed before its adoption, but only a few of these studies, carried out in India and Egypt, have been reported[16-18].

In Bahrain, the prevalence of HCV infection is estimated to be 1.7% (1.39%–2.21%)[2]. The predominant HCV genotype among Bahraini patients is type 1, followed by genotypes 3 and 4, and the lowest frequency is for genotype 2[19,20]. There is a real-

world study of DAAs for hepatitis C treatment in Bahrain[21], but no study has compared the effectiveness of generic *vs* brand DAAs for hepatitis C treatment in the country. Therefore, the objective of this study was to compare the efficacy and safety of generic *vs* brand DAAs for chronic hepatitis C treatment in Bahrain.

MATERIALS AND METHODS

Study design

This was a retrospective observational study involving 289 patients with a real time reverse transcriptase-polymerase chain reaction (real-time RT-PCR) diagnosis of chronic HCV infection (*i.e.*, for over 6 mo) who qualified for antiviral treatment. The patients were enrolled from the hepatology clinic of Salmaniya Medical Complex, Bahrain, from January 2016 to December 2018. All patients gave written informed consent before participating in the study, and approval for the study was received from the Secondary Health Care Research Sub Committee, Ministry of Health, Kingdom of Bahrain (Reference number 22G45-40-01925).

Study participants

Patients' enrolment in the study was in accordance with The European Association for the Study of the Liver (EASL) guidelines, 2016 and 2018[22,23]. All patients who were aged 18 years or over with a real-time RT-PCR diagnosis of chronic liver disease from HCV infection (*i.e.*, based on the presence of HCV RNA for over 6 mo) were included in the study.

Measurements

All the patients underwent full clinical assessment at baseline and after 12 wk of treatment. The baseline data collected included a history and physical examination, complete blood count, prothrombin time, partial thromboplastin time (PTT), INR, serum total bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (gGT), albumin, creatinine, and serum HCV-RNA by real-time RT-PCR assay with lower limit of detection of 15 IU/mL (Abbott Real time

HCV kits, m²000rt machine, Des Plaines, IL, 60018, United States). Abdominal ultrasound was carried out to detect the presence of liver cirrhosis and to exclude hepatocellular carcinoma and metastatic liver disease.

Treatment groupings

The patients were classified into two groups, brand and generic. The brand group included 149 patients who were treated with brand-name antiviral therapy according to EASL guidelines for 2016 and 2018. The generic group included 140 patients treated with generic DAAs according to EASL guidelines, 2016 and 2018[22,23].

Most of the patients who were treated with brand name antiviral agents received Ombitasvir/Paritaprevir/Ritonavir ± Dasabuvir ± Ribavirin [Omb/Par/Rit ± Das ± Rib] 44 (44.3%), or Sofosbuvir/Ledipasvir ± Ribavirin [Sof/Lep ± Rib] 55 (36.9%), Sofosbuvir/Declatasvir ± Ribavirin [Sof/Dec ± Rib] 26 (17.4%) and Sofosbuvir ± Ribavirin [Sof ± Rib] 2 (0.7%). These brand name agents included Sovaldi (Sofosbuvir), Harvoni (Sofosbuvir / Ledipasvir), Viekira Pak (Ombitasvir / Paritaprevir / Ritonavir / Dasabuvir), Viekirax (Ombitasvir / Paritaprevir / Ritonavir), Daclinza (Daclatasvir), and Rebetol (Ribavirin), respectively. Of the patients treated with generic medications, 118 (84.3%), received Sofosbuvir/Daclatasvir ± Ribavirin [Sof/Dec ± Rib] while 22 (15.7%) received Sofosbuvir/Ledipasvir ± Ribavirin [Sof/Lep ± Rib]. These generic agents (all meant for use in Egypt) included Nucleobuvir (Sofosbuvir), Daclavirdine (Daclatasvir), Harvoni (Sofosbuvir/Ledipasvir), and Ribavirin (Ribavirin-Egypt). It should be noted that some of the generic medications used were produced by the same brand-name company at a lower price and for use only in LMICs such as Egypt.

Treatment outcomes

The primary study endpoint was the proportion of patients having HCV-RNA below detectable limits 12 wk post treatment (SVR) within each patient group, and comparing the findings of the patients who received brand-name *vs* generic DAAs. We also assessed the proportion of patients who abandoned treatment due to adverse effects of

the antiviral therapy. Treatment failure was defined as the presence of HCV-RNA above detectable limits in patients after 12 wk of having completed therapy, irrespective of the type of DAAs received. Further clinical and laboratory evaluation was carried out at 12 wk post treatment in order to compare the laboratory parameters at baseline and after treatment in each group.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, (Version 24.0. Armonk, NY: IBM Corp, United States). The normality of continuous variables was assessed using the Shapiro-Wilk's test, and they were reported as mean ± standard deviation (SD), or for non-normally distributed variables as median (interquartile range). Categorical variables were presented as frequency and percentages, and compared using the Chi-Square test. Independent samples *t*-test was used to compare continuous variables with normal distribution, while Mann-Whitney *U* test was used to compare non-normal continuous data. Paired *t*-test was used to compare continuous paired-samples of laboratory parameters before and at the end of treatment for each group. Univariate and multivariable logistic regression analysis was performed to determine the predictors of not achieving SVR 12 wk post treatment. Not achieving SVR was the dependent variable, while the treatment group was the main independent variable. Known predictors of SVR and variables with a *P* value of < 0.2 in the univariate analysis were the criteria for inclusion in the final model. A *P* value (two-sided) < 0.05 was considered statistically significant.

RESULTS

Characteristics of the patients

A total of 289 patients completed the study; 140 patients (48.4%) were treated with generic medications and 149 (51.6%) received brand medications. The demographic and clinical characteristics of the patients is as shown in Table 1. There were no significant sex differences in the study participants, and except for the serum level of PTT and

platelet count, there were no significant differences in the laboratory parameters explored among patients who received generic and brand medications (Table 1). Patients who received brand medications had a higher proportion of co-morbidities, such as cirrhosis (33.6 *vs* 10.0%), diabetes mellitus (31.5 *vs* 10.7%), dyslipidemia (15.4 vs. 5.7%), hypertension (24.8 *vs* 14.3%), and sickle cell disease (6 *vs* 5.7%); while those who received generic medication had a higher proportion of co-morbidities like hypothyroidism (5.0 *vs* 1.3%) and human immunodeficiency virus (2.1 *vs* 0.7%). The baseline median (interquartile range) HCV RNA level among patients who received brand medications was 717465 (356749 – 1489 361) IU per ml compared to 712,023.5 (331131 – 1820183) IU per ml among those who received generic medications (Mann-Whitney U; $P = 0.81$).

Treatment outcome of the patients

By 12 wk following treatment, SVR was achieved by 271 (93.8%) of the patients. Figure 1A-1F summarizes the outcomes of treatment among patients treated with brand and generic medications and their sub-groups. Of the patients who were treated with generic medications, 134 (95.7%) achieved SVR at 12 wk post treatment. In comparison, 137 (91.9%) of the patients who were treated with brand DAAs achieved SVR at 12 wk post treatment (Figure 1A. X^2 1.76; $P = 0.19$). In patients who received generic medications, 6 (4.3%) did not achieve SVR at 12 wk post treatment due to treatment failure, whereas for patients treated with brand medications, not achieving SVR was due to 7 (4.7%) patients abandoning treatment due to adverse effects, and treatment failure for 5 (3.4%) patients.

Among patients without liver cirrhosis (Figure 1B), 109 (96.5%) patients treated with generic medications and 88 (98.9%) of those treated with brand medications achieved SVR ($P = 0.27$). Similarly, among patients with cirrhosis (Figure 1C), there was no difference in the SVR rates among patients treated with brand or generic medications ($P = 0.19$). However, among patients with HCV genotype 1 (Figure 1D), 87 out of 88 patients (98.9%) treated with generic medications had SVR, compared to 100 of

109 (91.7%) patientswho were treated with brand medications (P = 0.02). All patients with genotype 2, irrespective of the type of medication given, had SVR (100%). There was no significant difference in the SVR observed for patients with genotype 3 and 4 according to the regimen received (Figure 1E and F).

Predictors of not achieving sustained virologic response

Table 2 shows the predictors of not achieving SVR after 12 wk of treatment. In univariate analysis, having more than two co-morbidities, and having ultrasound-diagnosed cirrhosis were significant determinants. On multivariable logistic regression analysis, being in the 40 – 65 years age group (OR: 0.26, 95%CI: 0.67–0.99), having USD-cirrhosis (OR: 9.41, 95%CI: 2.47–35.84) and having HCV genotype 3 (OR: 3.56, 95%CI: 1.03–12.38) were significant independent predictors of not achieving SVR after 12 wk of treatment.

Table 3 shows the predictors of not achieving SVR 12 wk post treatment in patients receiving only sofosbuvir-based generic and brand medications. In univariate analysis, only having USD-cirrhosis and having HCV genotype 3 were significant determinants. On multivariable logistic regression analysis, having USD-cirrhosis (OR: 8.99, 95%CI: 1.83–44.16) and having HCV genotype 3 (OR: 4.44, 95%CI: 1.17–16.89) remained significant independent predictors of not achieving SVR 12 wk post treatment.

Changes in laboratory parameters at baseline and after treatment

Table 4 shows the changes in the laboratory parameters at baseline and after treatment among patients treated with generic and brand medications. There was no significant difference in the WBC count before and after treatment among patients treated with generic medications (P = 0.15) but there was a significant increase in WBC among those treated with brand medications (P = 0.005). Treatment with both generic and brand medications were associated with significant increase in serum albumin level (P < 0.001) and platelet count (P <0.001). Similarly, treatment with both generic and brand medications were associated with a significant decline in serum total bilirubin (< 0.05),

serum ALT ($P < 0.001$) and gGT ($P < 0.001$). Generic medication use was associated with significant reduction in serum ALP levels at the end of treatment ($P < 0.001$), however treatment with brand medications was associated with insignificant reduction in serum ALP levels (Table 4).

DISCUSSION

The adoption of a new low-cost generic DAA therapy for the treatment of chronic HCV infection has remained a game changer for several national treatment programs as it has improved access to treatment and has provided significant progress towards the elimination of HCV. In most countries, generic formulations are required to undergo pharmaco-equivalence studies[9,12] and are therefore required to demonstrate similar rate of absorption and bioavailability compared to the original brand name drug before its approval for use. Several studies carried out in multiple countries have shown that generic and brand DAAs have similar bioequivalence[13,24]. Several studies have revealed the real-life effectiveness of generic DAAs[7,14,15], but only a few studies have assessed their clinical efficacy compared to the original brand DAAs. This study is a comparative assessment of chronic hepatitis C patients treated with either brand or generic DAAs. Although we did not randomize the study patients, most of the baseline laboratory tests and viral load did not significantly differ between patients treated with the generic or the brand DAAs. However, the patients significantly differed by their age group, HCV genotype, and number of co-morbidities including the proportion with USD-cirrhosis.

In this study, we compared the safety and efficacy of generic *vs* brand DAAs for the treatment of chronic hepatitis C. The study findings revealed that the generic DAAs used were very effective with SVR rate of 95.7% compared with 91.9% in patients receiving brand DAAs. Our findings are generally consistent with findings of other studies. In Argentina, Marciano *et al*[25] compared treatment with generic or brand Sofosbuvir-based therapy for 321 patients with chronic hepatitis C of whom 91% had cirrhosis. The study revealed an SVR rate of 91% among patients receiving brand and

89% among those receiving generic Sofosbuvir-based regimen. In Egypt, two studies among patients with chronic hepatitis C revealed SVR rates of 98.2% – 100% among patients receiving generic DAAs compared with rates of 98.1% – 99% in those receiving brand DAAs[17,18]. In India, Tang *et al*[16] carried out a non-randomized comparative study among 66 patients with chronic hepatitis C. SVR rates were 72.4% *vs* 75.7% among patients treated with generic *vs* brand DAAs. The lower SVR rates in the studies from Argentina and India compared to ours may be due to a higher proportion of patients with cirrhosis, and some of their patients were previously-treated cases who had treatment failure[16,25]. Overall, our study adds to the literature on the similarity in effectiveness in patients receiving both brand and generic formulations of DAAs for chronic hepatitis C.

Being a middle-aged patient, having USD-cirrhosis and having genotype 3 were all predictors of not achieving SVR. Middle-aged patients were 74% less likely to achieve SVR while patients with cirrhosis were 9.4 times less likely to achieve SVR, and patients with HCV genotype 3 were almost 4 times less likely to do so. Furthermore, our analysis revealed that receiving brand or generic DAAs was not an independent risk factor for not achieving SVR. Moreover, when we restricted our analysis to patients treated with Sofosbuvir-based brand and generic regimens, our study revealed that having cirrhosis and genotype 3 were the independent predictors of not achieving SVR. A previous study in the same setting using brand DAAs for hepatitis C treatment revealed that having cirrhosis at baseline was the only risk factor for not achieving SVR [21]. The findings of this study indicate that adequate care and attention need to be given during treatment of patients with cirrhosis and genotype 3 HCV in our setting. Another study found that having a positive HCV RNA at four weeks post treatment was a risk factor for not achieving SVR[17]. In the present study, we did not assess the level of HCV RNA at four weeks post treatment. This should be considered in future studies.

In terms of safety, this study revealed that 4.3% of HCV patients treated with generic DAAs had treatment failure compared with 3.4% among patients who received brand DAAs. None of the patients who received generic DAAs abandoned treatment

due to adverse drug reaction/effects while 4.7% of those receiving brand DAAs did. Considering intention-to-treat analysis, although the proportion of patients with a poor outcome was higher among patients treated with brand medications, the difference was not statistically significant. Similar findings were documented by other investigators and this suggests that the safety profile of both generic and brand DAAs for HCV treatment are good. Both the generic and the brand DAA formulations showed significant changes in the level of serum transaminases and hemoglobin level, and this is consistent with findings of previous studies involving brand or generic DAAs[26-31]. Total Bilirubin substantially decreased at 12 wk post treatment[17,26,27,30,31]. ALP, ALT and gGT all substantially declined at 12 wk post treatment when compared to baseline values in both groups in accordance with previously published reports.

The study has some limitations. This was a non-randomized retrospective observational clinical study from a single center. Not all the patients received the same type of brand or generic DAA formulation which might have accounted for minor differences in the treatment outcome. The type of DAA medication given to the patients was based on the EASL guidelines at the time of enrolment[22,23]. Another important limitation is that, although the majority of our patients were treatment naïve, we do not have data on the proportion of previously treated hepatitis C patients included in this analysis, which might have affected the treatment outcomes[16-18]. This should be considered during further studies in our setting. Moreover, other factors that might have influenced the treatment outcome is the choice of the DAA medication used. In our study, the choice of DAA regimen used was physician driven *i.e.*, based on the physicians' interest in treating the greatest number of patients effectively considering the best available evidence, as well as the most effective medications according to the patients' profile at a reduced cost.

CONCLUSION

This study shows that treatment of chronic hepatitis C patients with generic and brand DAAs demonstrate comparable effectiveness, were well tolerated, and were equally

effective in improving biochemical markers of hepatic inflammation. Therefore, generic DAAs could revolutionize the treatment of hepatitis C – providing access to treatment for millions of people infected with HCV. Closer monitoring should be given to HCV patients with genotype 3 and cirrhosis during treatment.

ARTICLE HIGHLIGHTS

Research background

Further studies are needed to better evaluate the long-term efficacy and safety of generic Direct-Acting Antiviral (DAA) agents in previously-treated Hepatitis C Virus (HCV) patients and in patients with cirrhosis and HCV genotype 3.

Research motivation

Generic DAA agents had similar clinical efficacy and safety levels compared for brand DAA agents in the treatment of chronic HCV. The also show similarity in their improvement of hepatic function in these patients.

Research objectives

In general, there was no significant differences in the treatment outcome of patients who received brand *vs* generic DAA agents in terms of their sustained virologic response after 12 wk of treatment. Both generic and brand DAAs showed marked improvement in liver function evidenced by substantial reduction in serum alanine and aspartate aminotransferase levels and total bilirubin levels. Overall, patients who had cirrhosis and HCV genotype 3 were significantly less likely to achieve sustained virologic response after 12 wk of treatment.

Research methods

In this observational study, 149 patients were enrolled and treated with brand DAA agents (brand group), and another 140 patients were enrolled and were treated with generic versions of DAA agents (Generic group) over a two – year period. The primary

outcomes included sustained virologic response after 12 wk of treatment and its determinants.

Research results

This study evaluated the effectiveness and safety of generic compared to brand DAA agents for chronic HCV treatment.

Research conclusions

Data on the clinical efficacy of generic DAA agents for chronic HCV treatment is rare in Bahrain.

Research perspectives

DAA agents has revolutionised the treatment of HCV infection because they are highly effective. However, the brand DAA agents are very expensive and unaffordable to many patients who need them. Generic versions of the DAA agents are being developed to address this challenge but research on whether their effectiveness is comparable to brand DAA agents are limited

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