Research Article

# Generic Sofosbuvir-Declatasvir for Hepatitis C patients in Qatar: A Real-Life Observational Study

**Elkomy NM[1*], Derbala MF[1], Kaabi SA[1] and Chandra P[2]**

[1]Department of Gastroenterology and Hepatology, Hamad Medical Corporation, Doha, 3050, Qatar

[2]Department of Gastroenterology, Medical research center, Hamad Medical Corporation, Doha, 3050, Qatar

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***Corresponding author:**
Nasrein M Elkomy, Department of Gastroenterology and Hepatology, Hamad Medical Corporation, Doha, Qatar, Tel: 0097450663175, E-mail: nasreink@yahoo.ie

## 1. Abstract

**1.1. Background:** The hepatitis C virus (HCV) has been considered one of the most pathogens currently challenging the medical community worldwide. Due to the development of new Direct Acting Anti-viral (DAAs, it is expected that almost all patients with HCV infection will achieve a Sustained Viral Response (SVR) in the near future. However, DAA treatment is expensive and inaccessible for some patients with HCV. Recently, new data has been published indicating that generic treatments are a feasible alternative to DAA treatment for hepatitis C sufferers. In Qatar, there is little data about the safety and efficacy of generic Sofosbuvir/Declatasvir combination.

**1.2. Aim:** To assess the safety and efficacy of generic Sofosbuvir/Declatasvir in the treatment of HCV patients in a real-world setting.

**1.3. Methods:** This retrospective longitudinal Single-Centre cohort study included all HCV patients who received the new generic DAA combination of Sofosbuvir/Declatasvir at the Hamad Medical Corporation between August 2016 and November. Measures were assessed by reviewing clinical and electronic records of patients diagnosed with HCV. The primary efficacy end point was Sustained Viral Response at !2 weeks (SVR12). To assess safety participants were evaluated on an outpatient basis for adverse events.

**1.4. Results:** Efficacy Outcome measure: The overall rate of SVR 12 was 95.5% (95% CI, 89.9 to 98.1).

Safety Outcome measure: Only one patient stopped the assigned drug treatment due to side effects.

**1.5. Conclusion:** In our study, Anti HCV generic therapy Sofosbuvir/Declatasvir is well-tolerated and provides comparably high SVR12 rates in the treatment of HCV infection in Qatar.

**2. Keywords:** HCV; Generic Sofosbuvir/Declatasvir; SVR 12; Qatar

## 3. Core Tip

Generic Sofosbuvir/Declatasvir combination were recently introduced in HMC, Qatar to treat HCV infected patients. The aim of the study is to assess its efficacy and safety in the treatment of HCV patients. 129 patients were included in our study. The overall rate of SVR 12 was 95.5% (95% CI, 89.9 to 98.1) and only one patient stopped the assigned drug treatment due to side effects.

## 4. Introduction

The hepatitis C virus (HCV) has been considered one of the most potential pathogens currently

challenging the medical community worldwide. Since its discovery in 1989, HCV has been recognized as a major cause of chronic liver disease globally [1]. Data reported by the World Health Organization (WHO) estimated that the prevalence of HCV infection is 2.2%, and more than one million new cases were reported annually [2]. Studies have shown worldwide variation in the epidemiology of HCV. It is responsible for infecting over 20 million people in Arab countries, including Egypt, Morocco and Jordan, which have a very high prevalence of the disease [3]. In Qatar, an incidence rate of 6.3 was reported in the general population, and in 2013, the prevalence rate was estimated to be 0.8% among Qatari and 2% among residences. Without immediate and effective intervention, these numbers have been predicted to increase tremendously in the next two decades [4].

Due to the development of new Direct Acting Anti-viral (DAAs), which are safer and have stronger antiviral effects than other drugs currently available, it is expected that almost all patients with HCV infection will achieve A Sustained Viral Response (SVR) in the near future [5]. However, DAA treatment is expensive and inaccessible for some patients with HCV. Therefore, when selecting an anti-HCV therapy, it is necessary to consider not only treatment efficacy but also cost. Recently, new data has been published indicating that generic treatments are a feasible alternative to DAA treatment for hepatitis C sufferers. Generic DAAs have been evaluated recently in Australia. In the REDEMPTION-1 trial, across all genotypes, the SVR rate was 94% after treatment with generic DAAs [6]. Moreover, the difference in cure rate between branded medicines and low-cost generic DAAs was a less than 6%. This indicated that generic DAAs can deliver the same treatment success as branded equivalents at 1/100th of the current cost [7].

## 5. Study Objectives and Hypothesis

In August 2016, Sofosbuvir/Declatasvir, a new generic DAA treatment was introduced at the Hamad Medical Corporation in Qatar. This treatment is available for Qatari and non-Qatari patients at an affordable price. In Qatar, there is little data about the safety and efficacy of this specific generic combination. The aim of this study was to assess the safety and efficacy of Sofosbuvir/Declatasvir in the treatment of HCV patients in a real-world setting.

## 6. Methodology

### 6.1. Study Cohort

This retrospective longitudinal single-center cohort study included all HCV patients who received the new generic DAA combination of Sofosbuvir/Declatasvir at the Hamad Medical Corporation between August 2016 and November 2016. Measures were assessed by reviewing clinical and electronic records of patients diagnosed with HCV. For all patients, the following variables were recorded: age, sex, viral load, viral genotype, nationality, MELD and CHILD scores, duration of treatment, stage of liver fibrosis, previous anti-HCV treatment. Eligible patients were assigned to either 12 or 24 weeks of treatment of Sofosbuvir 400 mg/Declatasvir 60 mg with or without oral ribavirin treatment. Serum HCV RNA levels were recorded at baseline, Week 4, at the end of treatment and 12 weeks after the end of treatment. Fibrosis stage was determined using US elastography or liver biopsy. The METAVIR scoring system was used to assess the extent of fibrosis, grading it from F0–F1 (non-cirrhotic) to F2–F3 (low fibrosis) and F3–F4 (advanced fibrosis).

HCV RNA was assessed by HCV□ RNA extraction using the QIA amp viral RNA and RNeasy mini kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions.

### 6.2. Assessment of Efficacy

Sample size was 129 patients. The primary efficacy end point was Sustained Viral Response at 12 weeks,SVR12, which was defined as undetectable levels of HCV RNA\15 IU/ml at the end of treatment (Week 12) and 12 weeks after the planned end of treatment. Viral relapse was defined as undetectable levels of HCV RNA\15 IU/ml at the end of treatment but detectable levels of HCV RNA\15 IU/ml 12 weeks after the planned end of treatment. Non-responders had detectable levels of HCV RNA\15 IU/ml at the end of treatment. The breakthrough group had undetectable levels of HCV RNA\15 IU/mL during treatment followed by the appearance of HCV RNA\15 IU/ml despite continued treatment.

### 6.3. Assessment of Safety

All patients were assessed regularly in outpatient Department (clinically and laboratory tests) for drugs safety. All adverse events reported by patients were recorded.

## 7. Statistical Analysis

Baseline demographic, clinical, laboratory and biochemical characteristics were described with frequencies, percentages and mean ± SD or median and range as appropriate. The proportion of patients who achieved SVR12 was computed and presented with 95%Confidence Intervals (CIs) calculated using exact binomial methods. Overall survival was estimated using the Kaplan–Meier method, and differences in survival between groups were assessed by the log-rank test. A Cox regression model was used to determine and assess the effect of various covariates and prognostic factors on

Data

| Parameters | Mean or % |
|---|---|
| Age | 47.1 ± 11.7 years |
| Sex: | |
| • Male | 76% |
| • Female | 24% |
| Nationalities: | |
| • Qatari Arab | 15.50% |
| • Non-Qatari Arab | 76.70% |
| • Asian | 7.80% |
| Genotypes: | |
| • Genotype 1 | 19.40% |
| • Genotype 2 | 1.50% |
| • Genotype 3 | 10.90% |
| • Genotype 4 | 68.20% |
| MELD score: | |
| • < 10 | 88% |
| • > 10 | 12% |
| Child Score: | |
| • A | 93% |
| • B or C | 7% |
| Liver fibrosis: | |
| • Non cirrhotic | 66.40% |
| • Low liver fibrosis | 15.60% |
| • Advanced liver fibrosis | 18% |
| Total Bilirubin | 22.7 ± 79.1 µmol/L |
| ALT | 57 ± 49.1 IU/L |
| AST | 48 ± 44.7 IU/L |
| Creatinine | 71 ± 12.4 µmol/L |
| AFP | 11.8 ± 34 ng/mL |
| Median duration of treatment and last follow-up | 16.6 months |

survival time. A two-sided p value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using Statistical Package for the Social Sciences version 22.0 (SPSS Inc. Chicago, IL).

## 8. Results

### 8.1. Patient Characteristics

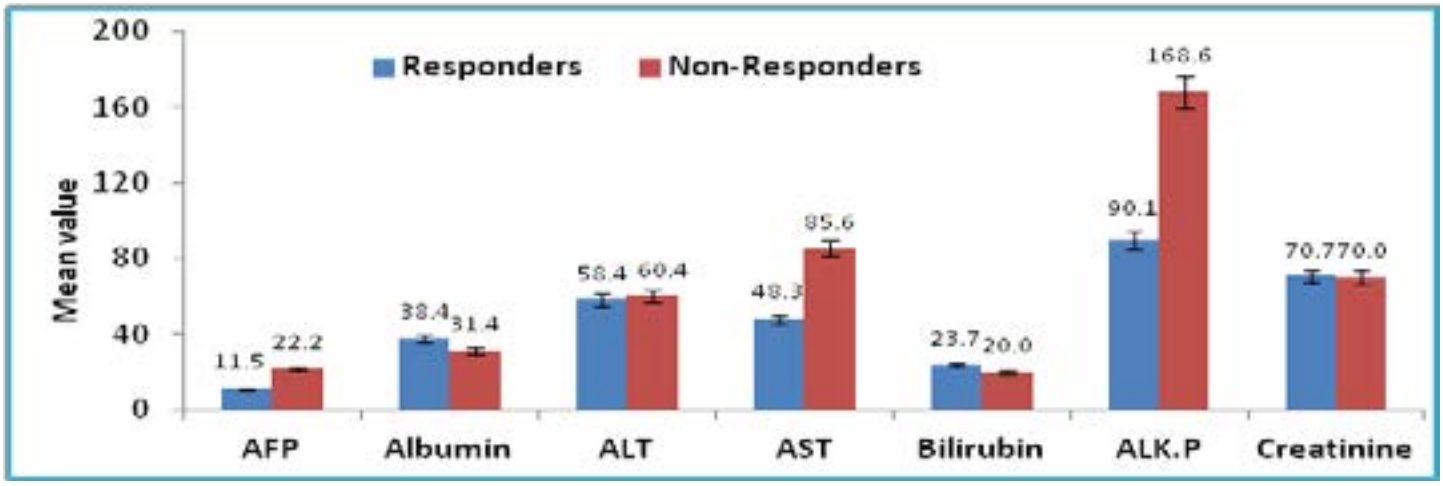
Participants' mean age was 47.1 ± 11.7 years (range 21–82 years), and 76% (98/129) were male. The percentage of Qatari Arab, non-Qatari Arab and Asian patients were 15.5%, 76.7% and 7.8%, respectively. Most patients had genotype 4 (n = 88, 68.2%), followed by genotype 1 (n = 25, 19.4%) and genotype 3 (n = 14, 10.9%). Only two patients had genotype 2. Most patients (n = 93/106, 88%) had a baseline MELD score of ≤ 10, and 93% (120/129) were Childs-Turcotte–Pugh (CTP) class A. Nearly a quarter (18%) had advanced liver fibrosis, 15.6% had low liver fibrosis, and 66.4% had non-cirrhotic liver disease. Patients' mean total bilirubin was 22.7 ± 79.1 µmol/L (median 12.8, range 3.7–908 µmol/L), and the mean ALT was 57 ± 49.1 IU/L (median 39, range 11–313 IU/L). The mean AST 48 ± 44.7 IU/L (median 35, range 13–295 IU/L), while the mean AFP was 11.8 ± 34 ng/mL (range 2–289 ng/mL), and the mean creatinine level was 71 ± 12.4 µmol/L (median 70, range 43–107 µmol/L). The median duration between treatments and the final follow-up was 16.6 months (mean 14.1 ± 5.4 months, range 0–22 months) (Table 1).

### 8.2. Efficacy Outcome Measures

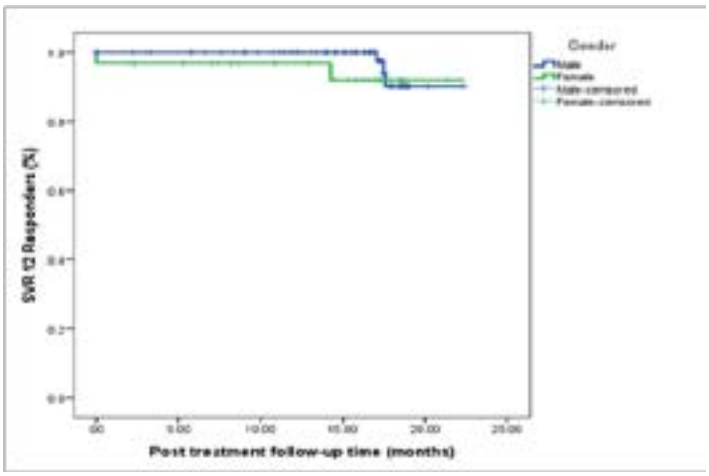
The overall rate of SVR 12 was 95.5% (95% CI, 89.9 to 98.1). In this study, SVR12 was significantly higher in patients treated with Sofosbuvir/Declatasvir than in those treated with ribavirin and Sofosbuvir/Declatasvir (86/88, 97.7% and 20/23, 87%, respectively; p = 0.027). In this study, SVR12 rates were similar in patients with HCV genotype 4 (71/73, 97.3%), 1 (95.5%), 2 (100%) and 3 (85.7%; p = 0.291). However, SVR12 rate was higher in patients with non-cirrhotic liver disease (98.6%) than in those with low (90%) and advanced liver fibrosis (88.9%; p = 0.0.086). Similarly, SVR12 rates were higher in patients with MELD scores of less than 10 than in those with scores of more than 10 (95.1% and 88.9%, respectively). However, this difference was statistically insignificant (p = 0.443). Patients with Child-Pugh A had better SVR12 rates than those with Child-Pugh B (96.2% vs 83.3%, p = 0.140). Higher SVR12 rates were found in patients who had responded to previous IFN treatment than in those who had no response (97.3% vs 91.7%, p = 0.178). This was similar for DAA treatment (96.2% vs 83.3%, p = 0.140). However, these differences were statistically insignificant (p > 0.05). There was no significant association between age, gender and SVR12 rate (p > 0.05). However, SVR12 rate was higher in males than females (96.4% vs 92.9%; p = 0.436). In addition, SVR12 rate was higher among non- Qatari Arab nationals (96.6%) than Qatari Arab (93.8%) and Asian (85.7%) nationals, p = 0.384. Mean albumin was significantly higher among SVR12 responders compared to non-responders (38.43 ± 5.1 vs 31.4 ± 5.4; p = 0.010). In contrast, mean AFP and ALK-P were significantly lower in SVR12 responders compared to non-responders (p < 0.05). Bilirubin was higher among responders than non-responders, whereas AST and ALT were lower among responders compared to non-responders. However, these differences were statistically insignificant (p > 0.05; (Figure 1)).

### 8.3. Kaplan Meir Survival Curve and Cox Regression

Males were more likely to be SVR12 responders than females (hazard ratio 0.52; 95% CI 0.09, 3.11), but this difference was statistically insignificant (p = 0.472; (Figure 2)). Qatari Arabs (hazard ratio 0.43; 95% CI 0.03, 6.97; p = 0.551) and non-Qatari Arabs (hazard ratio 0.26; 95% CI 0.02, 2.51; p = 0.245) were more likely to be




**Figures 1:**

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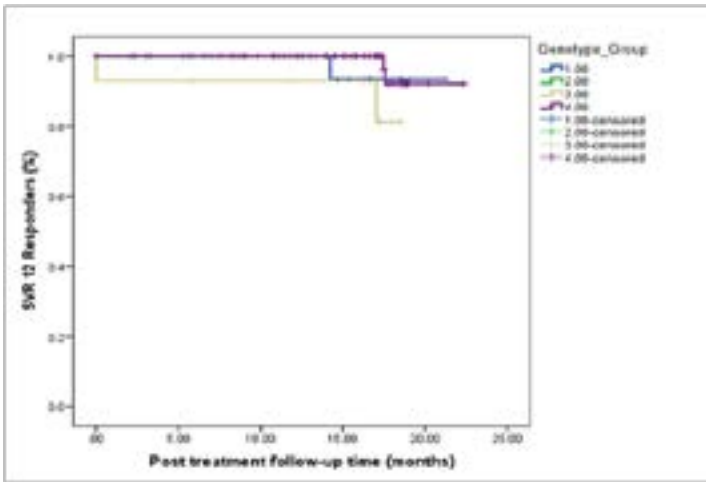


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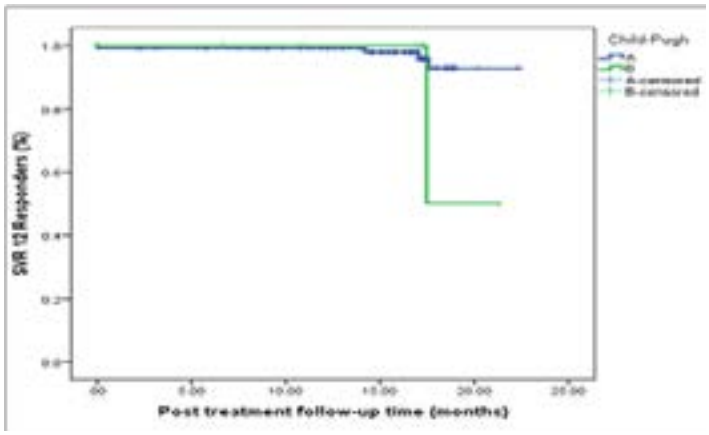


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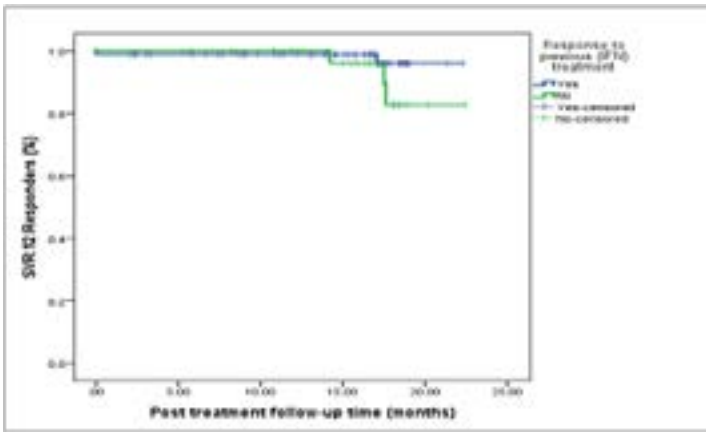
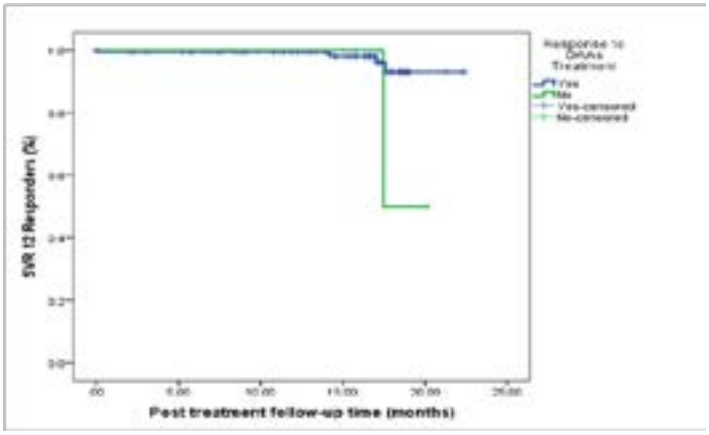



**Figures 5:**

SVR12 responders than Asian patients; however, this difference was statistically insignificant ($p > 0.05$). Covariates age and viral load had no statistically significant association with SVR12 response.

The percentage of SVR12 responders was lower among patients with genotype 1 (hazard ratio 1.91; 95% CI 0.17, 21.18) and genotype 3 (hazard ratio 5.62; 95% CI 0.79, 40.07) compared to patients with genotype 4; however, this difference was statistically insignificant ($p > 0.05$; (Figure 3)). Patients with Child-Pugh A were more likely to be SVR12 responders than those with Child-Pugh B (hazard ratio 0.24; 95% CI 0.03, 2.10); however, this difference was statistically insignificant ($p = 0.207$; (Figure 4)).

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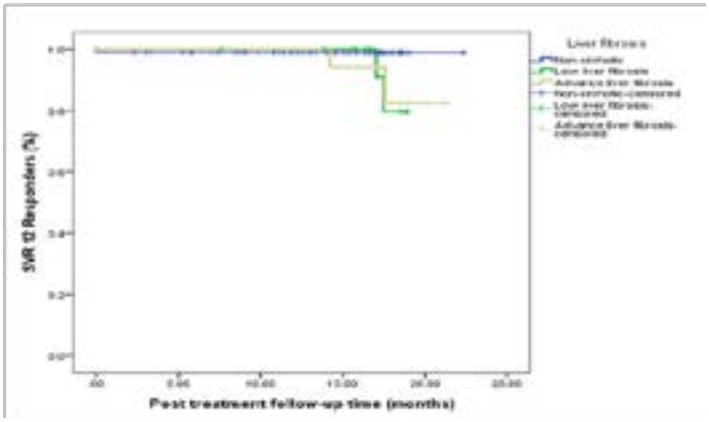


**Figures 7:**

The percentage of SVR12 responders was higher among patients who responded to previous IFN treatment compared to patients who had no response (hazard ratio 0.35; 95% CI 0.06, 2.09); however, this difference was statistically insignificant (p = 0.248; (Figure 5)). Similarly, the percentage of SVR12 responders was higher among patients who had responded to previous DAA treatment than those with no response (hazard ratio 0.21; 95% CI 0.02, 1.9); however, this difference was statistically insignificant (p = 0.158; (Figure 6)). Though statistically insignificant (p > 0.05), patients with non-cirrhotic liver disease had better SVR12 rates than those with advanced liver fibrosis (hazard ratio 0.18; 95% CI 0.02, 2.03; p = 0.166; (Figure 7)).

### 8.4. Safety profile

Only one patient stopped the assigned drug treatment due to side effects.

## 9. Discussion

Sofosbuvir /Declatasvir combination treatment is an appealing choice for the treatment of HCV infection. Compared to other HCV DAA treatments, it is a potent regimen with pan-genotypic activity, has a relatively lower pill burden, fewer drug-drug interactions and can be applied to patients with decompensated cirrhosis.

Our study showed that the overall SVR12 rate in patients receiving generic Sofosbuvir/Declatasvir was excellent alone (95.5%) or with ribavirin (87%). This was comparable to response rates in patients receiving brand-name agents. The per-protocol SVR12 rate was 98% and 82.2% per intention-to-treat analysis. Previous research including 343 patients who received different regimens based on generic or branded Sofosbuvir showed that branded anti-HCV medications outperformed generics [8]. Subsequently, two Egyptian studies that recruited larger numbers of patients (N = 107,213 and N = 18,378) and treated them with generic SOF□ DCV with or without RBV reported SVR12 rates of 98.4% and 95.1%, respectively, which was similar to our study [9,10]. Regarding safety, more than 99% of our patients completed the scheduled treatment without any reported side effects. In total, one patient stopped the assigned treatment after 2 weeks, as she developed Steven-Johnson Syndrome, from which she recovered after receiving methotrexate. In a recent study of generic SOF□ DCV, the most common adverse events recorded by patients were fatigue, headache, nausea, asthenia and gastrointestinal troubles, and none of them discontinued treatment due to severe adverse events [11].

Although SVR12 response was similar across the four HCV genotype groups, nearly 70% of patients in our study were infected with HCV genotype 4. Therefore, our findings may not reflect the response rate of patients infected with other genotypes. Moreover, a large Egyptian study of generic SOF□ DCV showed that SVR12 response was unaffected by liver cirrhosis and previous treatment with interferon or DAAS [12]. In contrast, an Australian study of branded SOF□ DCV showed that SVR12 response rates in advanced liver disease were lower than in compensated disease, though the treatment improved MELD and Child-Pugh scores in most patients [13].

## 10. Study Limitations

Although all patients were treated with the same generic SOF□ DCV in the same center, their response was not compared to patients treated with branded drugs, and the patient number was relatively small. Moreover, a relatively significant number of them did not attend follow-up appointments during their treatment course, which affected the final analysis. Despite this, our study showed that generic SOF□ DCV treatment was safe and effective while being available at a fraction of the cost of branded treatments. In addition, generic DAAs are currently available in many developing countries, especially

in Egypt and Pakistan, which has transformed the HCV epidemics in those areas. In our study, we showed that generics are as highly effective as branded DAAs, and the wide availability of generic DAAs is crucial for achieving WHO HCV elimination targets.

## 11. Conclusion

Our study showed that generic therapy is well-tolerated and provides comparably high SVR12 rates in the treatment of HCV infection in Qatar. Therefore, with generic SOF-DCV treatment, HCV medications were become accessible and affordable at fraction priced of counterpart brand HCV medications for most population in Qatar. Moreover, non-adherence to recommended follow-up visits is a major barrier for completing treatment. Therefore, patient education is crucial to improve patients' compliance and ultimately treatment outcomes.

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