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Original Research Article

Safety and efficacy of the generic products of sofosbuvir and daclatasvir in treatment of HCV genotype 4 Egyptian patients

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Abstract

Hepatitis C virus (HCV) is a major medical problem in Egypt, with genotype 4 the prevalent genotype. The introduction of the new oral directly acting antiviral drugs (DAAs) in the national treatment program in Egypt since late 2014 was a great achievement. Patients with genotype 4 maybe treated with daily combination of Sofosbuvir/Daclatasvir with or without ribavirin for 12 or 24 weeks. However, little data is available regarding the safety and efficacy of generic products of those DAAs used so the aim of this study was to assess the safety and efficacy of the generic products of sofosbuvir and daclatasvir in treatment of HCV genotype 4 Egyptian patients. Where 139 Egyptian patients chronically infected with HCV genotype 4 were enrolled. They received the generic products of sofosbuvir (Sofolanork, Mash premiere) 400 mg plus daclatasvir (Daklanork, Mash premiere) 60 mg with or without ribavirin for 12 or 24 weeks in Kasr Al Ainy Viral Hepatitis Center and Ain Shams Hospital. Most of the studied patients were males (61.15%), 30 were cirrhotics, 18 patients had a history of previous sofosbuvir based treatment. Treatment was by sofosbuvir plus daclatasvir for 12 weeks in 75 patients and for 24 weeks in 7 patients. Ribavirin was added in 39 patients for 12 weeks and in 18 patients who had previous history of failure to sofosbuvir based therapy for 24 weeks. All patients had SVR12 (100%). A significant improvement occurred in ALT, AST, AFP and Albumin. Moreover, a slight regression in the fibrosis markers was shown through reduction of Fib-4 index. The findings of this study showed that the generic products of the relatively more expensive brand DAAs have almost the same efficacy and safety allowing for the mass treatment of Egyptian patients chronically infected with HCV making the dream of HCV elimination in Egypt achievable.

Keywords: Daclatasvir, Generic, Genotype 4, HCV, Sofosbuvir

INTRODUCTION

Hepatitis C is a worldwide problem with a prevalence estimated to be 3 % according to the World Health Organization (WHO). Egypt has the highest prevalence of HCV which was estimated to be 7.3% with predominance of genotype 4 (Waked et al., 2014).

Until 2011, the treatment of choice for chronic HCV patients was the combination of pegylated interferon (PegIFN) and ribavirin for 24 or 48 weeks (EASL Clinical Practice Guidelines 2011). Using this combination, patients infected with HCV genotype 4 had intermediate SVR rates (50-60%) (Antaki et al., 2010).

Later on, new drugs named the directly acting antiviral drugs (DAAs) became widely available showing better tolerability and efficacy. Those DAAs affect HCV at

specific steps within its life cycle (Poordad et al., 2012).

There are multiple available interferon-free regimens used in treatment of HCV genotype 4 infections (Abdel-Razek et al., 2015). One of those regimens include the use of NS5B polymerase inhibitor Sofosbuvir along with the NS5A inhibitor Daclatasvir.

Sofosbuvir was approved by the FDA in December 2013 and it is considred the backbone of all DAAs used since it is pangenotypic. It is always used along with another DAA sometimes also in addition to Ribavirin for different treatment durations (12-24 weeks) (Hassanein et al., 2012).

Daclatasvir is an NS5A inhibitor that is still not FDA approved for genotype 4. Nevertheless, given the antiviral effectiveness of both sofosbuvir and daclatasvir against genotype 4 in vitro, it is likely that it can be effective for use in HCV genotypes 4 patients (EASL Clinical Practice Guidelines 2015).

Different clinical trials were done using both sofosbuvir and daclatasvir in HCV genotype 4 patients such as the ALLY-1 trial and the French ANRS CO22 HEPATHER where SVR12 rates ranged 75% and 100% respectively (Poordad et al., 2016) (Victor et al., 2015).

Little data is available regarding the safety and efficacy of generic products of those DAAs used. This was our area of interest since having drugs at a cost convenient to citizens of a developing country like Egypt is regarded as the magical solution for elimination of HCV.

The aim of our study was to assess the safety and efficacy of the generic products of sofosbuvir and daclatasvir in treatment of HCV genotype 4 Egyptian patients.

PATIENTS AND METHODS

One hundred and thirty nine Egyptian patients chronically infected with HCV genotype 4 were enrolled, they received the generic products of sofosbuvir (Sofolanork, Mash premiere) 400 mg plus daclatasvir (Daklanork, Mash premiere) 60 mg with or without ribavirin for 12 or 24 weeks in Kasr Al Ainy Viral Hepatitis Center and Ain Shams Hospital. The work was carried out in accordance with Helsinki declaration, and following the guidelines of the ethical approval committees in Egypt. Also, this study was approved by the institutional review board of faculty of medicine, Cairo university number N-38-2016.

Patients were included according to the approved treatment recommendations by EASL 2015 (EASL Clinical Practice Guidelines 2015) All patients had HCV RNA positivity, their age ranged between 18-70, they were either naïve to HCV treatment or had a previous treatment experience whether interferon based or sofosbuvir based and no restrictions were put on either BMI or fibrosis stage.

Patients who were excluded were those who had hypersensitivity to the drugs used, pregnant or breast feeding, poorly controlled diabetics (HbA1C >8), patients with decompensated liver disease such as those with Ascites, history of Ascites, history of hepatic encephalopathy and hepatocellular carcinoma (except 4 weeks after intervention aiming at cure with no evidence of activity by dynamic imaging). Also, patients with renal disease in the form of serum creatinine >2.5 mg/dl or eGFR <30 ml/min. as well as patients with INR >1.7, serum albumin <2.8 g/dl, total bilirubin >3 mg/dl or platelet count <50,000/mm^3 were excluded (Guerra et al., 2012).

All patients were subjected to full history taking, including history of other causes of chronic liver disease. They were investigated using the following laboratory investigations: Liver biochemical profile including total and direct Bilirubin, Aspartate transaminase (AST), Alanine transaminase (ALT), Albumin (ALB), International normalized ratio (INR). Also complete blood count (CBC), HBsAg, HCV PCR quantitative, serum Creatinine, Alpha feto protein (AFP), and Fasting blood sugar (FBS), HbA1c if diabetic. Pregnancy test was done for female patients in childbearing period. Fib-4 index was calculated to all patients using the formula: age (years) X AST [U/L] / (platelets [10^9/L] X (ALT [U/L])$^{1/2}$ (Sterling et al., 2006).

Abdominal ultrasonography was done to each patient to detect echopattern of the liver (ultrasonographic features of cirrhosis), presence of signs of portal hypertension, and to exclude hepatocellular carcinoma. Patients were then categorized into easy and difficultto-treat groups to guide treatment plan nationwide, where easy to treat group included those who were noncirrhotic (by clinical & ultrasonographic examination), Fib-4 <3.25, albumin >3.5, total serum Bilirubin <1.2 mg/dL, INR<1.2 and Platelet count >=150 000 mm3, while difficult-to-treat group included those who were cirrhotic (by clinical & ultrasonographic examination), Fib-4 >3.25, albumin ≤3.5, total serum Bilirubin >1.2 mg/dL, INR >1.2, and platelet count <150 000 mm3 (Guerra et al., 2012).

Treatment regimen

All patients received Sofosbuvir (Sofolanork, Mash premiere) 400 mg plus Daclatasvir (Daklanork, Mash premiere) 60 mg with or without Ribavirin for 12 or 24 weeks according to EASL guidelines (EASL Clinical Practice Guidelines 2015). Ribavirin dosage was initiated at 600mg per day and gradually titrated upwards after exclusion of its significant side effects to reach either 1000mg (in patients <75 kg) or 1200mg (in patients >75kg). The end point was a sustained virological response at 12 (SVR12) weeks post treatment.

The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions were

Table 1. Demographic and laboratory criteria in all patients

	Mean (SD)
Age	51.34 (12.2)
HCV_RNA	1,417,100 (3044568)
HG g/dl	13.75 (1.84)
WBCs	6.38 (2.14)
ANCs	3.37 (1.34)
Platelets	201.12 (77.16)
PC	84.42 (17.27)
INR	1.19 (0.54)
Bilirubin	0.83 (0.64)
Albumin	3.87 (0.57)
ALT fold elevation	1.28 (0.83)
AST fold elevation	1.31 (0.74)
Creatinine	0.87 (0.27)
FBS	107.83 (46.25)
HBA1C	6.46 (1.67)
AFP	8.46 (10.36)
Fib_4	2.53 (2.45)
	Number (%)
Gender	
Male	85 (61.15)
Female	54 (38.85)
Cirrhotic	30 (40.54)
Treatment experienced (sofosbuvir based) 18	(12.95)
Hard to treat	64 (44.89)

revised prior to initiation of therapy and whenever possible, an interacting co-medication stopped for the duration of HCV treatment or switched to an alternative drug with less interaction potentials.

Monitoring of treatment safety

Patients were followed up every 4 weeks while on treatment and for 12 weeks post treatment (to test for SVR12) where history taking was done to document and manage any adverse event, and patients were asked specifically about the commonly reported adverse effects as headache, nausea, insomnia, fatigue, rash, dyspnea, etc.

Monitoring of treatment efficacy

Quantitative HCV-PCR was measured using the COBAS Ampliprep/COBAS TaqMan (CAP/CTM) assay with a lower limit of detection of 15 IU prior to treatment, and 12 weeks after treatment where virologic response was considered when HCV RNA is less than lower limit of detection week 12 post treatment (SVR12) while treatment failure was defined as confirmed HCV RNA above LLOQ 12 weeks post treatment. Treatment discontinuation due to adverse events was considered treatment failure.

Statistical analysis

Data analysis was done using Statistics/Data Analysis (STATA) version 13.1 software. Continuous variables were tested for normality by the Shapiro-Wilk normality test. Values are presented as mean ± standard deviation, or in the case of non-normally distributed data as median and inter-quartile range.

Normally distributed paired samples were analyzed using the paired t-test. Non-normally distributed paired samples were analyzed using the Wilcoxon signed-rank test.

RESULTS

This study included 139 Egyptian patients with HCV Genotype 4 infection. Most of patients were males (61.15%), 30 were cirrhotics by laboratory and ultrasonographic evidence as well as a Fib-4 index>3.25, Sofosbuvir based treatment experience was present in 18 cases who were then treated using Sofosbuvir Plus Daclatasvir Plus Ribavirin for 24 weeks (Table 1). According to the previously mentioned classification, 75 patients were considered easy to treat and so they were treated using sofosbuvir plus daclatasvir for 12 weeks, 7 cirrhotic patients who were intolerant to ribavirin received sofosbuvir plus daclatasvir for 24 weeks while in the other 57 patients who were considered hard to treat,

Table 2. Type of treatment and duration

	Number (%)		Duration
SOF/DAC	82 (58.99%)	75	12 weeks
		7	24 weeks
SOF/DAC/RIB	57 (41.01%)	39	12 weeks
		18	24 weeks

Table 3. Treatment response

	Number	Percentage
Responders	139	100%
Non responders	0	0%
SVR12	139	100%

Table 4. Changes in laboratory values and Fib-4 at SVR-12

	Baseline	SVR-12	P value
INR Median (IQR)	1.09 (1-1.2)	1.1 (1-1.18)	0.3
Albumin Mean (SD)	3.85 (0.58)	4.04 (0.59)	0.01
AST fold elevation Median (IQR)	1.11 (0.77-1.65)	0.68 (0.5-0.88)	<0.001
ALT fold elevation Median (IQR)	0.93 (0.73- 1.66)	0.52 (0.37-0.77)	<0.001
AFP Median (IQR)	6.46 (4-10.5)	1 (0.8-4)	<0.001
Fib-4 Median (IQR)	1.78 (1.09-2.64)	1.60 (0.95-2.62)	0.6

ribavirin was added and treatment duration was either 12 or 24 weeks according to previous treatment experience (Table 2). All of the studied patients had SVR12 (100%) (Table3)

Regarding the effect on liver biochemical profile, results showed a significant improvement in ALT and AST levels, AFP and Albumin levels. However, a non significant improvement occurred in Fib-4 index showing slight fibrosis regression (Table 4). Eleven (7.9%) patients who received ribavirin required dose reduction during treatment while only 2 of them necessitated stopping it later on after development of hemolytic anaemia. The cut off used was Hb 9.5 gm/dl and 8.5 gm/dl for dose reduction and stoppage respectively.

Minor side effects were observed in the form of fatigue (30%), headache (24%), nausea (15%) and insomnia (11%).

DISCUSSION

The introduction of the new oral directly acting antiviral drugs at a very low cost compared to their original price in the national treatment program in Egypt since late 2014 was a great achievement towards elimination of HCV. However, being a country with a low gross national income per capita, the majority of patients had difficulties in obtaining treatment. Emerging needs for the development of drugs at a lower price led to the introduction of generic products of sofosbuvir and daclatasvir since December 2015.

The findings of this study showed that the drugs used were very effective where SVR12 rate was 100%. These results were matching with the French clinical trial ANRS CO22 HEPATHER which evaluated the use of the brand product of both sofosbuvir plus daclatasvir in 47 patients chronically infected with HCV genotype 4; most of whom were cirrhotics, 36 patients received treatment for 12 weeks while the remaining 11 patients received treatment for 24 weeks and ribavirin was added in only 15 patients. SVR12 rate was 100% in this clinical trial (Victor et al., 2015).

Results obtained in this study were also superior to the ALLY-1 trial which is a phase III trial that evaluated the use of daclatasvir, sofosbuvir, and ribavirin in post chronic HCV cirrhotic patients and patients post liver transplantation. In this trial, only 4 patients had HCV genotype 4. They were all cirrhotics and none was a post transplant subject. SVR12 rate was shown in 3 patients achieving SVR12 rate of 75 % (Poordad et al., 2016).

However, this comparison might not achieve equity due to the great difference in sample size as well as the type of patients enrolled since all patients in the ALLY-1 trial were cirrhotics which was not the case in this study.

Regarding side effects of the drugs used, this study showed nearly the same incidence known for the brand drugs. However, less incidence of hemolytic anemia with ribavirin was observed (7.9%) compared to an estimated incidence of 10%, which might be attributable to the low dose used initially with a step wise titration upwards.

The main limitation in this study was the relatively low number of patients enrolled along with the absence of treatment failure hindering the accurate assessment for minor drawbacks in the drugs used.

CONCLUSION

The introduction of generic products of the relatively more expensive brand DAAs with almost the same efficacy and safety will allow the mass treatment of Egyptian patients chronically infected with HCV making the dream of HCV elimination in Egypt achievable.

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