

A Real Life Study on Treatment of Egyptian Patients with HCV Genotype IV with Simeprevir and Sofosbuvir

A. Hanno¹, D. Elwazzan¹, M. Ibrahim¹, R. Hafez²

¹Tropical Medicine Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

²Chemical Pathology Department, Medical Research Institute, Alexandria University, Alexandria, Egypt

Email: marwaibrahim90@yahoo.com

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Abstract

Background and Aims: Treatment with a combination of the nucleotide polymerase inhibitor sofosbuvir and NS3A (non-structural protein 3A) protease inhibitor simeprevir resulted in high rates of sustained virological response in chronic hepatitis C Genotype 4. **Methods:** We conducted a real life study on Egyptian patients coming to tropical medicine department clinic at El Mery main university hospital from February 2015 to February 2016 for treatment naïve and treatment experienced patients with chronic HCV genotype 4, including cirrhotics and non cirrhotics. Naïve (cirrhotics and non cirrhotics) and relapsers (non cirrhotics) received nucleotide polymerase inhibitor sofosbuvir and NS3A inhibitor simeprevir once daily for 12 weeks and 24 weeks for relapsers cirrhotic patients. The primary end point was a sustained virologic response at 12 weeks after end of treatment. An informed consent was obtained from each patient at the beginning of the study (Real life study: a study on Egyptian patients when the drug was available in the market). **Results:** 30 naïve patients with HCV genotype 4 and 20 relapsers (10 non cirrhotic and 10 cirrhotic patients) were enrolled. **Patient inclusion criteria:** Naïve patients are those who tested positive for HCV RNA by PCR and had no experience to HCV treatment; Relapsers are those who tested positive for HCV RNA by PCR and had a previous treatment for HCV. Cirrhosis was diagnosed on ultrasound basis. Mean age was 53.57 ± 10.682 years old in naïve patients and 48.30 ± 5.100 years old in relapsers. Median baseline HCV RNA was 360,069 IU/mL for naïve patients and 1,245,000 IU/mL for relapsers; using Fib4 20% of naïve patients were F3-F4, while 40% of relapsers were F3-F4. Degree of fibrosis was confirmed by fibrotest in relapsers. Upon treatment of patients with sofosbuvir and semiprevir once daily for 12 weeks and 24 weeks only to cirrhotic relapsers, end of treatment PCR was negative in 100% in all groups including cirrhotics and non cirrhotics. Primary end point (SVR 12) was achieved in 100% of all patients. Second end point (SVR 24) was achieved in 96.6% of naïve patients; SVR 24 for non-cirrhotic relapsers was achieved in 100% of patients and in 90% of cirrhotic relapsers. One patient had transient total bilirubin elevations without in-

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creased ALT (alanine aminotransferase) or AST (aspartate aminotransferase). One patient developed cutaneous rash. **Conclusion: Once daily sofosbuvir and simeprevir for 12 weeks provided high rate of sustained virological response among treatment naïve and treatment experienced patients with HCV genotype IV.**

Keywords

Egyptians, HCV, Genotype IV, Simeprevir, Sofobuvir

1. Introduction

In Egypt, hepatitis C virus (HCV) infection is considered as a public health problem as it has the highest prevalence rate in the world, which is estimated at 14.7% nationally and it is higher among those over age 50 reaching more than 35% for anti-HCV antibodies [1] [2]. More than 90% of HCV infection in Egypt is due to genotype 4 which is the most common genotype in the Middle East and Africa [3]. HCV is the most common cause of chronic hepatitis which progresses in most of the patients into cirrhosis, portal hypertension, hepatocellular failure and hepatocellular carcinoma, thus HCV is an important cause of liver transplantation [4] [5]. The first drug used for treatment of patients with chronic HCV genotype 4 was conventional interferon (IFN)-alpha monotherapy that showed poor rates of sustained viral response (SVR) [6], then ribavirin was added which led to slight improvement of the results [7].

A dramatic amelioration of SVR rates were obtained when Pegylated IFN (PEG-IFN) and ribavirin (RBV) combination therapy was used to treat HCV genotype 4 infected patients with SVR exceeded 60% [8]. However, PEG-IFN has many side effects including fever, bone aches, headache, fatigue, neuropsychiatric symptoms and bone marrow suppression in addition to ribavirin side effects as haemolytic anemia, dyspnea and cutaneous complications [9] [10]. Recently, direct acting antiviral drugs (DAAs) were developed for treatment of HCV infection. These drugs target the HCV-encoded proteins that are vital to the replication of the virus, these drugs have fewer side effects, shorter duration of treatment and some of them improve the SVR up to 100% [11].

Telaprevir and boceprevir were the first DAAs used for treatment of HCV in 2011, each administered in combination with PEG-IFN/RBV (pegylated interferon/ribavirin); they acted by inhibiting HCV-encoded NS3/4A protease, which was an essential enzyme for viral replication [12]. These drugs demonstrated higher SVR rates in treatment-naïve and treatment-experienced populations than PEG-IFN/RBV alone; moreover they shortened the duration of treatment from 48 to 24 - 28 weeks [13] [14]. However, the co-administration of telaprevir or boceprevir with PEG-IFN/RBV increased the severity and the frequency of side effects such as anemia and rash, in addition, SVR rates with TPV or boceprevir remain low in some patients, such as null responders to previous PEG-IFN/RBV therapy and those with advanced liver disease, moreover, they showed activity against HCV genotype 1 only [15] [16].

Simeprevir (SMV) was one of the DAAs that were approved by FDA in November 2013. It inhibits the HCV NS3/4A (non-structural 3/4A) protease, which is essential for viral replication. SMV is effective against HCV genotypes 1, 2, 4, 5 or 6, but has no activity in genotype 3 infections [17]. SMV can be added to sofosbuvir, NS5B (non-structural protein 5B) polymerase inhibitor, to treat HCV-4 patients as an IFN-free regimen with or without ribavirin for either 12 or 24 weeks. This combination has proved its efficacy in naïve, treatment experienced, non-cirrhotic and cirrhotic patients [18]. SMV is considered as a safe and well tolerated drug, few side effects have been reported including photosensitivity, nausea, muscle pain, and indigestion [19].

2. Patients and Methods

1) Study patients

30 naïve patients with HCV genotype 4 and 20 relapsers (10 non cirrhotic and 10 cirrhotic patients) were enrolled.

2) Patient inclusion criteria

Naïve patients: patients who tested positive for HCV RNA by PCR and had no experience to HCV treatment.

3) Relapsers

Relapsers are patients who tested positive for HCV RNA by PCR and had a previous treatment for HCV. Cirrhosis was diagnosed on ultrasound basis.

4) Study design

We conducted a study on treatment naïve and treatment experienced patients with chronic HCV genotype 4, including cirrhotics and non cirrhotics. Naïve (cirrhotics and non cirrhotics) and relapsers non cirrhotics received nucleotide polymerase inhibitor sofosbuvir and NS3A inhibitor simeprevir once daily for 12 weeks and 24 weeks for relapser cirrhotic patients. Laboratory investigations including complete blood count, AST (aspartate amino transferase), ALT (alanine amino transferase), serum urea, serum creatinine, total serum bilirubin, direct serum bilirubin, prothrombin activity, serum albumin and serum alfafetoprotien were done before treatment, at week 2, week 4, week 12 on treatment for naïve patients and at week 24 for relapsers. Quantitative PCR for HCV was done before treatment and one month on treatment. End of treatment response was determined by Quantitative PCR for HCV at end of treatment for each of the study groups. The primary end point was a sustained virological response at 12 weeks after end of treatment determined by quantitative PCR for HCV. Second end point was a sustained virological response at 24 weeks after end of treatment also determined by quantitative PCR for HCV.

5) Statistical analyses

The results obtained were statistically analyzed using SPSS program. A normality test was done. Data were then presented in tables and figures and the different parameters were correlated with each other. An internal comparison between each laboratory investigations before treatment (data 1), one month on treatment (data 2) and 3 month on treatment (data 3) was done using Wilcoxon Signed Ranked test to determine whether improvement or deterioration in laboratory investigations has occurred.

3. Results

1) Baseline patient demographics and characteristics

30 naïve patients with HCV genotype 4 and 20 relapsers (10 non cirrhotic and 10 cirrhotic patients) were enrolled. 80% of naïve patients were males, while 70% of relapsers were male (**Table 1**). Mean age was 53.57 ± 10.682 years in naïve patients and 48.30 ± 5.100 years in relapsers. Median baseline HCV RNA was 360,069 IU/mL for naïve patients and 1,245,000 IU/mL for relapsers; using Fib4 20% of naïve patients were F3-F4, while 40% of relapsers were F3-F4 (**Table 1**). Degree of fibrosis was confirmed by fibrotest in relapsers.

2) Efficacy outcomes

All 50 patients completed 12 weeks of treatment with SIM/SOF (simeprevir/sofosbuvir), Rapid serum HCV RNA decline was observed with 100 % of patients (50/50) below detection limits at treatment week 4. End of treatment PCR (polymerase chain reaction) was negative in 100% in all groups including cirrhotics and non cirrhotics (**Table 2**). 100% of patients in all groups achieved SVR12 (primary end point), Second end point (SVR 24) was achieved in 96.6% of naïve patients; SVR 24 for cirrhotic relapsers is 90% (**Table 2**). One patient had transient total bilirubin elevations without increased ALT or AST. One patient developed cutaneous rash.

3) Improvement in laboratory assessments

Liver enzymes mean values rapidly declined by week 2 of treatment. Aminotransferases median AST values before treatment were 35 IU while at week 2 AST median values were 26.5 IU for naïve patients, while for relapsers median AST values before treatment were 43 IU while at week 2 AST median values were 33.5 IU for naïve patients. Median ALT values before treatment were 41.5 IU while at week 2 ALT median values were 24

Table 1. Patient's demographic and clinical data.

	Naïve	Relapsers
Mean Age	53.57 ± 10.682 years	48.30 ± 5.100 years
Sex	80% males	70% males
Median Baseline PCR	360,069 IU/mL	1,245,000 IU/mL
Fibrosis	F0-F2 (80%) F3-F4 (20%)	F0-F2 (60%) F3-F4 (40%)
Child Scoring	Child A: 86.6 Child B: 13.3	Child A: 70% Child B: 30%

IU for naïve patients, while for relapsers median ALT values before treatment were 49 IU while at week 2 ALT median values were 34.5 IU for naïve patients. Improvement of AST values from before treatment to week 12 after treatment, were observed for naïve patients (−3.062), also this was observed for relapsers (−2.66). This is in consistency with ALT values from before treatment to week 12 after treatment, were also improved for naïve patients (−3.180), also this was observed for relapsers (−2.66) (**Table 3**).

Mean improvements in laboratory values at post-treatment week 12 were also observed for albumin (+0.13 g/dl) for naïve patients and (+0.11 g/dl) for relapsers, alpha fetoprotein (−10.0 ng/ml) for naïve patients and (−9.0 ng/ml) for relapsers, total bilirubin (−1.22 mg/dl) for naïve patients and (−1.604 mg/dl) for relapsers.

4. Discussion

Treatment of HCV is considered very important issue as it reduces the risk of decompensated liver cirrhosis and hepatocellular carcinoma hence reducing the morbidity and mortality [20]-[22]. In Egypt, PEG-IFN and RBV were introduced by ministry of health through a national treatment program for patients with chronic HCV infection since 2006, SVR rates ranged from 54% to 59% [23] [24]. The recent approval of DAAs for treatment of HCV-4 promises significant improvement in the outcome of therapy.

In this study, treatment with Simeprevir 150 mg/Sofosbuvir 400 mg once daily without RBV for 12 weeks and 24 weeks for treatment experienced cirrhotics, resulted in a SVR12 rate of 100% in HCV-4 infected naïve, both cirrhotics and non-cirrhotics, moreover, SVR24 was 96.6% in the same group. In treatment experienced patients SVR12 was 100% including cirrhotics and non-cirrhotics, while SVR24 was 100% in non-cirrhotics and 90% in cirrhotics.

These results were in agreement with OSIRIS trial findings which was done on Egyptian HCV-4 infected patients both treatment naïve and treatment experienced, with and without liver cirrhosis. SVR12 was 100% in patients treated for 12 weeks, and 75% in patients treated for 8 weeks with Sim/Sof [25]. Furthermore, the current

Table 2. Follow up PCR of patients involved.

End of treatment	Naïve	Relapsers	
	100% negative	100% negative	
SVR 12	100% (cirrhotics and non cirrhotics)	100% non cirrhotics	100% for cirrhotics
SVR 24	96.6% (cirrhotics and non cirrhotics)	100% non cirrhotics	90% for cirrhotics

End of treatment: 100% of patients achieved a negative PCR for HCV at the end of treatment which was at 12 weeks for all groups and at 24 weeks for cirrhotic relapsers. SVR 12: a sustained negative PCR done at 12 weeks after the end of treatment. SVR 24: a sustained negative PCR done at 24 weeks after the end of treatment.

Table 3. differences in ALT and AST before and after treatment.

Patient	Marker	Z Value	P value
Naïve	AST3-AST1	−3.062	0.002
Naïve	AST2-AST1	−2.546	0.011
Relapsers	AST3-AST2	−2.666	0.008
Relapsers	AST2-AST1	−2.499	0.012
Naïve	ALT3-ALT1	−3.180	0.001
Naïve	ALT2-ALT1	−2.701	0.007
Relapsers	ALT3-ALT2	−2.666	0.008
Relapsers	ALT2-ALT1	−2.397	0.017

AST 1: AST value measured before treatment. ALT 1: ALT value measured before treatment. AST 2: AST value measured one month on treatment. ALT 2: ALT value measured one month on treatment. AST 3: AST value measured three month on treatment. ALT 3: ALT value measured three month on treatment.

results were consistent with the SVR12 rates achieved in patients from COSMOS trial, including non-cirrhotics patients with HCV-1b infection and previous null responders to IFN/RBV treatment who received Sim/Sof for 12 weeks (93%). In the same trial, cirrhotic (including naïve and treatment experienced) patients achieved SVR12 of 93% [26].

Another trial, the OPTMIST II, evaluating Sim/Sof without RBV for 12 weeks in patients with cirrhosis, 26 of 31 (84%) HCV-1b infected patients achieved SVR [27]. The results of this trial can be compared to data available for other IFN-free DAA regimens used for treatment of HCV-4. The regimen of ombitasvir (NS5A inhibitor) plus paritaprevir (NS3/4A) plus ritonavir with or without ribavirin achieved, in treatment naïve, SVR12 rates of 100% in the ribavirin-containing regimen and 90.9% in the ribavirin-free regimen, all treatment experienced patients achieved SVR12. However, this regimen is used only in child pugh score a patients [28].

Ledipasvir (NS5A inhibitor) LDV/SOF is another regimen for treating HCV-4 infected patients, it achieved 89% SVR12 when RBV was added to this combination for 12 weeks in HCV1 and 4 infected patients with decompensated cirrhosis [29].

In the current study, a significant improvement of liver functions including serum albumin and prothrombin time was noted; in addition, liver enzymes values were improved after than before starting treatment for both treatment naïve and experienced patients.

Rates of adverse events for Sim/Sof in this study were numerically very low may be due to the lack of RBV. One patient had transient total bilirubin elevations without increased ALT or AST and another patient developed cutaneous rash. Overall, simeprevir has demonstrated favorable safety profile which was reported from many clinical trials including QUEST-1, QUEST-2 and PROMISE, discontinuation of treatment due to severe adverse events occurred in 2% of patients receiving a simeprevir plus PegIFN/RBV combination [30]-[32].

5. Conclusion

Once daily sofosbuvir and simeprevir for 12 weeks provided high rate of sustained virological response among treatment naïve and treatment experienced patients (cirrhotics and non cirrhotics) with chronic HCV genotype 4.

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