JOURNAL OF INTERFERON & CYTOKINE RESEARCH
Volume 37, Number 8, 2017

DOI: 10.1089/jir.2016.0131

Serious Adverse Events with Sofosbuvir Combined with Interferon and Ribavirin: Real-Life Egyptian Experience

Tamer Elbaz,[1] Magdy Elserafy,[1] Wafaa Elakel,[1] Mohammad A. Mohey,[1] Mahmoud Abdo,[1] Mohamed Hassany,[2] Mai Mehrez,[2] Mahmoud Abouelkhair,[1] Ayman Yosry,[1] Ashraf Omar,[1] Imam Waked,[3] Manal Hamdy Elsayed,[4] Zakaria Mahran,[5] Yahia Elshazly,[6] Noman Elgarem,[7] Aly Gaballa,[7] Wahid Doss,[1,2] and Gamal Esmat[1]

Viral hepatitis is a serious problem worldwide that was under-recognized till recently. The prevalence of chronic hepatitis C virus (HCV) is estimated to be 180 million people worldwide. Treatment of chronic HCV using combined pegylated interferon and ribavirin (PEG/RIBA) has long been the standard of care with modest response. In our study, we will report the real-life experience of serious adverse events (SAEs) that were reported by the National Committee for Control of Viral Hepatitis (NCCVH, Cairo, Egypt) program while treating chronic HCV using the triple therapy, sofosbuvir combined with pegylated interferon and ribavirin (PEG/RIBA/SOF), which led to premature discontinuation of treatment. This retrospective analysis included a total of 6,989 chronic HCV patients who were treated by the NCCVH. They received the triple antiviral therapy in 26 treatment centers in Egypt using PEG/RIBA/SOF for 12 weeks. Among 6,989 patients who were treated in 26 treatment centers related to NCCVH, 406 cases (5.9%) reported SAEs and prematurely stopped their treatment. Triple therapy PEG/RIBA/SOF was an important intermediate milestone between interferon-based therapy and the interferon-free all-oral direct acting antiviral agents (DAAs). Results of this study were the leading cause of discontinuation of interferon-based therapy and introduction of interferon-free all-oral treatment protocols, incorporating DAAs from different classes as soon as they gain approval.

Keywords: interferon, HCV, genotype 4, serious adverse events, sofosbuvir

Introduction

Viral hepatitis is a serious problem worldwide that was under-recognized till recently. According to the World Health Organization (WHO), viral hepatitis leads to 1.4 million deaths compared with 1.3 million for tuberculosis and 1.6 million for HIV (WHO 2014). The prevalence of chronic hepatitis C virus (HCV) is estimated to be 180 million people worldwide (Messina and others 2015). In Egypt, chronic HCV accounts for 8 million people who represent 7%–10% of the population, predominantly genotype 4 (93%) (Sievert and others 2011; Bruggmann and others 2014; Gower and others 2014; Waked and others 2014).

Treatment of chronic HCV using combined pegylated interferon and ribavirin (PEG/RIBA) has long been the standard of care with modest response (Elbaz and others 2015). Sustained virologic response (SVR) rates ranged from 40% to 60% (Kamal and Nasser 2008). Although serious adverse effects of treatment regimens using PEG/RIBA are considered uncommon, fatal or life-threatening adverse effects that could require treatment discontinuation have been previously reported (Sulkowski and others 2011).

By 2011, DAAs that act directly on specific viral targets revolutionized the management of HCV. In the beginning, these DAAs were incorporated in the regimen with PEG/RIBA to increase SVR rates compared with interferon and ribavirin regimen alone (Calleja and others 2015). Combined DAAs with interferon and ribavirin regimens were approved and became the main lines of treatment in international guidelines at that time (EASL 2014; AASLD-IDSA 2015).

[1]Faculty of Medicine, Endemic Medicine and Hepatology Department, Cairo University, Cairo, Egypt.
[2]Tropical Medicine Department, National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt.
[3]National Liver Institute, Menoufiya University, Shebeen EL Kom, Egypt.
[4]Faculty of Medicine, Pediatric Department, Ain Shams University, Cairo, Egypt.
[5]Faculty of Medicine, Tropical Medicine Department, Ain Shams University, Cairo, Egypt.
[6]Faculty of Medicine, Internal Medicine Department, Ain Shams University, Cairo, Egypt.
[7]Internal Medicine Department, Cairo University, Cairo, Egypt.

In Egypt and since 2006, the National Committee for Control of Viral Hepatitis (NCCVH, Cairo, Egypt) has been formed by the Ministry of Health and Population and it took responsibilities to manage patients, according to adopted national guidelines inspired from international ones. This depended on the interferon-based regimen till the appearance of DAAs. By September 2014, the NCCVH started incorporating DAAs into the treatment protocols of HCV (CDC 2012; Waked and others 2016). The primary lines of treatment used at the start of the program were sofosbuvir combined with pegylated interferon and ribavirin (PEG/RIBA/SOF) for 12 weeks and sofosbuvir/ribavirin therapy (SOF/RIBA) for 24 weeks. Both lines achieved better SVR rates than pegylated interferon alone, but were associated with considerable side effects.

In our study, we will report the real-life experience of serious adverse events (SAEs) that were reported by the NCCVH program while treating chronic HCV using the triple therapy PEG/RIBA/SOF, which led to premature discontinuation of treatment.

Materials and Methods

This retrospective analysis included a total of 6,989 chronic HCV patients who were treated by the NCCVH. They received triple antiviral therapy in 26 treatment centers in Egypt using PEG/RIBA/SOF for 12 weeks.

As per inclusion criteria, patients are of either sex, aged from 18 to 70 years, and positive for HCV RNA by quantitative polymerase chain reaction. According to the protocol of treatment, the triple therapy PEG/RIBA/SOF was provided to patients with rather preserved liver functions without features of decompensation, while SOF/RIBA was given for 24 weeks to patients with borderline liver functions. Both lines of treatment were among the first protocols to be used during the national program to control HCV in Egypt using DAAs. Later, the NCCVH adopted other lines of treatment that were all interferon-free regimens (sofosbuvir/simeprevir, sofosbuvir/daclatasvir, and sofosbuvir/ledipasvir with/without ribavirin).

Selected patients for triple therapy must have serum bilirubin levels not exceeding 1.2 mg/dL, serum albumin more than 3.5 mg/dL, international normalized ratio (INR) <1.2, and platelet count exceeding 150.000/mm^3. Patients with hepatocellular carcinoma (HCC) are excluded till 4 weeks after intervention, aiming at cure with no evidence of activity detected by dynamic imaging (computed tomography or magnetic resonance imaging). Patients with extrahepatic malignancy are treated after 2 years of disease-free interval. Diabetic patients are treated after better control of blood sugar levels (HbA1c < 8.5). All patients signed an informed consent form demonstrating treatment protocol and possible adverse events. This consent form is adopted by NCCVH after approval of the ethics committee.

All data, including side effects, were collected on weekly bases, tabulated, and processed on a database server. SAEs that led to discontinuation of treatment are carefully represented. Numerical data are reported as means ± standard deviations or median and range. Categorical data are represented as counts and percentages.

Results

Among 6,989 patients who were treated in 26 treatment centers related to NCCVH, 406 cases (5.9%) reported SAEs and prematurely stopped their treatment. Their mean age was 48.82 ± 10.76. Majority of patients were males (61%) and the mean body–mass index was 29.24 ± 4.59.

Most patients were treatment naïve (87.5%), while 12.5% had previously experienced treatment using PEG/RIBA. Using transient elastography, the mean value for liver stiffness is 20.40 ± 15.52 kPa. Almost all patients had compensated liver status as represented by mean levels of total bilirubin (0.88 mg/dL), albumin (4.08 mg/dL), INR (1.11), and platelets (187,920/mm^3). Moreover, no patients gave history of previous hepatic encephalopathy, while 3 patients previously suffered from mild ascites that was completely controlled by the time of starting treatment. Only 6 patients were with Child-Turcotte-Pugh (CTP) score B7, while the others were with CTP score A (Table 1).

Concerning the timing of discontinuation of treatment, 65.5% of patients stopped treatment due to SAEs during the period 4–8 weeks, followed by 21.1% who stopped during the period 8–12 weeks. Early discontinuation of treatment was recorded in 13.4% who stopped during the first 4 weeks of treatment (Table 2).

Table 1. Baseline Characteristics of the Studied Patients

	All treated patients (n = 406)
Age, years	
Mean ± SD	48.82 ± 10.76
Range	19–69
Gender, *n* (%)	
Male	246 (61)
Female	160 (39)
Mean BMI ± SD	29.24 ± 4.59
Treatment status, *n* (%)	
Treatment naive	347 (85.5)
Treatment experienced	59 (14.5)
Diabetes mellitus, *n* (%)	71 (17.5)
Hypertension, *n* (%)	8 (2)
Previous encephalopathy, *n* (%)	0 (0)
Previous ascites, *n* (%)	3 (0.7)
Previous HCC, *n* (%)	1 (0.2)
Portal vein thrombosis, *n* (%)	3 (0.2)
Bilirubin total (mg/dL), mean ± SD	0.88 ± 0.46
ALT (IU/L), mean ± SD	56.09 ± 34.92
AST (IU/L), mean ± SD	61.21 ± 39.06
Albumin (g/dL), mean ± SD	4.08 ± 0.53
INR, mean ± SD	1.11 ± 0.13
AFP (IU/L), mean ± SD	10.84 ± 21.44
HCV RNA (IU/m), mean ± SD	1,764,511 ± 5,035,852
Hemoglobin (g/L), mean ± SD	13.86 ± 1.70
Leukocyte count ($\times 10^3$/mm^3), mean ± SD	7.23 ± 7.17
Platelet count ($\times 10^3$/mm^3), mean ± SD	187.92 ± 59.53
Creatinine (mg/dL), mean ± SD	0.89 ± 0.36
Liver stiffness (kPa), mean ± SD	20.40 ± 15.52
Evidence of early hepatic decompensation (CTP score B7), *n* (%)	6 (1.5)
Presence of varices, *n* (%)	24 (5.9)

AFP, alfa feto protein; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body–mass index; CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; SD, standard deviation.

Table 2. Timing for Treatment Discontinuation

Week of treatment	n *(%)*
Week 1—before week 2	27 (6.7)
Week 2—before week 4	27 (6.7)
Week 4—before week 8	266 (65.5)
Week 8—before week 12	86 (21.1)

Among the different causes of discontinuation of treatment, hepatic decompensation was the leading cause for discontinuation of treatment (42.4%), followed by hematological causes (38.4%). Features of hepatic decompensation included development of hepatic encephalopathy that necessitated hospital admission, development of poorly controlled ascites, and attacks of gastrointestinal bleeding (hematemesis and melena that were due to ruptured esophageal and/or gastric varices). Hematological causes were mainly represented by severe anemia. In such cases, we usually reduced the dose of ribavirin and prescribed hematinic (erythropoietin). Drop of hemoglobin to levels below 8 g/dL necessitated discontinuation of treatment (Table 3).

One patient was diagnosed as having lymphoma during treatment and stopped therapy. Seven patients newly developed HCC that showed aggressive behavior; 3 of them stopped treatment due to hepatic decompensation and were then discovered to have HCC. Other causes that led to stopping of treatment due to their severity included intractable itching, myalgia, anxiety, insomnia, headache, and persistent vomiting. Two patients suffered from ischemic heart disease and 1 patient developed acute renal impairment. One patient got pregnant during treatment despite signing a consent form prohibiting pregnancy during treatment, which necessitated discontinuation of treatment. Total recorded mortality was 21 patients (Table 3).

According to the causes of discontinuation, we could classify patients into 2 groups; hepatic cause group (including HCC patients) and nonhepatic cause group. The hepatic cause group included 176 patients representing 43.35% of the study population. In a univariate analysis, a statistically significant difference was reported between the 2 groups in values of different parameters, including age, basal HCV RNA, bilirubin, serum albumin, platelet count, and INR. Liver stiffness and Fib-4 values, however, were not significantly different between the 2 groups (Table 4).

Table 3. Causes of Discontinuation

Cause of discontinuation	n *(%)*
Hepatic decompensation	172 (42.4)
Hematological causes	156 (38.4)
Other causes	78 (19.2)
Hepatocellular carcinoma	7 (1.7)
Itching	14 (3.4)
Myalgia	11 (2.7)
Anxiety	9 (2.2)
Insomnia	7 (1.7)
Headache	4 (1)
Renal impairment	1 (0.2)
Ischemic heart disease	2 (0.4)
Persistent vomiting	1 (0.2)
Malignancy[a]	1 (0.2)
Pregnancy	1 (0.1)

Mortality: 21 patients.
[a]Malignancy: 1 case diagnosed with lymphoma.

Discussion

In Egypt, a nationwide treatment program was started in 2014, targeting all patients suffering from chronic HCV. As it was reported that more than 8 million people are chronically infected with HCV, prioritization was a necessity in the early phases of the program. The National Committee prioritized patients who had advanced fibrosis for treatment to prevent progression of fibrosis, maintain compensation, and prevent the development of HCC.

Liver biopsy has long been the gold standard for grading of necroinflammation and staging of fibrosis. However, its main limitations are its invasiveness and possibility of sampling error (Shehab and others 2014a). It was not possible to use it as the main tool for categorization of the patients. On the other hand, transient elastography (Fibroscan®; Echosens, Paris, France), previously demonstrated to be a simple, valid, and noninvasive tool to assess liver stiffness, is characterized by its good accuracy as well as good reproducibility in cases of advanced fibrosis (Vignier and others 2011; Esmat and others 2013; Bonnard and others 2015). The mean value of liver stiffness of our patients was 20.40 ± 15.52 kPa. This is clear by the primary aim mentioned before to treat advanced fibrosis patients. Simultaneously, all laboratory values proved their well-preserved liver status before treatment.

Among more than 6,000 treated patients, SAEs occurred in 406 patients (5.9%). Putting in consideration the advanced fibrotic stage of treated patients (even with well-compensated hepatic reserve), treatment using the triple therapy PEG/RIBA/SOF led to hepatic decompensation that ranked as the first cause to discontinuation of treatment (42.4%). Such patients deteriorated to advanced CTP scores and did not tolerate continuing therapy.

Ribavirin plays an important role in HCV treatment. The mechanism of action is complex and remains poorly understood. It is probable that ribavirin acts at different levels of viral replication. Recent studies suggest an action through the interferon system by stimulating interferon genes, thereby enhancing the production of endogenous interferon (Testoni and others 2013). Adding ribavirin to pegylated interferon increases SVR rates by 25%–30% and ribavirin became an integral component of interferon-based therapies for HCV (Bronowicki and others 2006). However, ribavirin induced side effects responsible for 3% –11% of early treatment cessation that may reach 35% among cirrhotic patients (Zoulim and others 1998). Ribavirin induces allergic reactions such as dry cough and/or pruritus, but the most frequent side effect is hemolytic anemia due to intraerythrocyte accumulation. In our study, hematological abnormalities were the second common cause for treatment discontinuation and seen in 38.4% of the patients who experienced SAEs. Previous studies on PEG/RIBA demonstrated that 25% of patients developed anemia with the hemoglobin level <10 g/dL and 13% of patients needed ribavirin dose modification (Fried and others 2002). In another study using pegylated interferon regimen, discontinuation of treatment due to side effects occurred in 7% of patients, predominantly due to hematological side effects (neutropenia, anemia, and thrombocytopenia).

Table 4. Univariate Analysis for Different Variables in Relation to Hepatic and Non-Hepatic SAEs

	Hepatic cause (N = 176)	*Nonhepatic cause (N = 230)*	P
Age, years, mean ± SD	52.9 ± 9.2	45.7 ± 10.9	<0.0001
Basal HCV RNA ($\times 10^5$), mean ± SD	26.8 ± 74.14	10.7 ± 14.2	0.002
Albumin (g/dL), mean ± SD	3.9 ± 0.6	4.2 ± 0.4	<0.0001
Total bilirubin (mg/dL), mean ± SD	1.0 ± 0.6	0.8 ± 0.3	<0.0001
Hemoglobin (g/L), mean ± SD	13.8 ± 1.8	13.9 ± 1.7	0.283
WBC ($\times 10^3/mm^3$), mean ± SD	7.8 ± 6.2	7.5 ± 7.1	0.318
Platelets ($\times 10^3/mm^3$), mean ± SD	174 ± 59.3	198.4 ± 57.7	<0.0001
INR, mean ± SD	1.1 ± 0.2	1.1 ± 0.1	<0.0001
Stiffness (kPa), mean ± SD	22.0 ± 17.8	16.3 ± 6.0	0.264
Fib-4, mean ± SD	5.65 ± 34.62	2.32 ± 2.08	0.147

Other causes included retinopathy, glomerulonephritis, cancer prostate, facial palsy, and ischemic heart disease (Shehab and others 2014b).

DAAs combined with PEG/RIBA definitively improved SVR rates (Kowdley and others 2013; Lawitz and Gane 2013; Lawitz and others 2013; Elsharkawy and others 2017). However, serious related adverse events are considerable. In a recent study using the triple therapy, 96% of patients reported at least 1 side effect. Nine percent had SAEs (anemia, decompensated cirrhosis, bleeding esophageal varices, sepsis, and cholecystitis). None of these adverse events was considered related to sofosbuvir (Lawitz and others 2015). In another systematic review and network meta-analysis, SVR assessed at 24 weeks post-treatment showed that pooled incidence of SVR24 is much higher for PEG/RIBA/SOF compared with PEG/RIBA alone (81% versus 48%, respectively). In such study, sofosbuvir–interferon therapy had the highest probability for being the best treatment. At same time, pooled incidence of SAEs was 4.1% for triple therapy using PEG/RIBA/SOF in comparison with 7.5% for PEG/RIBA alone (Suwanthawornkul and others 2015). Given that adverse events are usually due to interferon and ribavirin, this difference of incidence of SAEs between both lines may be related to the shorter duration of therapy in triple therapy (12 weeks only).

Interferon-free trials showed fewer incidences of side effects. FUSION trial used SOF/RIBA alone. No treatment discontinuation occurred and hemoglobin dropped in 2% only of patients. In a POSITRON trial using the same regimen, 1% only reported anemia (Jacobson and others 2013). In a similar Egyptian study comparing 12 versus 24 weeks of treatment using SOF/RIBA, no discontinuation of therapy was reported due to adverse events (Doss and others 2015). Many trials were looking also for ribavirin-free therapy. A real-life experience of safety and efficacy of sofosbuvir plus simeprevir (SOF/SIM) treatment regimen in Egyptian patients reported 94% SVR rate with only 1.6% of patients who experienced an SAE that led to treatment discontinuation and/or mortality, of whom 91% were due to hepatic decompensation (Eletreby and others 2017). Two other studies assessed the efficacy of sofosbuvir/simeprevir or sofosbuvir/daclatasvir combinations with or without ribavirin in genotype 1 patients with or without cirrhosis. The addition of ribavirin to any of these combinations for 12–24 weeks did not improve SVR and was more frequently associated with side effects (Lawitz and others 2014; Sulkowski and others 2014). These results seem to indicate no clear benefit of ribavirin when added to DAA combinations containing a nucleoside polymerase inhibitor with high genetic barrier and another antiviral. However, some preliminary results indicate that such combinations may not be sufficient in difficult-to-treat patients such as genotype 1 or 3 decompensated cirrhotics and suggest that the addition of ribavirin could improve virological response (Gane and others 2014). The role of ribavirin within new DAA combinations will probably decrease in the future.

In our study, we reported 7 patients (1.7%) who developed HCC while on treatment. Although the incidence is low and expected bearing in mind that most of the recruited patients had significant hepatic fibrosis (fertile soil for developing HCV-associated HCC), yet the aggressiveness of the tumor could not be explained and needs further studies. An alarming report was recently published and demonstrated an unexpectedly early recurrence of tumors (27.6%) in patients with HCV-related primary liver malignancy who achieved complete response before treatment. However, this study excluded patients receiving interferon as part of their treatment regimen and recruited only those treated with combined DAAs (Reig and others 2016).

In our study population, hepatic causes of treatment discontinuation represented 43.35% of all causes and some factors were found to be significant predictors such as age, bilirubin, albumin, and INR, and these parameters are strongly correlated with hepatic function. However, liver stiffness and Fib-4 score were found to be insignificantly related to the cause of discontinuation, although they reflect the actual fibrosis status of the liver, and this can be explained by the fact that almost all in the study population had advanced fibrosis as it was a prioritizing factor for treatment then.

Finally, we conclude that triple therapy PEG/RIBA/SOF was an important intermediate milestone between interferon-based therapy and the interferon-free all-oral DAAs. In real-life experience, SAEs related to interferon-based therapy are likely to occur, bearing in mind that patients who received this protocol of therapy had advanced fibrosis complying with the policy of prioritization adopted by NCCVH at that time. Results of this study with consequent development and availability of more affordable DAAs led to eventual discontinuation of interferon-based therapy and introduction of interferon-free all-oral treatment protocols, incorporating DAAs from different classes as soon as they gain approval.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Prof. Mohammad A. Mohey
Faculty of Medicine
Endemic Medicine and Hepatology Department
Cairo University
Cairo
Egypt

E-mail: ma_mohey@kasralainy.edu.eg

Received 19 January 2017/Accepted 22 May 2017