HIGH SUCCESS RATES FOR THE USE OF SOFOSBUVIR/OMBITASVIR/PARITAPREVIR/RITONAVIR+RIBAVIRIN, AND SOFOSBUVIR/SIMEPREVIR/DACLATASVIR+RIBAVIRIN IN RETREATMENT OF CHRONIC HEPATITIS C AFTER UNSUCCESSFUL SOFOSBUVIR/DACLATASVIR THERAPY: A REAL-LIFE EXPERIENCE

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Conflicts of interest: none declared

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ABSTRACT

**Background:** Direct acting antiviral agents (DAAs) revolutionized chronic hepatitis C (CHC) treatment. However, the limited DAAs failure is still challenging.

**Objective:** Assessment of efficacy and tolerability of the combination of sofosbuvir (SOF), ritonavir boosted paritaprevir, ombitasvir (OBV/PTV/r) and ribavirin (RBV), or SOF, simeprevir (SMV), daclatasvir (DCV) and RBV in re-treatment of CHC patients who failed response to SOF/DCV-based therapy.

**Patients and methods:** This prospective study included 104 Egyptian CHC patients who failed response to SOF/DCV-based therapy. Patients were allocated to 2 groups; group A (n=54) received SOF plus OBV/PTV/r+RBV and group B (n=50) received SOF/SMV/DCV+RBV. Efficacy was assessed by achievement of sustained virological response (SVR), defined as undetectable HCV RNA 12 weeks after treatment completion. Tolerability was assessed through monitoring of treatment related adverse events (AEs) and laboratory abnormalities.

**Results:** The SVR12 rates were 94.4% (51/54) in group A and 96% (48/50) in group B, with no significant difference (p=1.000). Only one patient in group B discontinued treatment due to development of hepatic decompensation. Most reported AEs were mild to moderate in severity according to Common Terminology Criteria for Adverse Events (CTCAEV5.0) with no deaths during the study. Dermatological AEs (photosensitivity and pruritis) were significantly predominant in group B (p=0.005), while headache was more significant in group A (p=0.032). Fatigue was the commonest AE in both groups (29.6% and 28% in group A and B respectively), followed by headache and abdominal pain in group A (20.4% and 18.5% respectively), compared to photosensitivity and itching (both 14%) in group B.

**Conclusion:** Multi-target DAAs combinations are efficient in re-treatment of Egyptian CHC relapsers after failure of SOF/DCV-based therapy in real world management.

**Key words:** DAA failure; HCV; NS5A inhibitor; relapsers.
INTRODUCTION

Hepatitis C virus (HCV) infection is one of the most prevalent causes of chronic hepatitis worldwide affecting approximately 3% of world’s population (about 185 million individuals). It represents a leading cause of severe liver disease and liver cancer in several countries [1]. Egypt is one of the highest countries in chronic hepatitis C (CHC) prevalence where about 4.4% of the population aged 1-59 years had an active HCV infection [2].

Diagnosis of CHC is based on detection of anti-HCV antibodies. Confirmation of active CHC relies mainly on direct detection of HCV RNA (Ribonucleic acid) via molecular assay [3]. The end point of therapy in CHC is viral clearance and achievement of sustained virological response (SVR) defined as undetectable HCV RNA at 12 weeks after end of treatment [4]. Understanding HCV structure, life cycle and replication opened the door for innovation of the direct acting anti-viral agents (DAAs) that directly inhibits target viral proteins [5].

Owing to the high rates of SVR, DAAs triggered a major revolution in HCV treatment and totally replaced the old Interferon (IFN)-based therapy that had been the standard of care in CHC for many years. Currently, several DAA regimens for treatment of CHC were approved including pan-genotypic regimens. These all oral IFN-free regimens show excellent efficacy and tolerability profiles, and accordingly offer a unique opportunity to achieve HCV elimination [6].

In 2006, Egypt established the National Committee for the Control of Viral Hepatitis (NCCVH) which took the lead in HCV management via a large nationwide network of centers for specialized viral hepatitis treatment. Due to consequent changes in international HCV treatment guidelines and based on DAAs availability, the Egyptian practice guidelines were repeatedly modified [7]. The NCCVH treatment protocol in CHC relies on the combination of sofosbuvir (SOF) plus daclatasvir (DCV) with or without ribavirin (RBV) as the main treatment regimen. On large scale application the SOF/DCV based regimens were well tolerated and yielded SVR rates of about 95% in Egyptian CHC patients [8].

Despite the high success rates accompanying DAAs use, treatment failures attributed to several host, drug, and virus-related factors still occur in substantial numbers of treated patients (1-15%) and still represent a problematic issue [9].
Re-treatment after DAAs failure is a challenge especially in those who failed an non-structural protein 5A (NS5A)-based regimen owing to the persistence of NS5A resistance-associated substitutions (RASs) that convey viral resistance up to 96 weeks in follow-up after treatment failure [10]. The current updates of international HCV treatment guidelines recommend the single tablet combination of SOF plus velpatasvir and voxilaprevir (SOF/VEL/VOX) for 12 weeks as the standard treatment after failure of NS5A-based regimens. Addition of RBV or extension of treatment duration of SOF/VEL/VOX regimen as well as combining SOF with Glecaprevir and Pibrentasvir (GLE/PIB) could be considered in difficult to treat patients [11] [12].

Due to the limited availability of some newer DAAs in Egypt; accordingly the NCCVH recommends treatment of CHC patients who failed previous SOF/DCV-based regimens with a combination of either SOF plus ritonavir boosted paritaprevir and ombitasvir (OBV/PTV/r) ±RBV, or SOF plus simeprevir (SMV) and DCV ±RBV for 12 or 24 weeks according to RBV eligibility [13].

PATIENTS AND METHODS

This prospective observational study was conducted on 104 CHC patients who failed response to SOF/DCV-based regimens attended New Cairo viral hepatitis treatment center in Cairo, Egypt, in the period from March to November 2018.

The study protocol was approved by the ethical committee of Benha University Hospitals, Benha University and an informed written consent was obtained from all patients participating in this study.

Patients included in this study were adults (≥ 18 years), of both sexes, with CHC and detectable HCV RNA 12 weeks after completion of SOF/DCV-based regimen and eligible for antiviral therapy as recommended by the Egyptian NCCVH treatment protocol (December 2016). On the other hand all patients with decompensated cirrhosis (grade B and C by modified Child-Turcotte-Pugh CTP score), platelet count less than 50000/ mm³, hepatocellular carcinoma (except after 6 months of intervention aiming at cure with no evidence of tumoral activity confirmed by a dynamic study), an extra hepatic malignancy (except after 2 years disease-free interval, in case of lymphomas and chronic lymphocytic leukemia treatment can be initiated immediately after remission based on treating oncologist report), pregnancy or inability to use effective contraceptive method or inadequately controlled diabetes mellitus were excluded from the study.
The clinical/pathological data of patients were recorded including age, sex, full history taking, thorough clinical examination, HCV RNA quantitative PCR (polymerase chain reaction), biochemical liver function tests, complete blood count (CBC), serum creatinine, alfa fetoprotein level (AFP), hepatitis B virus surface antigen (HBsAg) and serum beta human chorionic gonadotropin for females in childbearing period.

Pelvi-abdominal ultrasound examination was performed for all patients at baseline and 12 weeks after end of treatment. Severity of liver disease was assessed by modified CTP score.

As the applied treatment protocol allows for the use of both regimens, enrolled patients were allocated to one of the two regimens by consecutive randomization: group A included the first 54 patients and received a combination of SOF (one tablet, 400 mg) with two co-formulated tablets of OBV/PTV/r (12.5mg/75mg/50mg) and RBV for 12 weeks, group B included the next 50 patients and received a combination of SOF (one tablet, 400 mg), SMV (one tablet, 150 mg), DCV (one tablet, 60 mg) and RBV for 12 weeks.

The recommended RBV starting dose was 600 mg/day with trial to reach 1000 or 1200 mg/day based on patient’s body weight and tolerability.

Laboratory assessments during follow up included CBC, liver transaminases, serum total bilirubin, and serum creatinine at week 4 and 8 during treatment and at end of treatment. Assessment of AFP level was done at baseline and 12 weeks after end of treatment.

Treatment efficacy was assessed by achievement of SVR12 defined as undetectable HCV RNA by PCR 12 weeks after end of treatment.

Safety and tolerability were evaluated through reporting of adverse events (AEs) and monitoring of laboratory abnormalities related to study drugs. AEs and laboratory abnormalities were categorized according to severity based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [14].

STATISTICAL ANALYSIS

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 18.0, IBM Corp., Chicago, USA, 2009. Descriptive statistics were done for quantitative data as minimum and maximum of the range as well as mean ±SD (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage.
Inferential analyses were done for quantitative variables using Shapiro-Wilk test for normality testing, independent t-test in cases of two independent groups with normally distributed data, repeated measure ANOVA test (RMANOVA) for more than time analysis with normally distributed. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions and Fisher’s Exact test for variables with small expected numbers. The level of significance was taken at P value < 0.05 is significant, otherwise is insignificant.

RESULTS

Study population

One hundred and four patients were enrolled in this study and were allocated to 2 groups; group A (n=54) received a combination of SOF plus OBV/PTV/r +RBV, and group B (n=50) received a combination of SOF/SMV/DCV+RBV.

The demographic and basal characteristics were matching between both groups. Male sex was more common among both groups (61.1% and 60% in group A and B respectively). The age of enrolled patients was matching in both groups (mean ±SD = 51.5±10.7, 51.5±10.9 years for group A and B respectively, p=0.992).

Regarding DAA experience before enrollment in the current study, in group A, 33 patients out of 54 (61.1%) were SOF/DCV-experienced, while 21 patients were SOF/DCV/RBV-experienced. On the other hand in group B, 26 patients out of 50 (52%) were SOF/DCV-experienced, while 24 patients were SOF/DCV/RBV-experienced.

Patient’s demographics and basal characteristics are summarized in Table 1.

Outcomes

Achieved SVR rates showed no significant difference between both study groups, SVR12 rate was 94.4% (51/54 patients) and 96% (48/50 patients) in group A and group B respectively (p=1.000) (Table 2 & figure 1).

Regarding safety and tolerability, both regimens were generally safe and well tolerated with no deaths due to AEs. Among all study patients only one patient in group B discontinued treatment after 4 weeks due to hepatic decompensation in the form of significant elevation in serum total bilirubin (6.4 mg/dl) and development of ascites, surprisingly, this patient achieved SVR12.
Table (1): Demographic and basal characteristics of the studied groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A (N=54)</th>
<th>Group B (N=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean ±SD</td>
<td></td>
<td>^0.992</td>
</tr>
<tr>
<td>Sex (n, %)</td>
<td>Male</td>
<td>33 (61.1%)</td>
<td>30 (60.0%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>21 (38.9%)</td>
<td>20 (40.0%)</td>
</tr>
<tr>
<td>Tobacco smoking (n, %)</td>
<td>14 (25.9%)</td>
<td>17 (34.0%)</td>
<td>#0.368</td>
</tr>
<tr>
<td>IV drug addiction (n, %)</td>
<td>2 (3.7%)</td>
<td>0 (0.0%)</td>
<td>&amp;0.496</td>
</tr>
<tr>
<td>Alcohol intake (n, %)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>--</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>8 (14.8%)</td>
<td>5 (10.0%)</td>
<td>#0.458</td>
</tr>
<tr>
<td>DM (n, %)</td>
<td>17 (31.5%)</td>
<td>15 (30.0%)</td>
<td>#0.870</td>
</tr>
<tr>
<td>Previous HCV treatment</td>
<td>SOF/DCV</td>
<td>33 (61.1%)</td>
<td>26 (52.0%)</td>
</tr>
<tr>
<td></td>
<td>SOF/DCV/RBV</td>
<td>21 (38.9%)</td>
<td>24 (48.0%)</td>
</tr>
<tr>
<td>HCV RNA (x10^3/mL)</td>
<td>Mean ±SD</td>
<td>631.6±986.0</td>
<td>787.8±1080.1</td>
</tr>
</tbody>
</table>

^Independent t-test, #Chi square test, &Fisher's Exact

Table (2): HCV RNA by PCR 12 weeks after end of treatment

<table>
<thead>
<tr>
<th>Findings</th>
<th>Group A (N=54)</th>
<th>Group B (N=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>3 (5.6%)</td>
<td>2 (4.0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Negative</td>
<td>51 (94.4%)</td>
<td>48 (96.0%)</td>
<td></td>
</tr>
</tbody>
</table>

&Fisher's Exact test.

Reported AEs were generally mild to moderate (grade 1 or 2 severity) in both study groups, however dermatological AEs were significantly more frequent in group B patients \((p=0.005)\), and headache was significantly more frequent in group A patients \((p=0.032)\).

In group A patients the most common reported AEs were fatigue (29.6%), headache (20.4%), abdominal pain (18.5%) and musculoskeletal pain (14.8%). While in group B patients, the most common reported AEs were fatigue (28%), Photosensitivity (14%), itching (14%) and abdominal pain (10%).

Reported AEs related to treatment are demonstrated in table 3 and figure 2.
Figure (1): HCV RNA by PCR 12 weeks after end of treatment

![Figure 1](image)

Table (3): Treatment related adverse events among study patients

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Group A (N=54)</th>
<th>Group B (N=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>18 (33.3%)</td>
<td>22 (44.0%)</td>
<td>~0.264</td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>18 (33.3%)</td>
<td>27 (54.0%)</td>
<td>~0.034*</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (29.6%)</td>
<td>14 (28.0%)</td>
<td>~0.855</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (20.4%)</td>
<td>3 (6.0%)</td>
<td>~0.032*</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>0 (0.0%)</td>
<td>7 (14.0%)</td>
<td>~0.005*</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>8 (14.8%)</td>
<td>3 (6.0%)</td>
<td>~0.144</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (18.5%)</td>
<td>5 (10.0%)</td>
<td>~0.217</td>
</tr>
<tr>
<td>Itching</td>
<td>2 (3.7%)</td>
<td>7 (14.0%)</td>
<td>~0.084</td>
</tr>
</tbody>
</table>

#Chi square test, &Fisher's Exact test, *Significant
Laboratory abnormalities

Regarding recorded laboratory abnormalities, clinically significant hemoglobin drop was observed in both study groups during treatment; however this was statistically insignificant between both groups (33.3% and 44% in group A and B respectively, $p=0.264$). Hemoglobin drops were almost of grade 1 or 2 severity except for one patient in group A who suffered a severe (grade 3) drop in hemoglobin (7.0g/dl), that might be RBV induced [14].

Clinically significant hyperbilirubinemia was observed in both study groups during treatment, in addition significantly higher total bilirubin levels were observed in group B as compared to group A at week 4 of treatment (54% versus 33.3%, Mean ±SD = 1.1±0.6 and 1.4±0.9 mg/dl in group A and B respectively, $p=0.031$). However; elevations in total bilirubin among all study patients were generally mild to moderate (grade 1 or 2) apart from 2 patients, one in each group who suffered severe (grade 3) hyperbilirubinemia (4.2 and 6.4 mg/dl) [14].
Changes in hemoglobin and serum total bilirubin during treatment among study groups are demonstrated in table 4.

**Table (4): changes in Hemoglobin (gm/dL) and serum total bilirubin (mg/dL) during treatment**

<table>
<thead>
<tr>
<th>Times</th>
<th>Measures</th>
<th>Group A (N=54)</th>
<th>Group B (N=50)</th>
<th>^P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week-0</td>
<td>Hemoglobin</td>
<td>13.9±1.6</td>
<td>14.0±1.7</td>
<td>0.918</td>
</tr>
<tr>
<td></td>
<td>Total bilirubin</td>
<td>0.8±0.4</td>
<td>0.8±0.3</td>
<td>0.968</td>
</tr>
<tr>
<td>Week-4</td>
<td>Hemoglobin</td>
<td>12.6±1.7</td>
<td>12.6±1.6</td>
<td>0.964</td>
</tr>
<tr>
<td></td>
<td>Total bilirubin</td>
<td>1.1±0.6</td>
<td>1.4±0.9</td>
<td>0.031*</td>
</tr>
<tr>
<td>Week-8</td>
<td>Hemoglobin</td>
<td>12.4±1.7</td>
<td>12.5±1.4</td>
<td>0.694</td>
</tr>
<tr>
<td></td>
<td>Total bilirubin</td>
<td>1.1±0.7</td>
<td>1.2±0.7</td>
<td>0.420</td>
</tr>
<tr>
<td>Week-12</td>
<td>Hemoglobin</td>
<td>12.1±1.6</td>
<td>12.3±1.4</td>
<td>0.460</td>
</tr>
<tr>
<td></td>
<td>Total bilirubin</td>
<td>1.2±0.6</td>
<td>1.1±0.5</td>
<td>0.744</td>
</tr>
<tr>
<td>#P</td>
<td></td>
<td>&lt;0.001*</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
</tbody>
</table>

^Independent t-test (comparison between groups), #RMANOVA (comparison between times), *Significant

**DISCUSSION**

CHC remains a major health concern worldwide, especially in countries with highest prevalence like Egypt [1]. Introduction of the new DAAs-based therapies is certainly one of the most clinically significant breakthroughs in recent medical histories [7].

Despite the high success rates accompanying DAAs use, treatment failures still occur in substantial numbers of treated patients. Re-treatment after DAAs failure is a challenge especially in those who failed an NS5A-based regimen, which may be attributed to persistence of NS5A RASs for long periods and occurrence of cross resistance among members of NS5A inhibitors. In addition, the limited availability of some recently approved DAAs in some countries (as in Egyptian situation) augments this challenge [9] [10].

The current updates of CHC treatment guidelines recommend the combination of SOF/VEL/VOX for 12 weeks as the standard treatment after failure of
NS5A-based regimens. Another alternative in very difficult to cure patients is a combination of either SOF/VEL/VOX or SOF plus GLE/PIB that should be used with the addition of RBV and/or extension of treatment duration in such patients [11] [12].

Due to the limited availability of some newer DAAs in Egypt; accordingly the NCCVH recommends treatment of patients who failed response to SOF/DCV-based regimens with a combination of SOF plus OBV/PTV/r ±RBV, or SOF/SMV/DCV±RBV for 12 or 24 weeks according to RBV eligibility [13].

The aim of this study was to evaluate the efficacy and tolerability of the two standard regimens recommended by the Egyptian NCCVH for treatment of CHC patients who failed response to SOF/DCV-based regimens.

The demographic and basal characteristics were matching between both study groups. Male sex was more common in both groups (61.1% and 60% in group A and B respectively). The age of patients was matching in both groups (year, mean ±SD = 51.5±10.7, 51.5±10.9 years for group A and B respectively, p=0.992). Baseline demographics and basal characteristics were matching to those reported by Abdel-Moneim et al. who used a combination of SOF plus OBV/PTV/r + RBV in treatment of DAA-experienced Egyptian CHC genotype 4 patients (male sex 52.2%, age, mean ±SD= 45.6±9.7 years) [15].

Baseline values of liver transaminases as well as values at the end of treatment were insignificantly different between both study groups; however both ALT (alanine aminotransferase) and AST (aspartate aminotransferase) levels significantly decreased in both groups at the end of treatment as compared to baseline values. This was in agreement with El Kassas et al. who reported that ALT levels significantly decreased after the end of treatment in CHC patients [16].

Baseline HCV RNA levels were insignificantly different between the two groups of the present study; the mean HCV RNA at baseline was 631.6 x10^3 IU/mL and 787.8 x10^3 IU/mL for group A and B respectively (p=0.782).

In the current study, SVR rates showed no significant difference between both study groups, SVR12 rate was 94.4% (51/54 patients) and 96% (48/50 patients) in group A and group B respectively (p=1.000), these results were in agreement with the results achieved by Abdel-Moneim et al. who used a combination of SOF plus OBV/PTV/r +RBV in treatment of DAA-experienced Egyptian CHC genotype 4 patients. In that study the overall SVR12 rate was 97% (109/113 patients); of note 95 out of the whole 113 patients (84%) were SOF/DCV experienced [15].

Also, SVR rates in the current study were comparable to those reported by Bourlière et al. in the POLARIS-1 study, in that trial 12 weeks of the triple
combination of SOF/VEL/VOX was used in treatment of CHC patients after unsuccessful NS5A-containing DAA regimen. Overall SVR rate was 96% (253/263) of treated patients, while SVR was 91% in patients with HCV genotype 4 (20/22 patients) [17].

Reported SVR rates in the present study were also comparable to Ledinghen et al. who used a combination of GLE/PIB or GLE/PIB plus SOF in re-treatment of CHC difficult to treat patients who failed previous DAAs-based regimens (including different NS5A inhibitors). In that study SVR12 rates were 100% and 93.3% in the GLE/PIB plus SOF group and GLE/PIB group respectively [18].

Also, Gane et al., achieved comparable SVR rates to these observed in the present study, in that study SVR rate was 91% (63/69 patients) when a combination of SOF/VEL+RBV for 24 weeks was used in re-treatment of CHC patients who failed after a regimen of SOF/VEL, SOF/VEL/RBV or SOF/VEL/VOX for different treatment durations (4-12 weeks) [19].

Hèzode et al. in a real world study used SOF/SMV combination for 12 weeks in treatment of CHC patients who failed previous DCV-based regimen. In that study SVR rate was 87.5% (14/16) which is slightly lower than the current study, this could be due to the small number of patients (16 patients) and the inclusion of patients only with advanced fibrosis or cirrhosis at baseline. This difference may also be attributed to lack of NS5A inhibitor and RBV in the used treatment regimen [20].

Reported SVR rates in the present study were better than those achieved by Lawitz et al. who evaluated the efficacy of SOF plus ledipasvir (LDV) for 24 weeks in re-treatment of CHC genotype 1 patients who failed after 8 or 12 weeks courses of SOF/LDV±RBV (SVR=73%, 30/41 patients). This difference between both studies was probably due to difference in HCV genotype and/or the absence of protease inhibitor and RBV in the regimen used in that trial [21].

Regarding safety and tolerability, both regimens of the present study were generally safe and well tolerated with no deaths due to AEs. Among the whole study patients only one patient in group B discontinued treatment after 4 weeks due to hepatic decompensation in the form of significant elevation of total bilirubin (6.4 mg/dl) and development of ascites, surprisingly, this patient achieved SVR12.

Reported AEs in the current study were generally mild to moderate (grade 1 or 2 severity) in both study groups, however dermatological AEs were significantly more common among group B patients, while headache was significantly more common in group A [14].
In group A patients the most common reported AEs were fatigue (29.6%), headache (20.4%), abdominal pain (18.5%) and musculoskeletal pain (14.8%), that were quietly similar to AEs reported by Abdel-Moneim et al. in patients who received a combination of SOF plus OBV/PTV/r +RBV. The commonest AEs observed in that study were headache (22%), fatigue (20%), asthenia (18%), dyspnea (17%), nausea (14%), and abdominal troubles (13%) [15].

In group B patients, the most common reported AEs were fatigue (28%), photosensitivity (14%), itching (14%) and abdominal pain (10%). AEs observed in the current study share some similarity with those reported by Sulkowski and colleagues, in that trial 6 or 8 weeks of a combination of SOF/SMV/DCV were used in treatment of CHC genotype 1 naïve patients. AEs reported in that trial were grade 1 or 2 except for 1 patient who had serious AE. The most common AEs reported were headache (23.5%), fatigue (22.1%), nausea (14.7%) and diarrhoea (8.8%). Incidence of skin and subcutaneous tissue disorders was low in that study (pruritus: 4.4%; alopecia: 2.9%; photosensitivity: 2.9%; rash: 1.5%; skin exfoliation 1.5%) which was different from the current study, probably due to differences genetics, ethnicity, race or in degrees of exposure to sun light in between patients of both studies [22].

While the most common AEs observed in patients who received SOF/VEL/VOX regimen in the POLARIS-1 study were headache (in 25% of patients), fatigue (21%), diarrhea (18%), and nausea (14%) [17].

Regarding laboratory abnormalities noticed in the present study, clinically significant hemoglobin drop was observed in both study groups; however this was statistically insignificant between both groups (33.3% and 44% in group A and B respectively). Hemoglobin drops were almost of grade 1 or 2 severity except for one patient in group A who suffered a severe drop (grade 3) in hemoglobin (7.0g/dl), that might be RBV induced [14].

Clinically significant hyperbilirubinemia was noticed in both groups during treatment, in addition significantly higher total bilirubin levels were observed in group B as compared to group A at week 4 of treatment. Elevations in total bilirubin among all study patients were generally mild to moderate (grade 1 or 2) apart from 2 patients, one in each group who suffered severe (grade 3) hyperbilirubinemia (4.2 and 6.4 mg/dl) [14].

Changes in serum creatinine in both study groups were statistically significant only at week-8 of treatment where it was significantly higher in group A, however these changes were clinically insignificant. In addition there was no statistically or clinically important changes observed in platelet count, white blood cell count or AFP levels between both groups of the present study.
CONCLUSIONS

Reliance on SOF as a backbone of therapy in combination with 2 other DAAs targeting different viral proteins is an efficient strategy in re-treatment of CHC after failure of NS5A inhibitors-based regimens.

The combination of SOF plus OBV/PTV/r ±RBV or SOF/SMV/DCV ±RBV represents a lifeline for re-treatment of Egyptian CHC patients who failed response to SOF/DCV-based therapy especially in the setting of limited DAAs availability.

ACKNOWLEDGMENTS

The authors would like to thank all the staff members of New Cairo viral hepatitis treatment center, Cairo, Egypt for their great efforts and support throughout this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES


