International Journal of Infectious Diseases 96 (2020) 367–370

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Retreatment of chronic hepatitis C patients who failed previous therapy with directly acting antivirals: A multicenter study

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ARTICLE INFO

Article history:
Received 7 February 2020
Received in revised form 4 April 2020
Accepted 7 April 2020

Keywords:
HCV
non-responders
Retreatment

ABSTRACT

Aim of the study: The current study aimed to evaluate the efficacy of different DAAs regimens in the treatment of chronic hepatitis C (CHC) Egyptian patients who failed to achieve SVR after their treatment with SOF-based regimens.
Methods: This was a retrospective observational multicenter study that included CHC patients that failed to achieve cure on SOF-based regimens who were re-treated using different DAAs regimen and were allocated according to national guidelines for the treatment of hepatitis C. Primary outcome was to assess the SVR12 rate among prior non-responders after retreatment with a second course of DAAs.
Results: Our study included 172 patients who failed to achieve SVR after treatment with SOF-based treatment regimen [age: 51.2 ± 11.3, 58.7% men]. Included patients were retreated using SOF/DCV/RBV, SOF/ r/PAR /OMB /RBV, SOF/DCV/SIM, SOF/LDV ± RBV or SIM/SOF. SVR12 was successfully attained in 95.35% (164/172) of the included non-responders.
Conclusion: The current multicenter study proved the efficacy of various DAAs regimens issued by the National Committee for Control of Viral Hepatitis for retreatment of relapsed CHC Egyptian patients.

Introduction

Egypt is one of the countries with a high HCV burden; the percentage of HCV antibody positivity is 4.61 % of in Egyptian general population (Abdel-Moneim et al., 2018a). Egyptian National Committee for Control of Viral Hepatitis (NCCVH) implemented a model of care for HCV, aiming at providing a framework for control of HCV infection, reducing the prevalence

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https://doi.org/10.1016/j.ijid.2020.04.022

and burden of HCV, and targeting disease elimination by 2030 (Gomaa et al., 2017; Gore et al., 2017), which is also a major health target adopted by World Health Organization (WHO) (Esmat et al., 2013).

The advent of oral direct-acting antivirals (DAAs), as a treatment for chronic hepatitis C (CHC), has revolutionized the field with obvious safety and efficacy privileges (El Kassas et al., 2016). Despite the high rates of SVR achieved with DAAs, HCV is not eliminated from a considerable proportion of patients (1-15%) (Sarrazin, 2016; Pawlotsky, 2016). Factors associated with DAAs failure include advanced stages of liver fibrosis, response to previous antiviral therapy and viral factors such as baseline viral load and suboptimal interaction of the DAAs with the target based on viral variants (Sarrazin, 2016; Benítez-Gutiérrez et al., 2016).

Given the size of the infected population, it is estimated that a considerable number of patients who will not achieve sustained virological response will remain after the initial treatment course and this number will increase as more patients are being treated for HCV (Abdel-Moneim et al., 2018b). So, a new problem has emerged which is the need for re-treatment of patients who couldn't be cured with DAAs in the first instance.

Retreatment decisions after DAAs failure are challenging and influenced by the number of available agents and concerns about HCV drug resistance. The optimal treatment for patients who fail an NS5A inhibitor and those with multidrug-resistant variants remains to be defined (Benítez-Gutiérrez et al., 2016; Abdel-Hamid et al., 2007). Retreatment options were limited to longer courses of therapy, the addition of ribavirin, or novel combinations of approved DAAs, till the approval of a regimen that is pan-genotypic and active against resistance-associated substitutions (RASs), consisting of a fixed-dose combination of sofosbuvir/velpatasvir (VEL) and a second-generation HCV-protease inhibitor, voxilaprevir (VOX) by the Food and Drug Administration (FDA) in July 2017 (Abdel-Moneim et al., 2018a; Andres, 2020).

Unfortunately, new salvage therapies are still not available in many countries and also very limited data exist about the efficacy of different re-treatment regimens.

In this study, we evaluated the sustained virological response rate at post-treatment week 12 in patients who did not respond to a previous SOF- based therapy.

Methodology

Study design and Aims

In this multicenter retrospective observation study including all chronic HCV patients who presented to New Cairo, Ain Shams, and Damietta Viral Hepatitis Treatment Centers to receive SOF-based anti HCV treatment during the period between October 2014 and October 2017.

Patients and Recruitment

Patients were included in the study according to the standardized protocol for HCV management issued by the Egyptian National Committee for Control of Viral Hepatitis (NCCVH) (Gomaa et al., 2017). Key exclusion criteria were: Child-Turcotte-Pugh (CTP) class C, hemoglobin level < 10 g/dl, platelet count <50,000/mm^3, hepatocellular carcinoma (HCC) except 6 months following a successful cure with proof of no recurrence by dynamic imaging (CT, MRI), extrahepatic malignancy except after 2 years of cure, co-infection with hepatitis B or HIV and hypersensitivity to any of the study medications.

Patients who failed to achieve SVR to an initial SOF-based antiviral therapy were scheduled to receive another DAAs-based therapy according to the available medication at the time of enrollment and the applied treatment protocol issued by NCCVH. Regimens used for re-treatment of patients who did not achieve SVR with the first DAA course of treatment are shown in Table 1. During the treatment period, patients were followed-up as scheduled by the treatment protocol every 4 weeks, where they were examined, had laboratory investigations (hematologic panel, liver biochemical profile, and creatinine), and interviewed for reporting of any adverse events. HCV PCR testing was performed 12 weeks after cessation of therapy to test for the sustained virological response (SVR12).

Outcomes

The primary outcome of the current study was to estimate SVR response rate to retreatment and to determine baseline predictors of failure to achieve SVR among prior non-responders to SOF-based therapies.

The study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki after approval from the Institutional Review Board (IRB) for human subject research at National Hepatology and Tropical Medicine Research Institute in Egypt (Serial: 28-2015). Written informed consent was obtained from all participants before enrolment in the study.

Statistical analysis

Data were expressed as number (percent) for categorical variables and as mean (± SD) or median (interquartile range) for continuous variables. Baseline data were compared per administered treatment as well as per treatment outcomes (SVR versus non-SVR). SVR rate was compared in study sub-groups (cirrhosis versus non-cirrhosis, treatment-naïve versus experienced). All quantitative parametric and nonparametric variables were analyzed using either Student's test or Mann–Whitney test for comparison of two groups whenever appropriate. A chi-square test was used for comparison of categorical variables (Table 2).

Table 1
Treatment regimens used for the studied patients according to NCCVH protocol.

Used regimen and indication	Dose
Sofosbuvir/Daclatasvir/ribavirin (SOF/DCV/RBV), for Child B cirrhotic patients previously treated with (SOF/DCV) and for relapsers on (SOF/SIM).	Once-daily oral sofosbuvir 400 mg, oral Daclatasvir 60 mg, and oral weight-based ribavirin for 12 weeks
Sofosbuvir/ledipasvir (SOF/LVD) for decompensated cirrhotic patients previously treated with SOF/RBV.	Once-daily oral sofosbuvir 400 mg and oral ledipasvir 90 mg for 24 weeks
Sofosbuvir/simeprevir (SOF/SIM), for non-cirrhotic and compensated cirrhotic patients previously treated with (SOF/DCV)	Once-daily oral sofosbuvir 400 mg and oral simeprevir 150 mg for 12 weeks
Paritaprevir/ombitasvir/ritonavir/ribavirin (r/PAR /OMB /RBV) for non-cirrhotic patients previously treated with (SOF/DCV/RBV)	Once-daily two oral tablets of (75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir) and oral weight-based ribavirin divided into two daily doses for 12 weeks
Sofosbuvir/ledipasvir/ribavirin (SOF/LDV/RBV) for decompensated cirrhotic patients previously treated with SOF/RBV.	Once-daily oral sofosbuvir 400 mg, oral ledipasvir 90 mg, and oral weight-based ribavirin for 12 weeks

Table 2
Baseline characters of the studied patients (n = 5235).

Variables	SVR, n = 5063	Non- SVR, n = 172	P value
Age, yrs.	52.2 ± 11.3	51.2 ± 11.3	0.635
Male gender	2431 (48.0%)	101 (58.7%)	**0.006**
BMI, kg/m^2	30.04 ± 5.8	31.7 ± 7.1	0.472
Hypertension, n(%)	879 (17.4%)	30(17.6%)	0.945
Diabetes, n (%)	1015 (20.1%)	45 (26.5%)	**0.04**
viral load, log $_{10}$	5. 6 ± 0.84	5.06 ± 0.84	**0.001**
ALT (IU/L)	52.9 ± 39.4	53.1 ± 41.4	0.625
AST (IU/L)	51.1 ± 34.6	57.9 ± 50.0	**0.079**
Total bilirubin (mg/dL)	0.81 ± 0.38	0.89 ± 0.42	**0.018**
Albumin (g/dL)	3.93 ± 0.49	4.02 ± 0.55	**0.264**
Hb (g/L)	13.5 ± 1.6	13.5 ± 1.6	0.355
WBC x10^3/mm^3	6.1 ± 2.1	5.8 ± 3.5	**0.001**
Platelets x 10^3/mm^3	195.1 ± 74.7	156.7 ± 69.9	**0.001**
INR	1.11 ± 0.151.1	1.15 ± 0.19	0.01
median AFP (IU/L), (IQR)	5 (7.0)	5 (6.0)	**0.783**
Creatinine (mg/dL)	0.84 ± .21	0.86 ± 0.24	**0.358**
Fasting blood glucose (mg/dL)	103.8 ± 28.8	103.2 ± 28.2	0.798
Fib-4	2.6 ± 2.5	4.02 ± 5.3	**0.001**
Cirrhosis, n (%)	3927 (77.6%)	128(74.4%)	**0.33**

Results

Among 5235 chronic HCV patients who received SOF-based antiviral therapy, 5063 patients successfully attained SVR12 [age: 52.2 ± 11.3; 48% men) and the remaining 172 patients [age: 52.2 ± 11.3, 58.7% men] were non-responders. The non-responders population was predominantly male (58.7%). In comparison to responders, patients with a previous non-response had significantly higher prevalence of diabetes millets (26.5% vs. 20.1%, p value 0.04), higher baseline AST (57.9 ± 50.0 vs. 51.1 ± 34.6, p 0.079), bilirubin (0.89 ± 0.42 vs. 0.81 ± 0.38, p value 0.018) and INR (1.15 ± 0.19 vs. 1.11 ± 0.151.1, p value 0.01) but significant lower platelets (156.7 ± 69.9 vs. 195.1 ± 74.7, p value 0.001) leucocytic counts (5.8 ± 3.5 vs. 6.1 ± 2.1, p value 0.001) and viral load (5.06 ± 0.84 vs. 5. 6 ± 0.84, p value 0.001). Baseline demographic, clinical and laboratory data of included patients are presented in Table 1.

The 172 patients with previous treatment non-response were assigned to the second course of DAAs according to the protocol of the Egyptian National Committee for Control of Viral Hepatitis (Table 3). Overall, SVR12 was successfully attained by 95.35% (164/172) of the non-responders.

All patients who failed to achieve SVR12 to initial SOF/SIM (n = 47) or SOF/LED (n = 2) were able to successfully attain SVR12 to the second DAAs course. The SVR12 rate stratified according to the initial received DAA therapy is shown in Table 4.

Table 3
virological response rate to retreatment, n = 172.

Regimen	SVR 12, n (%)	non SVR, n (%)	P value
SOF/DCV/RBV, n= 50	50 (100.0)	0 (0.0)	0.42
SOF/ r/PAR /OMB /RBV, n=98	91 (92.9)	7 (7.1)	
SOF/DCV/SIM, n= 22	21 (95.5)	1 (4.5)	
SOF/LDV ± RBV, n=1	1 (100.0)	0 (0.0)	
SIM/SOF, n= 1	1 (100.0)	0 (0.0)	

Table 4
Retreatment virological response according to initially received treatment regimen, n = 172.

Regimen	SVR 12, n (%)	non SVR, n = 8	P value
SOF/SIM, n = 47	47 (100.0%)	0 (0.0%)	0.25
SOF/DCV/RBV, n= 61	56 (91.8%)	5 (8.2%)	
SOF/DCV n= 62	59 (91.8%)	3 (4.8%)	
SOF/LDV, n = 2	2 (100.0%)	0 (0.0%)	

Discussion

Chronic HCV infection and its complications are considered major health problems in Egypt for many years, the genotypic distribution in Egypt is mainly genotype 4 (GT4) which accounts for more than 90% of the infections, the remaining percentage is caused by GT1 (Buti et al., 2015). The introduction of new interferon-free DAAs combinations significantly improved SVR rates in CHC patients. The use of combination therapy of DAAs provides a better outcome as it targets different segments of the HCV genome replication and accordingly will be associated with a lower risk of occurrence of resistance and improved efficacy of used regimens in HCV eradication (Sarrazin, 2016).

How to treat patients with a previous failure to DAAs either with or without interferon is an era of ongoing research. It was considered that previously used DAAs (with the same resistance profile) can lose their effect on viral eradication on subsequent use (Abdel-Moneim et al., 2018b). So, a combination of DAAs with variable viral targets, mechanisms of action and non-overlapping resistance profiles may enhance the antiviral activity, this will result in improved SVR for difficult to treat patients.

Wyles et al., 2015 (Wyles et al., 2015) found that patients who relapsed on SOF-containing regimens achieved a high rate of SVR12 when retreated with the fixed-dose combination of LDV-SOF with RBV.

The current study is a retrospective observational study done between October 2014 and October 2017 and included 5063 chronic HCV,172 patients failed to achieve SVR12 and the remaining 5063 achieved SVR.

A significant relation between SVR and fibrosis score (FIB-4) was observed in our study and this is consistent with what was concluded by Abdel- Moneim et al., 2018 (Abdel-Moneim et al., 2018b).

The initial treatment course received by the included relapsers were SOF/SIM (n = 47, 27.33%), SOF/DCV/RBV (n = 61, 35.47%), SOF/DCV (n = 62, 36.05%), and SOF/LED, (n = 2, 1.16%). We concluded that addition of RBV to the previously failed regimen did not improve success rate much (SVR response rate for SOF/DCV/RBV and SOF/RBV relapsers were 91.80 % and 95.16 respectively) this state is in contrary with what Buti and Esteban said in their review (Buti et al., 2015).

In the current study, treatment regimens were selected according to the NCCVH protocol to provide the maximum efficacy and minimize the risk of failure as far as possible depending on the combination of 3 DAAs or 2 DAAs + RBV taking into consideration use of drugs with a different mechanism and higher barrier of resistance than the previously used regimen for the same patient SOF/ r/PAR /OMB /RBV was the most widely used combination in our study (56.98%), followed by SOF/DCV/RBV (29.07%), SOF/DCV/SIM (12.79%), SOF/ LDV + RBV (0. 58%), and SOF/ SIM (0.58%), from the total number of relapsed patients, only 8 (4.65%) failed to achieve SVR (failure of retreatment) and 164 patients have achieved SVR (95.35%), our results are comparable to results obtained by Abdel-Moneim et al., 2018 in their retreatment study using SOF/PAR/OMB/RBV (Abdel-Moneim et al., 2018b); and their study of retreatment using SOF/DCV/SIM/RBV (Abdel-Moneim et al., 2018a).

In consistence with our results, the QUARTZ II-III study studied the efficacy of combining three DAAs: SOF + OMB/r/PTV/ with or without RBV in treatment-naïve patients with HCV genotype 2 or genotype 3 infections without cirrhosis or with compensated cirrhosis (Shafran et al., 2018).

In agreement with our results, Hézode and Christophe, et al., 2016 obtained SVR rate of 87.5% in retreatment of HCV patients

using SOF/SIM combination for 12 weeks (Hézode et al., 2016), and comparable to Lawitz, Eric, et al. 2014 results using the same combination (Lawitz et al., 2014).

In 2016, EASL issued guidelines for the treatment of HCV GT4 by including the combination of SOF and DCV with or without RBV for 12 weeks, EASL settled that treatment-naïve and treatment-experienced patients infected with HCV genotype 3 with cirrhosis should be treated with the combination of sofosbuvir and DCV for 24 weeks with daily weight-based ribavirin (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) (Esmat et al., 2012). So, Leroy et al., 2016 evaluated DCV/SOF plus ribavirin (RBV) in treatment-naive or treatment-experienced genotype 3 patients with advanced fibrosis or compensated cirrhosis for 12 weeks. SVR12 for intention-to-treat was 88%, while in patients with cirrhosis; SVR12 was 83% (Leroy et al., 2016).

The limitation of our study is that we couldn't do genotyping or study baseline RASs for financial reasons, which would be beneficial in predicting SVR.

In conclusion, all present alternatives provided by the NCCVH to treat relapsers, namely (SOF/ r/PAR /OMB /RBV, SOF/DCV/RBV, SOF/DCV/SIM, SOF/LED, and SIM/SOF) are safe and effective, with nearly 100% SVR except for SOF/ r/PAR /OMB which carries the least outcome of 92.86% only. Such results on a larger cohort of patients carry much hope and pave the way to our ambitious plan to eradicate HCV.

Authorship Statement: All authors supervised patients' treatment and follow up. Heba Omar and Marwa Tahoon performed the statistical analysis. Mohamed Alboraie, Mohamed El Badry, and Heba Omar drafted the manuscript, Mohamed El Kassas, revised and edited the manuscript. Mohamed El Kassas is responsible for the overall content as guarantor. All authors revised and approved the final version.

Disclosure of Funding Source

None.

Ethical approval

Institutional Review Board (IRB) for human subject research at National Hepatology and Tropical Medicine Research Institute in Egypt (Serial: 28-2015)

Conflict of interest

The authors declare no conflict of interest.

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