Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol.(5) Issue(5) Part (2) (2020), (251-256) **online: ISSN 2356–976x**
http://bjas.journals.ekb.eg

Efficacy and Safety of Sofosbuvir Based Therapy in Hepatitis C Genotype 4 Infection: Retrospective Review Medical Record

S.M.Kabil[1] , A.M.El-Sawy[2], R.S.El-Desouky[3], E.El Kharbotly[1], A.kandil[1] and I.A.Badr[4]
[1]Hepatology& Gastroenterology and Infectious Diseases Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
[2] Hepatology &Gastroenterology and Infectious diseases Dept., Egyptian Armed Forces, Egypt
[3]community medicine Dept., Faculty of Medicine, Benha Univ., Benha, Egypt
[4](M.B.B.Ch), Faculty of Medicine ,Ain Shams Univ.
E-Mail: islam90anwar@gmail.com

Abstract

Chronic Hepatitis C is endemic in many regions worldwide. Roughly 71 million people are infected with HCV all over the world .Egypt has been among the highest prevalence rates of HCV in the world**.** HCV is a major cause of chronic hepatitis, hepatic cirrhosis and hepatocellular carcinoma, moreover the most common cause of liver transplantation. Portal hypertension induced esophageal varices is one of life threatening complications results from liver cell failure leading to many mortalities and co-morbidities. The spread of HCV infection in Egypt is thought to be due to needle re-use during mass treatment programs for Schistosmiasis during late fifties till the early eighties. Unfortunately, transmission continues to occur, primarily through iatrogenic sources such as blood transfusion, injections and dental cares. Many lines of treatment were approved through years however the most promising ones the direct acting antivirals (DAAs) as those medications target specific steps within the HCV life cycle. A retrospective observational study, sample was based on provided data of 101 Egyptian Chronic HCV patients, how had been treated with sofosbuvir between the year 2015 and 2016 at one of the reference centers under the authority of MOHP compared with 101 egyptian patients infected with HCV who didn't receive any type of antiviral treatment. Baseline laboratories, HCV RNA PCR, abdominal ultrasound, upper GI endoscopy was done for all patients in both groups, same investigations was done after 3 months, 6 months, 1 year for both groups The sample included 202 patients, divided over 2 arms treated and untreated with proportion 1:1, mean age for the whole sample were 51.1 ± 10.3 years old with high prevalence to males more than females n = 129 (63.8%), n = 73 (36.1%) respectively. Baseline characters showed significant differences in ALT, AST, AFP, INR, HB, PLT, albumin, F-score, upper GI endoscope and proportion of patients with cirrhosis with p value < 0.05. After 3 months of treatment with DAAs patients had significant reduction of HB and PLT with p value 0.03 and 0.005 respectively. There was significant difference between treated and untreated arms in terms of progressive liver cirrhosis(p 0.0001) , ascites(p 0.0001) and HFL(p 0.005) favoring treatment group over untreated group. Majority of treated sample didn't experience relapse(96%) while only(5%) relapsed post treatment, multivariate analysis revealed that relapse is correlated to liver cirrhosis with p value 0.013, PCR after 3 months of finishing treatment with p value 0.0001, relapse was correlated with increased fatigability in treated patients with (p 0.0001) HCV PCR load showed significant correlation to relpase after 3 months, moreover HCV PCR after 3 months is significantly correlated to relpas. DAAs have Higher safety and tolerability and the side effects of three groups were not sever enough to lead to treatment discontinuation.

1. Introduction

In Egypt, awareness of population about HCV and its modes of transmission have contributed to decreasing incidence of new HCV infections during past decades, nonetheless performing many biomarker survey has improved accessibility to diagnosis and treatment for HCV, preventing fatal side effects and long term chronic viral burden [1]

HCV is divided into 6 main genotypes that mainly identified by the virulence of infections, natural course of infection and consequent complications [1], it is believed that genotypes can differ in nucleotide sequence in 30-35% of cases, however their subtyping is mainly dependent on infectivity and burden of disease [15].

Each subtype have certain prevalence and geographic distribution as we can interpret from WHO hepatitis reports north America and Europe have the highest prevalence of genotype 1, while genotype 2 and 3 more commonly affect those living in north America and japan , genotype 4 is the commonest in Egypt and north Africa, it is believed to be the most virulent one in terms of hepatic fibrosis and progression into hepatocellular carcinoma (HCC), finally south Africa and Hong Kong harbor genotype 5 and 6 more commonly [1].

46% of all HCV cases are estimated to harbor genotype 1, 30% are genotype 3, while 23% are genotypes 2 adding to that 4 and 6 are less than 1% of all HCV cases are genotype 5. HCV genotype 7 is a very rare genotype and it has been isolated in one patient from Central Africa [12].

HCV had potentials for altering both adaptive and innate immune responses of host after infection, T cell cytotoxic is the one responsible for adaptive immunity and removal of infected cells with viral particles, during acute hepatitis phase a specific T cells CD8+ are produced to decrease viremia while liver damage and elevated liver enzymes are thought to be due to production of interferon ϒ [14] .

Infection with HCV and HBV are the major risk factors for development of hepatocellular carcinoma (HCC). The mechanism by which HCV causes HCC is unknown, but several studies have indicated the role of core protein, as it induce oxidative stress and steatosis, Cellular signaling pathways are also

changed by core protein. The development of liver fibrosis and cirrhosis also increases the risk for HCC. Approximately 1-3% of HCV patients will develop HCC after 30 years of chronic infection. Age, alcohol consumption, obesity, diabetes, genotype and co-infection with HBV or HIV can all increase the risk of developing HCC in HCV infected patients [13] .

the Egyptian National Committee for Control of Viral Hepatitis (NCCVH), started the treatment with interferon regimen, followed by direct acting antivirals in the year 2014, in the same year ministry of health(MOH)of Egypt launched "Plan of Action for the Prevention, Care and Treatment of Viral Hepatitis", this initiative aimed for specific steps for prevention and control of chronic viral hepatitis including surveillance, infection prevention and control, blood safety, hepatitis B vaccination, care and treatment, communication, and research [3].

This initiative in the year 2014 enormously improved the outcomes of HCV patients, as vaccines for HBV and DAA for HCV were available for free for all diagnosed cases, in addition to availability of diagnostic test for those who are unknown in terms of HCV infection. Efforts exerted in this field has been of greatly upgraded to whole another level when Egyptian president started a national campaign for screening of HCV and treatment of infected individuals, this campaign has included 30 million Egyptians above 18 years old were screened with estimated incidence 6% of screened populations, infected individuals were referred to tertiary health care centers to start their treatment based on their laboratory findings including renal impairment, thrombocytopenia, hepatic profile and hepatic decomposition [5].

2. Methods

Retrospective observational study was conducted using archived files of patients in Hepatology & Gastroenterology and infectious diseases department, kobri el kobba military hospital, El sahel teaching hospital and El haram hospital, patients had been treated with sofosbuvir between the year 2015 and 2016 at one of the referral centers under the authority of MOHP eligibility criteria were age above 18 and less than 70 years old, patient diagnosed with chronic hepatitis C using HCV RNA PCR and Child A classification. Exclusion criteria included vitally unstable patients, ICU admitted patients, hepatic encephalopathy, HIV co-infection and decompensated liver disease.

Sampling

Using a convenient sample we collected 202 chronic hepatitis C patients when 101 of them received treatment regimens and 101 chronic hepatitis C patients not treated (refused treatment or ineligible for treatment initiation). Data were colleted from patient sought medical advice in 3 tertiary hospitals from 2015 till 2016.

2.1 Statistical analysis

Statistical analysis was conducted using STATA 12 software, Continuous variables were presented as mean and SD and inter-group differences were compared using t-test. Skewed numerical data were presented as median and average rank and between-group differences were compared using the Mann-Whitney U-test. Paired numerical data were compared using the paired t-test. Categorical variables were presented as number and percentage and differences between groups were compared using Pearson chi-squared test or Fisher's exact test. Ordinal data were compared using the chi-squared test for trend. Paired binary data were compared using the McNemar test, p-values <0.05 were considered statistically significant.

3. Results

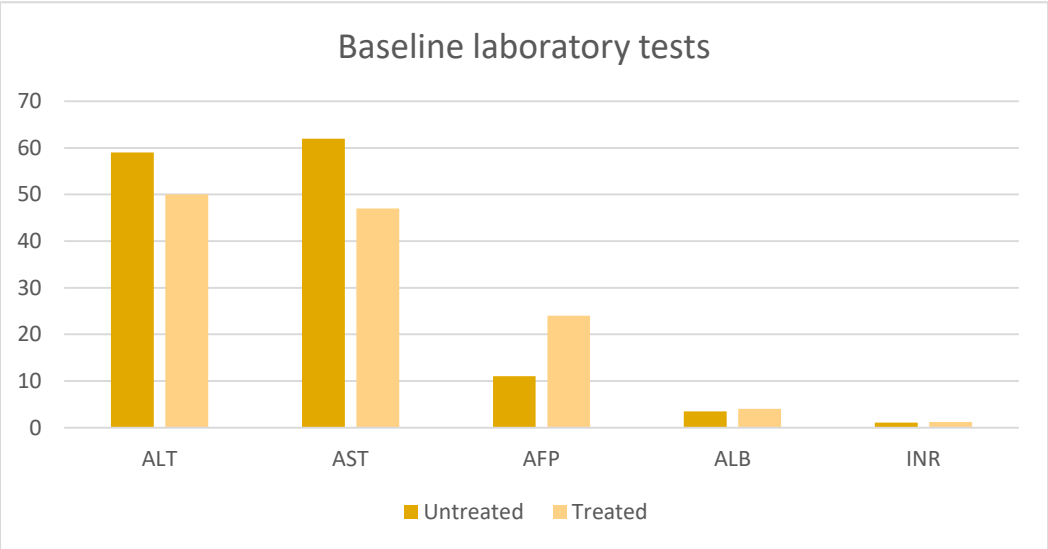
The sample included 202 patients, divided over 2 arms treated and untreated with proportion 1:1, mean age for the whole sample were 51.1 ± 10.3 years old with high prevalence to males more than females n = 129 (63.8%), n = 73 (36.1%) respectively with proportion 2:1, baseline characters are shown in table 1. Baseline characters showed significant differences in ALT, AST, AFP, INR, HB, PLT, Albumin, F-score, upper GI endoscope and proportion of patients with cirrhosis with p value < 0.05 Fig (1).

Table (1) baseline characters of both groups treated and untreated**.**

Item	Untreated	Treated	P value
Age	50.7 ± 10.3	51.6 ± 10.3	0.53
HCV PCR	1167787 ± 2289538	875048.5 ± 1490991	0.28
ALT	59 ± 26.8	50.1 ± 29	0.02
AST	62.3 ± 25.6	47.7 ± 25.7	0.0001
AFP	10.7 ± 9.6	23.9 ± 48.3	0.007
ALB	3.48 ± 0.49	3.98 ± 0.49	0.0001
BIL	0.9 ± 0.33	0.92 ± 0.34	0.76
HB	12.4 ± 1.3	12.7 ± 1.24	0.048
Creatinine	0.86 ± 0.27	0.85 ± 0.23	0.67
INR	1.1 ± 0.12	1.18 ± 0.20	0.0001
Platelets	142 ± 36.7	183.5 ± 69.9	0.0001

Table (1) Continue

Gender					
Male	60	(59.4%)	69	(68.3%)	0.18
Female	41	(40.6%)	32	(31.7%)	
Treatment status					
Naïve	101	(100%)	96	(95%)	Na
Experienced	0	(0%)	5	(5%)	
HBs-Ag					
Positive	0	(0%)	0	(0%)	Na
Negative	101	(100%)	101	(100%)	
Liver parenchyma by US					
Normal	17	(16.8%)	62	(61.4%)	0.0001
Cirrhosis	84	(83.2%)	39	(38.6%)	
Spleen size by US					
Normal	46	(45.5%)	53	(52.5%)	0.32
Enlarged	55	(54.5%)	48	(47.5%)	
F- score					
Normal	0	(0%)	6	(5.9%)	0.0001
F1	13	(12.8%)	64	(63.4%)	
F2	17	(16.8%)	29	(28.7%)	
F3	29	(28.8%)	1	(1%)	
F4	42	(41.6%)	1	(1%)	
Upper endoscopy					
Free	21	(20.8%)	80	(79.2%)	0.0001
Esophageal varices G1	29	(28.7%)	7	(6.9%)	
Esophageal varices G2	31	(30.7%)	14	(13.8%)	
Esophageal varices G3	15	(14.8%)	0	(0%)	
Esophageal varices G4	5	(5%)	0	(0%)	
HFL					
Yes	0	(0%)	1	(1%)	0.31
No	101	(100%)	100	(99%)	
Ascites					
Yes	0	(0%)	1	(1%)	0.31
No	101	(100%)	100	(99%)	



After 3 months of treatment with DAAs patients had significant reduction of Hb and PLT with(p value 0.03 and 0.005) respectively. After 3 months of ending treatment in treated group compared to patients in untreated group there was significant difference in HCV PCR ,ALT ,AST, ALB, creatinine, INR and PLT with(p value <0.05). There was significant difference between treated and untreated arms in terms of progressive liver cirrhosis (p value 0.0001), ascites (p value 0.0001)and HFL(p value 0.005) favoring treatment group over untreated group.

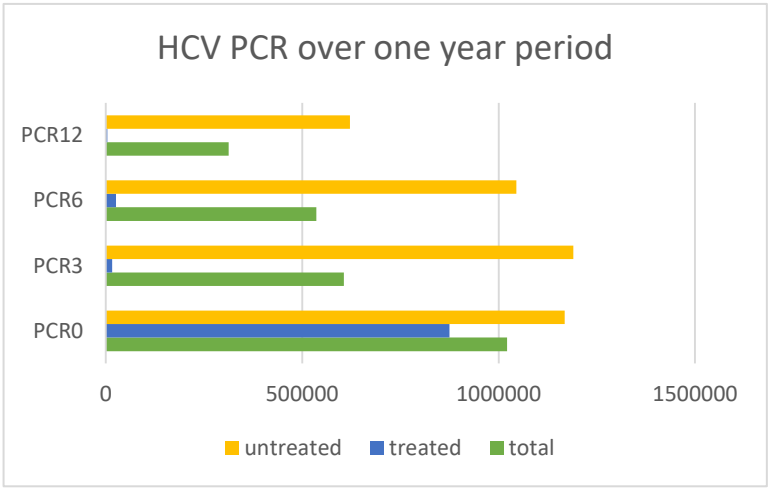
Table (2) Comparison between treated and untreated group after 3 months of ending treatment regimen.

Lab test	Untreated	Treated	P value
HCV PCR	1190136 ± 2289138	16206 ± 125709	0.0001
ALT	59.15 ± 25.2	32.5 ± 15.3	0.0001
AST	60.1 ± 27	38.9 ± 18.9	0.0001
ALB	3.16 ± 0.38	3.8 ± 0.41	0.0001
BIL	0.9 ± 0.24	0.94 ± 0.47	0.458
HB	12.4 ± 1.6	12.3 ± 1.19	0.58
Creatinine	1.11 ± 0.16	0.82 ± 0.2	0.0001
INR	0.94 ± 0.38	1.28 ± 0.22	0.0001
Platelets	123.9 ± 28.5	146.5 ± 39.8	0.0001
Liver parenchyma by US			
Normal	17 (16.8%)	62 (61.4%)	0.0001
Cirrhosis	84 (83.2%)	39 (38.6%)	
Spleen size by US			
Normal	46 (45.5%)	53 (52.5%)	0.32
Enlarged	55 (54.5%)	48 (47.5%)	
Ascites			
Yes	21 (20.8%)	1 (1%)	0.0001
No	80 (79.2%)	100 (99%)	
HFL			
Yes	14 (13.8%)	3 (3%)	0.005
No	87 (86.2%)	98 (97%)	
Pre-coma			
Yes	0 (0%)	2 (2%)	0.155
No	101 (100%)	99 (98%)	

After 6 months after finishing treatment in treated arm and 6 months in untreated group there was significant higher rates of HCV complications in untreated groups including progressive liver cirrhosis, development of HFL, ascites and incidence of pre hepatic coma with p values 0.0001, 0.005, 0.0001 and 0,002 respectively.

Table (3) Comparison between treated and untreated group after 6 months and one year of treatment.

Lab test	6 months			One year		
	Untreated	**Treated**	**P value**	**Untreated**	**Treated**	**P value**
HCV PCR	1045222 ± 2089525	25902.57± 244441.6	0.0001	621561.3±13 16971	3743.1±17725.8	0.0001
ALT	52.2 ± 27.3	27 ± 10.8	0.0001	58.9±29.3	23.9±7.9	0.0001
AST	51 ± 25.2	34.9 ± 11.4	0.0001	56.5 ± 28	33±13.2	0.0001
ALB	3 ± 0.3	3.8 ± 0.47	0.0001	2.9 ± 0.2	3.8±0.46	0.0001
BIL	0.94 ± 0.41	0.89 ± 0.44	0.0001	1.1 ± 0.44	0.9±0.5	0.008
HB	11.6 ±1.17	12.3 ±1.1	0.42	10.7 ± 0.9	13.3±1.4	0.0001
Creatinine	1.5 ± 0.36	0.7 ± 0.2	0.0001	1.6 ± 0.3	1±0.34	0.0001
INR	1.1 ± 0.2	1 ± 0.13	0.03	1.3 ± 0.2	1.1±0.13	0.0001
Platelets	121± 28.5	161 ± 56.5	0.0001	112.7±24	203.7±67.8	0.0001
Liver parenchyma US						
Normal	8 (8%)	62 (61.4%)	0.0001	6 (6%)	62 (61.4%)	0.0001
Cirrhosis	93 (92%)	39 (38.6%)		95 (94%)	39 (38.6%)	
Spleen size by US						
Normal	46 (45.5%)	53 (52.5%)	0.32	46 (45.5%)	53 (52.5%)	0.32
Enlarged	55 (54.5%)	48 (47.5%)		55 (54.5%)	48 (47.5%)	
Ascites						
Yes	34 (33.6%)	1 (1%)	0.0001	41 (40.6%)	1 (1%)	0.0001
No	67 (66.4%)	100 (99%)		60 (59.4%)	100 (99%)	
HFL						
Yes	14 (13.8%)	3 (3%)	0.005	27 (26.7%)	3 (3%)	0.0001
No	87 (86.2%)	98 (97%)		74 (73.3%)	98 (97%)	
Pre-coma						
Yes	14 (13.8%)	2 (2%)	0.002	39 (38.6%)	2	0.0001
No	87 (86.2%)	99 (98%)		62 (61.4%)	(2%) 99 (98%)	
Relapse						
Yes	-	5 (5%)	Na	-	5 (5%)	Na
No		96 (95%)			96 (95%)	



After one year of finishing treatment in treated arm and untreated group more complications were reported in untreated group, there was significantly higher rates of liver cirrhosis, ascites, HFL and pre hepatic come with p value 0.0001, 0.0001, 0.0001 and 0.0001 respectively. Majority of our treated sample didn't experience relapse 96% while only 5% relapsed post treatment, multivariate analysis revealed that relapse is correlated to liver cirrhosis with p value 0.013, PCR after 3 months of finishing treatment with p value 0.0001, relapse was correlated with increased fatigability in treated patients with p value 0.0001. Relapse wasn't correlated to baseline HCV PCR with p value 0.92, nor fibro-score with p value 0.61, besides age, gender, treatment status with p value >0.05, nonetheless baseline cirrhosis was significantly correlated to relapsed cases with p value 0.001.

4. Discussion

Egypt is situated as the country with the highest prevalence of Hepatitis C virus worldwide mainly transmitted through not scanned blood transfusions, different employments of syringes, and poor cleansing, as per the WHO, the introduction of direct acting antiviral agents shifted the management of chronic HCV infection to a new level [1].This study was conducted on double arm treated versus untreated population infected with HCV and confirmed by HCV PCR to show viral load mean age was 51.1 years old which is slightly higher than other studies conducted in the same country 2) however when compared to other studies conducted in 69 years old in a European center [5]. On other hand, males had the majority of samples reported in many studies including European , north American and north African representing 55-60% [9], however a cohort study conducted in rural areas of Egypt proved that majority of sample were females 57% versus 43% males (9. In the current study 95% (96 patients) had SVR12 while only 4% (5 patients) relapsed after 3 months of end of the treatment compared to other authors conducted cohort studies using same DA As including Sofosbuvir plus Daclatasvir on Egyptian populations reported almost same SVR12 96% [5]. In this study we had a 95% of our sample treatment naïve which is considered a large proportion of population selected, 38.9% had liver cirrhosis on baseline investigations which represent that lesser portion than 9) 54%, nonetheless SVR12 were a pit lower than our study 91%. In a study by [10]. reported lower SVR12 when using Sofosbuvir plus Daclatasvir was 88.9%, this low level of SVR could be explained by the fact that studied group included patients who are difficult to treat, as they were treatment-experienced or had an advanced liver disease, while Another large study conducted by [13] in Egypt documented considerably high SVR12 in patients receiving generic Sofosbuvir and Daclatasvir. All side effects in current study were tolerable and didn't require any discontinuation of treatment or reported any deaths as only 5-7% experienced side effects such as nausea, fatigue, hepatic encephalopathy and headache which mimic what is reported in many other studies [9], on the other hand [11] investigated side effects of DAAs specifically Sofosbuvir and Daclatasvir on a sample of 96 patients but he listed that side effects were much higher than reported in our study with 42.5% of those patients developed adverse events 27.5% suffered from fatigue, 25% headache, 7.5% nausea, 10% insomnia, 3% nausea, and 4% diarrhea. HCV PCR load showed significant correlation to relpase as PCR after 3 months of ending treatment, so it can be used in future follow up plans as an indicator for disease relapse and treatment resistance. Current study showed significant decline in liver transaminases after completion of treatment with p value 0.0001 as shown in the figure below, this came in cosistance with [14]. In the current study, neither age nor any of baseline laboratory tests including haemoglobin, platelet count, ALT, AST, albumin, INR, bilirubin, and PCR for HCV RNA showed

significant correlation with treatment outcome. At the end we conclude that untreated population had worse outcomes in terms of liver cirrhosis, development of HCC, hepatic encephalopathy, cirrhosis and ascitice with p value <0.05, relpase in addition to treatment resiatance is significantly correlated to PCR after 3 months of ending treatment which can be used in future as a surrogate indicator for treatment resistance.

5. Conclusion

All side effects of DAAs regimens in current study were tolerable and didn't require any discontinuation of treatment or reported any deaths. HCV PCR load showed significant correlation to relpase after 3 months of ending treatment. Age, pretreatment laboratory tests including haemoglobin, platelet count, ALT, AST, albumin, INR, bilirubin, and PCR for HCV RNA showed significant correlation with treatment outcome. Untreated population had worse outcomes in terms of liver cirrhosis, development of HFL, HCC, hepatic encephalopathy, cirrhosis and ascites. Relpase and treatment resiatance is significantly correlated to PCR after 3 months of ending treatment which can be used in future as a surrogate indicator for treatment resistance.

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