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Tolerance and Effectiveness of Oral Direct Acting Antivirals in Treatment of HCV Egyptian patients with Decompensated Liver Cirrhosis

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ABSTRACT

Background: Medical treatment of decompensated cirrhosis due to hepatitis C virus (HCV) remains a clinical challenge even in the era of direct-acting antiviral drugs (DAAs). We evaluated the efficacy and safety of DAAs in the management of HCV-related decompensated cirrhosis.

Objective: The current study aimed to evaluate the efficacy and safety of DAAs in managing HCV patients with decompensated cirrhosis and the impact of achieving sustained virological response on improving the quality of life, short term survival and if viral eradication would step down CTP score.

Patients and Methods: The study included a treatment group I (n = 25) composed of HCV patients with decompensated cirrhosis Child B and group II (n = 22) with decompensated cirrhosis Child C. both groups received DAAs (sofosbuvir 400 mg, daclatasvir 60 mg) plus ribavirin as tolerated for 3 months and follow-up was done for 6 months.

Results: In both treated groups, there were improvements in platelet count, albumin, Child-Torcout-Pugh (CTP) (p = 0.001) and a significant reduction in the frequency of hepatic encephalopathy (HE). Also, there was improvement in quality of life of both treated groups.

Conclusion: Treatment of HCV with decompensated cirrhosis with DAAS had improved CTP score, quality of life and survival.

Keywords: Direct Acting Antivirals, HCV, Decompensated Liver Cirrhosis

INTRODUCTION

The treatment varieties for patients with HCV-related decompensated cirrhosis remain a challenge. With the introduction of oral direct-acting antiviral (DAAs), SVR had been achieved in more than 90% with reduced risk of decompensation that needs liver transplantation. Reduced rates of SVR in decompensated cirrhosis were explained by the extensive porto-systemic collaterals and advanced fibrotic parenchyma which provides dormant foci for viral reactivation [(1)]. Achieving SVR is expected to improve portal hemodynamics and hepatic venous pressure gradient [(2)].

DAAs may induce rapid loss of anti-HCV immune responses with re-differentiation of memory T cell, T-lymphocyte deactivation, and normalization of NK-cell function leading to loss of immunological barrier against carcinogenesis [(3)].

Viral clearance is expected to be associated with reduced morbidity and mortality rates [(4)]; however, the important question that should be asked is SVR beneficial in reversing the functional hepatic impairment although it appears that they reached a point of no return.

AIM OF THE WORK

The current study aimed to evaluate the efficacy and safety of DAAs in managing HCV patients with decompensated cirrhosis and the impact of achieving sustained virological response on improving the quality of life, short term survival and if viral eradication would step down CTP score.

PATIENTS AND METHODS

Study design and patients selection

The study was conducted from the first of November 2017 till March 2019 in The Internal

Medicine Department of Al-Azhar University Hospitals (a tertiary referral center) in Egypt.

50 patients with decompensated cirrhosis were selected to receive DAAs. Patients were included if HCV-related decompensated cirrhosis was proved by the positivity of HCV RNA, elevated transaminases, ascites or frequent attacks of hepatic encephalopathy and CTP score > 7 [(5)].

Patients were excluded if they had compensated cirrhosis; exposure to previous antiviral therapy; hepatocellular carcinoma; grade III, IV hepatic encephalopathy; other causes of liver diseases, previous liver transplantation; patients with cardiomyopathy (left ventricular ejection fraction less than 50%).

Then treated patients were divided into two groups; group I (n=25) Child B classification and group II (n=22) Child C classification. Three patients died from sepsis and bleeding in group II during treatment so, were excluded from study.

The study patients were collected from the first of November 2017 till March 2019 and then the period follow-up was extended to three months after treatment.

A complete history taking and meticulous clinical examination were done for all of the patients to document features of liver cirrhosis and decompensation.

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Ethical approval and written informed consent:

An approval of the study was obtained from Al- Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Baseline laboratory investigation

Investigations preliminary to antiviral therapy: liver and kidney function tests, HBA1c if diabetic and serum AFP and CTP score were calculated.

Quantitative assessment of HCV load in the serum by real time quantitative PCR just before the study in both groups and after the first month, at the end of treatment and 3 months, 6 months post-treatment to detect SVR 12th, 24th in DAAs treated groups.

Medications

The treated patients in both groups were given sofosbuvir 400 mg, ribavirin 400–1000 mg, and daclatasvir 60 mg daily for 3 months. Ribavirin was added at a low dose and titrated up according to tolerability to avoid the occurrence of drug-induced anemia. In addition they were given supportive therapy which included diuretics for ascites. Post-treatment evaluation included sustained virological response (SVR), development of complications and impact of SVR on frequency of hepatic encephalopathy (HE), ascites control and short-term survival defined as a survival that extends more than 1 year after termination of DAAs.

Monitoring

All the patients had regular weekly visit during treatment period. Patients' evaluation in every visit included a full history taking, clinical examination and routine laboratory investigations.

Serious complications which required hospital admission during treatment were recorded such as life-threatening infections, gastrointestinal bleeding, hepatic encephalopathy, difficult-to-treat ascites, hepatocellular carcinoma, and death.

Difficult-to-treat ascites was defined as ascites that rapidly recurs after paracentesis or cannot be completely mobilized despite sodium restriction of less than 2 g/day with maximal dose of furosemide (160 mg) or spironolactone (400 mg) or inability to reach maximum diuretic dose due to emergence of side effects, and after confirming compliance with sodium restrictions proved by the 24-h urine sodium < 78 mEq.

Outcome evaluation:

The primary outcome was achievement of SVR 12^{th} and 24th defined as undetectable HCV RNA by real time quantitative PCR at 12 and 24 weeks, respectively after end-of treatment.

Secondary outcomes included intra-group improvement of the liver synthetic function, improvement in frequency or grading of hepatic encephalopathy and ascites control defined by significant weight loss > 10% with reduction or complete disappearance of ascites by ultrasonography, change in CTP score, and the occurrence of side effects during the period of study or death.

Statistical analysis

All data were analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA). Results were expressed as mean ± SD and range or as frequency and percentage. Categorical variables were analyzed using the $\chi 2$ test or Fisher's exact test and continuous variables were analyzed using the Student's t test. Independent t-test was used to compare means of 2 different groups and paired t-test was used to compare means of the same group before and after treatment. $P < 0.05$ was considered to be statistically significant.

RESULTS

Table 1 shows the baseline characteristics of both groups.

Table (1): Comparison between Group I: Child B and Group II: Child C according to parameters before treatment.

Before	Group I: Child B (n=25)	Group II: Child C (n=22)	p-value
Treatment Status			
Treatment Naïve	25 (100.0%)	22 (100.0%)	1.000
Alcohol Intake			
No	25 (100.0%)	22 (100.0%)	1.000
Quant (IU/ml)			
Mean±SD	732789±747288	5680199±15875009	0.126
Range	7900-2206000	911-74000000	
ANA			
Negative	25 (100.0%)	22 (100.0%)	1.000
WBC x10^3/mm^3			
Mean±SD	4.99±1.98	5.35±2.09	0.541
Range	2.3-10.4	1.9-10	
HBs Ag			
Negative	25 (100.0%)	22 (100.0%)	1.000
Liver			
Abnormal Echo pattern	14 (56.0%)	0 (0.0%)	<0.001**
Cirrhotic liver	10 (40.0%)	22 (100.0%)	
Normal	1 (4.0%)	0 (0.0%)	
PV			
Patent	25 (100.0%)	22 (100.0%)	1.000
Presence of focal lesions			
No	25 (100.0%)	22 (100.0%)	1.000
Upper Endoscopy			
No varices	1 (4.0%)	1 (4.5%)	0.824
Not Performed	18 (72.0%)	14 (63.6%)	
Varices	6 (24.0%)	7 (31.8%)	
Varices			
Eradicated	4 (16.0%)	7 (31.8%)	0.374
Non Risky	2 (8.0%)	0 (0.0%)	

Outcome of the study

Forty seven patients (35 males, 12 females) showed 23 patients with ascites. 7 patients experienced chronic recurrent episodes of hepatic encephalopathy grade II.

After 3 months, all the patients included in the study had completed the course of therapy without any reported major complications. There was a significant improvement in the baseline laboratory parameters as shown in Table 2.

7 patients had experienced chronic episodic hepatic encephalopathy before initiation of DAAs, but during the period of treatment and till the end of follow-up, a significant reduction in the number of patients who experienced hepatic encephalopathy was noted; only 2/47 still experiencing HE ($p = 0.002$). Additionally, the frequency of episodes was significantly reduced from 2.1 ± 0.6 to 1.4 ± 0.2 episodes/2.9 ± 0.9 months, ($p = 0.003$) (Table 2).

Ascites was prevalent in 23 patients before DAAs. After treatment, it became completely controlled in 40 patients, partially controlled in 7 patients (Table 2).

10 patients gave previous history of variceal bleeding with regular endoscopic surveillance aiming for variceal eradication; 29 patients showed grade I–II non-risky esophageal varices (EV) and followed up every 4–6 months 6. During the period of treatment and follow-up only 3 patients had experienced attack of variceal bleeding with no recorded deaths (Table 2).

Table (2): Comparison between the two studied groups according to clinical signs of liver decompensation before and after treatment

	Group I				Group II			
	Before		After		Before		After	
	No.	%	No.	%	No.	%	No.	%
Ascites	(n =25)		(n =25)		(n=22)		(n =22)	
No	22	88	24	96	2	9	5	23.8
Mild	3	12	1	4	7	31.8	10	45.2
Moderate	0	0	0	0	13	59.2	7	31.8
Tense	0	0	0	0	0	0	0	0
Significance	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$							
Encephalopathy	(n =25)		(n =25)		(n =22)		(n =22)	
No	24	96	25	100	16	74	20	90
Yes	1	4	0	0	6	26	2	10
Significance	$p_1=0.003^*$,$p_2<0.001^*$,$p_3<0.001^*$							
Variceal bleeding	(n =25)		(n =25)		(n =22)		(n =22)	
No	22	88	25	100	15	68	19	86
Yes	3	12	0	0	7	32	3	14
Significance	$p_1<0.001^*$, $p_2=0.008^*$, $p_3<0.001^*$							

Before starting DAAs treatment and After DAAs therapy, more than 30 patients (55.5%) had improvement in CTP score as shown in table 3.

Table (3): Comparison between the two studied groups according to Child-Torcout-Pugh (CTP) score before and after 6 months

	Group I				Group II			
	Before		After		Before		After	
	No.	%	No.	%	No.	%	No.	%
CTP class	(n =25)		(n =25)		(n =22)		(n =22)	
A	0	0.0	18	75	0	0.0	0	0.0
B	25	100	7	45.3	0	0	12	55
C	0	0.0	0	0.0	22	100	10	45
Significance	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$							
CTP score	(n =25)		(n =25)		(n =22)		(n =22)	
Min. – Max.	7.0 – 11.0		5.0 – 11.0		7.0 – 11.0		7.0 – 15.0	
Mean ± SD.	8.37 ± 1.19		7.14 ± 1.58		8.41 ± 1.22		10.16 ± 2.64	
Median	8.0		7.0		8.0		9.0	
Significance	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$							

Also, there was improvement in quality of life in treated groups before and after treatment as showed in (table 4)

Table (4): Comparison between the two studied groups according to Quality of life by Mcguill score before and after treatment.

Quality of life by Mcguill score	Group I: Child B (n=25)	Group II: Child C (n=22)	p-value
Before			
Mean±SD	107.39±16.86	105.06±16.33	>0.05
Range	87.6-122.6	87.6-122.6	
After 24 weeks			
Mean±SD	122.07±25.11	82.73±20.33	<0.001**
Range	9.3-140.1	13.4-122.6	
Diffence before vs. After 24wks	14.68	-22.33	
p-value	***<0.001*****	***<0.001*****	

DISCUSSION

The benefits of eradicating HCV virus in decompensated liver disease may be greater than other patients. The results of oral DAAs in the management of HCV-related liver disease are undoubted [(6)], however, their use in patients with decompensated cirrhosis is challenging especially in those who may frequently experience worsening of hepatic decompensation[(7)].

The current study evaluated the impact of DAAs on patients with decompensated cirrhosis regarding outcome, quality of life and survival in this special category of HCV patients.

In our study. The rate of SVR in the current study was 100% and treatment was well tolerated without discontinuation or non-compliance.

The treated groups showed an improvement in CTP score, suggesting the benefits of therapy in this category of patients and that was supported by a study which reported that even in non-responders to antiviral therapy; there was a modest improvement in CTP score[(8)], in addition, 55% of the treated patients had improved CTP score in both groups and became deferred completely from consideration for liver transplantation at the end of follow-up period and this finding shed light on an overlooked advantage of DAAs therapy in decompensated cirrhosis.

Patients who achieved SVR showed a significant reduction in the frequency of hepatic encephalopathy episodes, improvement in the management of ascites.

In studies which enrolled patients with decompensated cirrhosis due to HCV as SOLAR-1, SOLAR-2; SVR rates were lower when liver disease was progressive being 96% in patients without cirrhosis or 60–75% in patients with severe hepatic impairment [(9)]. In SOLAR-2, though a few patients infected with HCV genotype 4 were enrolled; it showed that DAAs were safe and well tolerated [(10)].

The ALLY-1 study evaluated the administration of sofosbuvir, daclatasvir and ribavirin in patients with advanced cirrhosis or post-transplant HCV recurrence involving all of the genotypes. 83% of the patients achieved SVR12. SVR in HCV-G4 in this study was 100%; however, the number of patients was small (4/4). Treatment was well tolerated, with no adverse events [(11)].

The use of sofosbuvir with daclatasvir or ledipasvir in decompensated cirrhosis was associated with improvement in CTP and MELD scores and synthetic liver function [(12-13)] and that was supported also by the meta-analysis of **Guarino *et al.*** [(14)].

In conclusion, this real-life study had enrolled an adequate number of patients with HCV genotype 4-related decompensated cirrhosis. Treatment of decompensated cirrhotic patients with CTP > 7 by a 3-month course of DAAs had led to SVR in 100% with improvement in CTP score and a significant reduction in hepatic encephalopathy episodes with better control of ascites and improved quality of life and short-term survival.

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