

The Impact of Achieving Sustained Virological Response with Direct Acting Antivirals on Gastroesophageal Varices and Variceal Bleeding.

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ABSTRACT

Background: The effect of treating chronic (HCV) by direct acting antiviral drugs (DAA) on gastroesophageal varices and variceal bleeding remain unclear

Aim of the study: To evaluate the effect of achieving SVR with DAA interferon free regimens on gastroesophageal varices.

Patients and Methods: prospective study we enrolled 200 patients with chronic HCV infection and gastroesophageal varices, Patients were treated with interferon free DAA, we had followed all patients for gastroesophageal varices size, site, risky signs as well as development of acute variceal bleeding before and six months after achieving sustained virological response (SVR)

Results: Development of acute variceal bleeding higher was in non SVR group B versus SVR group A (15% in SVR group versus 35% in non SVR group), significant higher mortality rate in non SVR group 10 % versus 1.1 % in SVR group, significant improvement variceal size in SVR group A as large varices (F3) become 11.2% six months after treatment versus 29.4% before treatment, still no significant changes regarding variceal size in non SVR group B. Significant improvement in variceal risky signs was found in SVR group, as risky variceal signs were presented in 143 (79.4%) patients before treatment versus 111 (62.4%) patients six months after treatment

Conclusion: We concluded that there is a reduction in size, risky signs of gastroesophageal varices and reduction in the risk of variceal bleeding and mortality rate after achieving SVR using interferon free regimens. These findings magnify the importance of early diagnosis and treatment of HCV infected patients

Keywords: hepatitis c virus; cirrhosis; portal hypertension; gastroesophageal varices.

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INTRODUCTION

Hepatitis C virus (HCV) is a worldwide health problem as HCV is a leading cause of morbidity and mortality that is explained mainly by high incidence of complications of liver cirrhosis as portal hypertension, liver cell failure and hepatocellular carcinoma.¹

Gastroesophageal varices are a serious consequence of portal hypertension that happen in about 50 % of cirrhotic patients, Variceal development happens mainly with of Clinically significant portal hypertension CSPH (hepatic venous pressure gradient HVPg ≥ 10 mmHg),² and occurs with a rate of 7-8% annually and progresses from small to large

varices by a rate of 10-12% annually, more seriously Variceal hemorrhage occurs by a rate of 5% annually

and if happens mortality rate would be as high as 15-25 %.³

With introduction of Direct-acting antivirals (DAA) a high rate of sustained virological response (SVR) exceeding 95 % with good safety and tolerability profile already achieved even in difficult-to-treat groups,^{4,5} accordingly nowadays almost all patients infected with HCV are advised to receive HCV treatment to decrease or to avoid its serious complications.⁶

Despite some data from previous studies revealed the beneficial effect of SVR achieved by DAA interferon free regimens on improvement of liver fibrosis,⁷

Moreover improvement of portal hypertension in a short term after SVR had been reported by some studies,⁸ Still scanty data present around the effect of SVR after DAA interferon free regimens on gastroesophageal varices and variceal bleeding. So, we conducted this study to evaluate the effect of achieving SVR with DAA interferon free regimens on gastroesophageal varices.

PATIENTS AND METHODS

In a prospective study that was done at Tanta University Hospital, Hepatology Gastroenterology and Endoscopy unit, from January 2019 to January 2021, we recruited our patients from those who presented to hepatology clinic with chronic hepatitis C virus infection and came for receiving HCV treatment, We included patients with chronic HCV and gastroesophageal varices candidate for DAA interferon-free regimens, after treatment we divided our patients into two groups group A (achieved SVR (defined by undetectable HCV RNA by real-time PCR at 12 weeks after end of treatment)⁹, Group B patients failed to achieve SVR from first time treatment (Non SVR), The most common DAA regimen was sofosbuvir/Daclatasvir followed by sofosbuvir/Ledipasvir.

Our exclusion criteria were:

- Patients with multiple comorbidities as chronic cardiac or renal disease.
- Age more 70 years old.
- Patients with hepatitis B virus, HBV co infection HCV or mixed caused of liver disease.
- Patients with alcohol intake.
- Patients with no gastroesophageal varices.
- Patients with hepatocellular carcinoma (either recently discovered or previously ablated).
- Patients who developed variceal bleeding within 90 days after DAA initiation.

We included 206 chronic HCV variceal patients who were candidate for DAA interferon free regimens. All patients underwent a full history taking, full clinical examination, as well as pretreatment radiological evaluation (ultrasound with or without triphasic liver C.T) prior to treatment and 6 month after treatment with the size of the spleen and portal vein diameter recorded, Esophagogastro-duodenoscopy (EGD) with documentation of the size, site and risky signs of the varices, patients with risky varices were subjected to variceal band ligation prior to HCV treatment, Investigations as full liver functions, full blood count, renal functions, alfa fetoprotein were done to all patients also Child-Pough scoring were applied to all patients before and 6 months after treatment, All patients had real time PCR at 12 weeks after treatment, all patients will be subjected to regular follow up upper endoscopy on 3-6 months interval, any bleeding episode after 90 days from DAAS therapy will be documented, after starting DAA 6 patients were excluded as (3 patients

died, 2 patients stopped treatment due to development of hepatic decompensation, 1 patient lost stopped follow up), So only 200 patients were enrolled in our study and divided into two groups : Group A: who achieved SVR (N= 180 patients); Group B: who failed to achieve SVR (non SVR, N=20 patients).

27 patients from group A as well as 7 patients from group B developed acute variceal bleeding, patients were presented to our emergency department with acute upper GIT bleeding episode, those patients underwent resuscitation by administration of colloids, crystalloids and blood transfusion according to hemoglobin level then patients underwent urgent EGD for control of bleeding, still 2 patients from group A and 2 patient from group B presented with sever bleeding and died before urgent EGD, For other patients Varices were classified by its site according to Sarin classification and by its size according to Japanese classification of varices,^{10,11} The severity of variceal bleeding episode was assessed by APASL (Asian Pacific Association for Study of the Liver score) the APASL severity score is the sum of five parameter's points, systolic blood pressure, Child-Turcotte-Pugh class, Platelet count, Infection and active bleeding at endoscopy).¹² All data were collected and statistically analyzed.

The research was conducted in line with the ethical principles of the Declaration of Helsinki.

Statistical Analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0 Quantitative data were expressed as mean \pm standard deviation (SD). Qualitative data were expressed as frequency and percentage. These tests were done in this study: Independent-samples t-test of significance was used when comparing between two means and Chi-square (X^2) test of significance was used to compare proportions between two qualitative parameters.

RESULTS

Basic Characteristics of study groups are shown in (table 1), no significant differences founded between the two groups related to age and sex, however significant predominance of Child-Pough A in SVR group A (139 patients 77.2%) versus Non SVR group B (5 patients 25%) with P-value 0.001. The main used DAA regimen in SVR group was sofosbuvir/Daclatasvir (150 patients 83.3%), However the main DAA regimen used in Non SVR group was sofosbuvir/Daclatasvir/Ribavirin (9 patients 45%).

(Table 2) show that significant higher incidence of developing acute variceal bleeding in Non SVR group B versus SVR group A (27 patients 15% in SVR group versus 7 patients 35% in Non SVR group), With significant higher mortality rate in Non SVR group 10 % versus 1.1 % in SVR group.

(Table 3) shows no significant difference regarding changing in Child-Pough scoring and laboratory characters before and after treatment in SVR non SVR groups put for significant improvement in platelet count after SVR (p 0.001).

(Table 4) shows significant improvement variceal size in SVR group A as large varices (F3) become 11.2% six months after treatment versus 29.4% before treatment, still no significant changes regarding variceal size in Non SVR group B before and 6 months after treatment, with overall

improvement in variceal size comparing SVR and Non SVR groups (p value 0.001). Also significant improvement in variceal risky signs was found in SVR group A as risky variceal signs were presented in 143 (79.4%) patients before treatment versus 111 (62.4%) patients six months after treatment, however no significant change regarding variceal risky signs in Non SVR group B before and 6 months after treatment, surprisingly no significant overall improvement in variceal risky signs in SVR group versus Non SVR group.

Parameter		Group A (n=180) SVR	Group B (N=20) Non SVR	X2	P value
Age	< 60 years	170 (94.4%)	18 (90%)	0.632	0.427
	60 -70 years	10 (5.6%)	2 (10%)		
Sex	Male	156 (86.7%)	16 (80%)	0.661	0.415
	Female	24 (13.3%)	4 (20%)		
Child-Pough score	A	139 (77.2%)	5 (25%)	40.228	0.001*
	B	32 (17.8%)	6 (30%)		
	C	9 (5%)	9 (45%)		
Treatment Regimens	Sofo+ Dacla	150 (83.3%)	8 (40%)	36.449	0.001*
	Sofo+Dacla+Riba	9 (5%)	9 (45%)		
	Sofo+ledi	21 (11.7%)	3 (15%)		
Prognosis	Survived	178 (98.9%)	18 (90%)	7.259	0.007*
	Died	2 (1.1%)	2 (10%)		

Table 1: Basic characteristics Distribution of the studied patients according to different parameters: (Sofo=sofosbuvir, Dalca=Daclatasvir, Riba=ribavirin, led=lidprevir), SVR=sustained virological response, P-value significant < 0.05.

		Group A (n=180) SVR	Group B(n=20) Non SVR	Test	P value
Number of Patients with acute bleeding		27 (15%)	7 (35%)	X2: 5.102	0.024*
APASL	Range	2 – 7	3 – 7	t: 0.673	0.505
Score	Mean ± SD	4.15 ± 1.18	4.48 ± 1.03		
Survived		178 (98.9%)	18 (90%)	7.259	0.007*
Died (mortality)		2 (1.1%)	2 (10%)		

Table 2: Acute variceal bleeding among studied groups (APASL= Asian Pacific Association for Study of the Liver score).

		Group A (SVR group)		Group B (non SVR group)	
		Before N= 180	After N=178	Before N=20	After N=18
Child-Pough score	A	139 (77.2%)	139 (78.1%)	5 (25%)	5 (27.8%)
	B	32 (17.8%)	31 (17.4%)	6 (30%)	5 (27.8%)
	C	9 (5%)	8 (4.5%)	9 (45%)	8 (44.4%)
P value		0.969			
Splenic diameters		9—16 cm	9.9 -15.8 cm	10.5-17 cm	11-17.5 cm
		12.35 ± 2.13	12.56 ± 1.96	13.25 ± 2.52	13.51 ± 2.64
P value		0.332			
Platelet counts		100000-235000	120000-260000	100000-190000	90000-190000
		165480.36 ± 35218.64	1197520.84 ± 34568.19	143697.28 ± 20364.89	145927.19 ± 19864.79
	P value	0.001*			
Portal vein diameter		12-14.3 mm	11.9-14 mm	11.5-14 mm	12-14.5 mm
		13.18 ± 1.46	12.95 ± 1.39	12.78 ± 1.84	13.23 ± 1.76
P value		0.128			
				0.441	

Table 3: Laboratory and clinical characters of studied groups before and 6 months after treatment (Significant p< 0.05).

Gastroesophageal varices		Group A (SVR group)		Group B (non SVR)		G A & G B	
		Before N=180	After N=178	Before N=20	After N=18	Before	After
Site Of GOV	Esophageal	145 (80.5%)	145 (81.5%)	12 (60%)	11 (61.1%)	0.101	0.124
	Isolated gastric	10 (5.5%)	9 (5.1%)	2 (10%)	2 (11.1%)		
	Gastroesophageal	25 (13.9%)	24 (13.5%)	6 (30%)	5 (27.8%)		
	P value	0.970		0.952			
Size of GOV	F1	30 (16.7%)	45 (25.3%)	2 (10%)	1 (5.6%)	0.547	0.001*
	F2	97 (53.9%)	113 (63.5%)	10 (50%)	7 (38.8%)		
	F3	53 (29.4%)	20 (11.2%)	8 (40%)	10 (55.6%)		
	P value	0.001*		0.612			
Risky signs	Present	143 (79.4%)	111 (62.4%)	13 (65%)	14 (77.8%)	0.139	0.195
	Absent	37 (20.6%)	67 (37.6%)	7 (35%)	4 (22.2%)		
	P value	0.001*		0.386			

Table 4: Gastroesophageal varices assessment among studied groups before and 6 months after treatment. (GOV=gastroesophageal varices, F1=Small Straight, F2=Moderate, F3=marked enlarged, Risky signs=red cherry spot red whale signs or both).

DISCUSSION

Gastroesophageal variceal bleeding is one of most serious complication of HCV hepatic cirrhosis, in our study we tried to clarify the relation between achieving SVR and gastroesophageal varices and variceal bleeding. We showed that achieving SVR by DAA interferon free regimens will reduce the risk of acute variceal bleeding moreover reduction in variceal bleeding related mortality was significant among patients achieved SVR when compared to non SVR group. Also, our results show significant reduction in the size and risky signs of gastroesophageal varices after achieving SVR, as well as reduction in size of varices when comparing SVR group to non SVR group, however we failed to achieve significant reduction in variceal risky signs when comparing SVR to non SVR group.

In patients included in our study no significant different regarding demographic data, however the main used DAA regimen in SVR group was sofosbuvir/Daclatasvir versus sofosbuvir/Daclatasvir/Ribavirin in non SVR group that explained by drugs availability, our local HCV treatment protocol, pretreatment hepatic cirrhosis assessment and Child-Pough scoring of the patients, those data as well as treatment completion and success rate with achieving SVR is going similar to results from other studies.^{13,14}

Our results demonstrate reduction in risk of variceal bleeding as well as variceal bleeding mortality rate after achieving SVR that could be explained by the regression of hepatic fibrosis and reduction of portal hypertension similar results founded by other cohort studies,¹⁵ Still our study added the presence of significant reduction in the variceal size and variceal risky signs after achieving SVR, as in the forementioned studies that could be explained by the same mechanism of fibrosis regression and reduction in portal blood pressure after achieving SVR.^{15,16}

Although our study revealed reduction in variceal size, risky signs, as well as variceal bleeding and mortality after achieving SVR still some patients of SVR group had risk of developing variceal bleeding

about 15%, furthermore non-significant reduction in variceal risky signs founded when compared SVR and non SVR groups, that could be explained by different biological response to SVR among different patients, as well as the presence of different predictors for variceal bleeding.¹⁷

CONCLUSION

We concluded that there is a reduction in size, risky signs of gastroesophageal varices as well as reduction in the risk of variceal bleeding and mortality rate after achieving SVR using interferon free regimens. these findings magnify the importance the of early diagnosis and treatment of HCV-infected patients, still we had limitations as small number of our studied sample, and our study was one center study, so we recommended further wide multicentric study to confirm the impact of achieving SVR on gastroesophageal varices and to further understanding the implicated mechanisms.

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