Med. J. Cairo Univ., Vol. 87, No. 5, September: 3003-3008, 2019
www.medicaljournalofcairouniversity.net

Efficacy and Safety of Daclatasvir and Sofosbuvir in Egyptian Patients with Chronic Hepatitis C Genotype 4 and Cirrhosis

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Abstract

Background: Hepatitis C virus (HCV) infection is a leading cause of Chronic Liver Disease (CLD) and liver transplantation globally. Currently, oral combinations of Direct Acting Antiviral agents (DAAs) are the standard of care for treating chronic HCV infection.

Aim of Study: To assess the efficacy & safety of combination of Daclatasvir and Sofosbuvir in Egyptian patients with chronic hepatitis C Genotype 4 and Cirrhosis.

Patients and Methods: 50 Egyptian, cirrhotic patients with HCV genotype 4 infection were treated with a generic form of sofosbuvir (SOF) 400mg, daclatasvir (DCV) 60mg with or without weight-based ribavirin (RBV) for only 12 weeks. 40 out of the 50 patients enrolled in the study, completed treatment, while the remaining 10 patients were lost for follow-up.

Results: The 12 weeks combination of SOF plus DCV achieved SVR in all treated patients (100%) whether treatment-naïve or experienced, with or without ribavirin. A significant improvement was observed in transaminases, while a non-significant improvement was observed in serum albumin, bilirubin, INR and the mean CTP score indicating improvement in liver functions. Regarding safety outcomes, all treatment-related AEs were only minor AEs with no major AEs.

Conclusion: The combination of SOF plus DCV with or without RBV for only 12 weeks is highly effective in treating HCV GT4 cirrhotic patients with SVR12 rate of 100%, safe and well tolerated by these cirrhotic patients. Moreover, there was a marginal improvement in liver functions observed 12 weeks after treatment.

Key Words: *H. C. V – Chronic liver disease (CLD) – Cirrhosis.*

Introduction

HEPATITIS C Virus (HCV) infection is a leading cause of Chronic Liver Disease (CLD) and liver transplantation globally [1]. HCV genotype 4 is responsible for approximately 13% of the cases of chronic HCV infection worldwide [2]. Egypt has the highest prevalence of HCV infection worldwide (15%), and genotype 4 represents 90% of all these cases, while the remaining 10% are due to HCV genotype 1 [3].

Among patients with chronic hepatitis C, those with cirrhosis have the greatest clinical challenge. These patients need effective antiviral therapy to prevent progression to decompensation, end stage liver disease and Hepatocellular Carcinoma (HCC) [4]. Currently, oral combinations of Direct Acting Antiviral agents (DAAs) are the standard of care for treating chronic HCV infection [5].

Therefore, in this real-life cohort, the primary aim of the present study is to assess the efficacy and safety of combination of daclatasvir and sofosbuvir with or without ribavirin in the treatment of a group of Egyptian patients with chronic hepatitis C genotype 4 and cirrhosis.

Patients and Methods

In the period from April 2017 to April 2018 a total of 50 Egyptian, cirrhotic patients with HCV genotype 4 infection which were the subject of the present study were selected and identified from Tanta Liver Center and outpatient clinic of Internal Medicine Department Tanta University.

All the study group were subjected to the following:

1- Full history taking including risk factors of HCV infection.

2- Complete physical examination searching for stigmata of liver cirrhosis.

3- Laboratory studies including: Urine, CBC, random blood sugar, prothrombin. (Activity and INR), liver biochemical tests including: Bilirubin, ALT, AST, serum albumin and viral

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markers: HCV Ab, HBS Ag, HCV RNA by RT PCR.

4- Abdominal US scan to assess liver status, splenic size and ascites.

5- Severity of liver cirrhosis was determined by estimation of Child-Turcotte Pugh (CTP) score depending on clinical, biochemical and US findings.

6- *Treatment regimen:* All the study group were assigned to receive an all oral fixed dose of sofosbuvir (400mg) plus daclatasvir (60mg) ± weight-based ribavirin (1000 or 1200mg in patients <75 or ≥75kg, respectively) for only 12 weeks. The primary end point is Sustained Virological Response (SVR) at 12 weeks after the end of treatment (SVR12).

7- Follow-up laboratory studies were done 4 weeks, 12 weeks after initiation of therapy as well as 12 weeks after the end of treatment including HCV RNA by RT PCR.

8- Also, treatment-related adverse events as well as any complications observed during the study were recorded and dealt with accordingly.

9- The CTP score was estimated after SVR and any changes from the pretreatment level were also recorded.

Exclusion criteria: Patients with decompensated cirrhosis, HCV/HBV or HCV/HIV co-infection, HCC were not eligible for enrollment. Patients with any of the following laboratory abnormalities were also excluded from enrollment: Hemoglobin level less than 10gm/dl, platelets count of 30.000 mm^3 or less, total bilirubin level greater than 10mg/dl, serum creatinine level greater than 2.5mg/dl and/or creatinine clearance <40ml/min.

Statistical analysis:

One-way analysis of variance (ANOVA) was used to assess significant differences among treated group. The Tukey Test was used to show the significant effect of treatment. Values are expressed as mean ± SD. The criterion for statistical significance was set at $p<0.05$ (SPSS Inc., USA Software).

Results

As regard patient disposition by the studied group Fig. (1): 50 Egyptian, cirrhotic patients with HCV genotype 4 infection were the subject of the present study. 44 patients (88%) were treatment naïve, while the remaining 6 patients (12%) were treatment experienced. Out of 44 treatment naïve patients 34 (77.3%) completed treatment and achieved SVR12 and 10 patients (22.7%) were lost for follow-up. All treatment experienced patients (n=6) completed treatment and achieved SVR12.

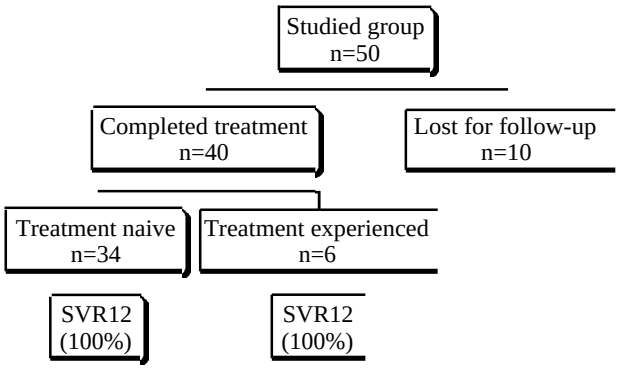

Fig. (1): Patient disposition by the studied group.

The clinical characteristics of the studied groups as regard demographic data, clinical examination, US findings, initial laboratory findings, viral markers & level of viremia are shown in (Tables 1-5).

Table (1): Demographic data of the studied group (n=50).

Item		No.	%
• *Age:*	Range	35-77y	
	Mean ± SD	56±9.63y	
• *Sex:*	Male	37	74
	Female	13	26
• *Residence:*	Rural	44	88
	Urban	6	12
• *Risk factors of HCV infection:*	Dental procedures	24	48
	Surgery	17	34
	Family history	14	28
	IVantibilharzial ttt	5	10
	Blood transfusion	4	8
• *Comorbidity:*	DM	8	16
	COPD	4	8
	Thyroid disease	1	2
• *Previous treatment:*	Treatment naïve	44	88
	Treatment experienced	6	12

Table (2): Results of clinical examination of the studied group (n=50).

Item	No.	%
Edema of lower limb	11	22
Palmar erythema	11	22
Jaundice	3	6
Liver status:		
Not palpable	47	94
Enlarged	3	6
Spleen:		
Enlarged	28	56
Normal	21	42
Splenectomy	1	2
Ascites	–	0

Table (3): US findings in the studied group (n=50).

Item	No.	%
Liver status:		
- *Size:*		
Normal	36	72
Enlarged	9	18
Shrunken	5	10
- *Echopattern:*		
Cirrhotic	37	74
Bright	7	14
PPF	6	12
- Hepatic focal lesion	–	0
- *Portal vein:*		
Dilated	26	52
Normal	24	48
Splenic size:		
Enlarged	31	62
Normal	18	36
Splenectomy	1	2
Ascites	–	0
Others:		
Gall stones	1	2

Table (4): Initial lab findings in the studied group (n=50).

Lab findings	Range	Mean ± SD
CBC:		
Hb%	10-16.3	13.35± 1.43
Platelets	41.000-361.000	146140±78382.63
WBC	2100- 13.500	5995.4±2412.39
Random blood sugar	71-332	127±54.94
S. Bilirubin	0.3-3.8	1.2±0.84
ALT	8-286	59.8±49.66
AST	8-331	66.1±55.37
S. Albumin	2.6-5	3.9±0.61
Prothrombin:		
Activity	43-100%	80%± 14.85
INR	1-2.4	1.3±0.27

Initial CTP score

CTP score	No.	%
Class A	40	80
Class B	10	20
Class C	–	0
Min-max	5-9	
Mean ± SD	6± 1.05	

Table (5): Viral markers & level of viremia in the studied group (n=50).

Item		No.	%
HCV Ab	+Ve	50	100
HCV RNA	+Ve	50	00
Range	673 - 13,234,758		
Mean	1,579,174		
High viral load (≥600,000)		24	48

Table (6): Review of laboratory findings in the treated group (n=40).

Item	Pre-treatment Mean ± SD	4W on treatment (RVR)		End of treatment (12W) (ETR)		12W after end of treatment (SVR)	
		Mean ± SD	*p*-value	Mean ± SD	*p*-value	Mean ± SD	*p*-value
Hemoglobin	13.31 ± 1.5	12.11 ± 1.3	<0.01	12.05± 1.7	<0.01	12.76±2	>0.05
Platelets count	157525±80589	170100± 82746	>0.10	171625±83804	>0.10	167375±81870	>0.10
Bilirubin	1.1±0.66	1.06±0.46	0.08	1±0.58	0.09	0.79±0.51	>0.10
ALT	63.03±50.11	27.73 ± 15.09	<0.001	22.35± 10.14	<0.001	16.4±5.99	<0.001 *
AST	69.15±58.99	34.33 ± 17.26	<0.001	29.25± 17.63	<0.001	21.03± 10.93	<0.001 *
S. albumin	3.98±0.65	3.89±0.55	0.0177	3.95±0.57	>0.10	4.11 ±0.6	>0.10
INR	1.26±0.23	1.12±0.18	0.241	1.02±0.03	0.262	1.05±0.08	0.234
HCV RNA	1457586± 186453	46755.83 ± 16666	<0.001	0	<0.001	0	<0.001 *

*: Significant *p*-value <0.05.

Table (7): Primary outcome of treatment with sofosbuvir plus daclatasvir ± ribavirin in the treated group (SVR 12) (n=40).

Variable	Complete RVR		Incomplete RVR		ETR		SVR12	
	No.	%	No.	%	No.	%	No.	%
Treatment-naïve (n=34)	31	91.1	3	8.9	34	100	34	100
Treatment-experienced (n=6)	6	100	–	0	6	100	6	100

Table (8): Treatment-related adverse events in the treated group (n=40).

Item	No.	%
Minor adverse events:		
Anaemia	21	52.5
Headache	4	10
Fatigue	4	10
Dry cough	3	7.5
Itching	1	2.5
Insomnia	–	0
Major adverse events:		
Death	–	0
Liver cell failure	–	0
Hepatic encephalopathy		0
Development of HCC	1	2.5

No major adverse event (death, liver cell failure or hepatic encephalopathy) was reported in any patient of the treated group (0%). However, one of our patient (2.5%) developed HCC 3 months after achieving a SVR.

Discussion

In this real-life cohort, the primary aim of the present study is to assess the efficacy and safety of combination of daclatasvir and sofosbuvir with or without ribavirin in the treatment of a group of Egyptian patients with chronic hepatitis C genotype 4 and cirrhosis. This population, which is often under-represented in clinical trials, is less likely to respond satisfactorily to treatment and also may experience more treatment-related adverse events.

Our results revealed, a non-significant improvement in serum albumin, bilirubin and INR, while a highly significant improvement was observed in the level of transaminases 12 weeks after the end of treatment with SOF, DCV ±RBV (Table 6). A finding that indicates the safety of this treatment modality regarding the synthetic functions of the liver. Moreover, the highly significant decrease in the level of transaminases 12 weeks after the end of treatment indicates marked improvement in the necroinflammatory process in the treated CHCV patients. Review of relevant publications, similar results were reported by 3 other national studies (Abdel-Moneim et al., [6], Ahmed et al., [7] and Abdel-Aziz et al., [8]) and 2 other international studies (Babatin et al., [9] & Welzel TM, et al. [5]).

Similarly, the current treatment with SOF, DCV ± RBV revealed non-significant changes in both hemoglobin and platelets count as compared to the baseline values. A finding that could be considered another advantage of this regimen besides its efficacy, especially in this group of cirrhotic patients in whom cytopenia is a common finding. Needless to say, the non-significant decrease in hemoglobin level observed 12 weeks after the end of treatment could be related to the use of ribavirin, however being non-significant, none of our treated patients required transfusion and/or discontinuation of RBV. Consequently, most of these cases were managed by reducing the RBV dose and in some cases addition of epoetin (EPO). It is noteworthy to mention that, concerning efficacy and antiviral response, the 12 weeks combination of SOF plus DCV achieved SVR in all treated patients (100%) whether treatment naïve or experienced, with or without ribavirin (Table 7). There was only one patient who didn't receive ribavirin due to anaemia achieving the same response for only 12 weeks (SVR12).

Review of relevant publications revealed, some discrepancies between the results of the present study and the other national and international studies. In keeping with our results, 2 other studies (Babatin et al., [9] & Fontaine et al., [10]) achieved SVR12 in 100% of their treated GT4 cirrhotic patients. On further subanalysis, the presence of detectable HCV RNA at week 4 in some patients in this study (8%) was not associated with virologic relapse, almost the same results observed in our study (8.9%). By contrast, 5 other national studies reported a relatively lower SVR12 rate in cirrhotic GT4 patients treated with this combination (SOF, DCV ± RBV), such as Abdel-Aziz et al., (91%) [8], El-Khayat et al. (94%) [11], Abdel-Moneim et al., (94%) [6], Omar et al., (95%) [12] & Ahmed et al., (96%) [7]. Regarding safety outcomes, all treatment-related AEs reported in our treated group were minor adverse events including, anaemia in 21 (52.5%), headache in 4 (10%), fatigue in 4 (10%), dry cough in 3 (7.5%) and itching in only one patient (2.5%) (Table 8). Interestingly, none of our patients (0%) developed serious AEs such as (death, liver cell failure or hepatic encephalopathy). A finding that confirms the safety and tolerability of this regimen in our treated cirrhotic HCV GT4 patients. On further follow-up beyond the study period, one (2.5%) of our cohort with HCV GT4 cirrhotic patients developed HCC 3 months after achieving a SVR. A finding that clearly shows that in cirrhotic CHCV patients, HCC can develop despite achieving a SVR. Therefore, continous surveillance for HCC should be done in cirrhotics even after achieving a SVR.

Conclusion:

The results of the present study clearly shows that, in cirrhotic GT4 Egyptian patients, the combination of SOF plus DCV with or without RBV

for only 12 weeks is highly effective with SVR12 rate of 100%. Also, it was equally effective in both naïve as well as treatment-experienced patients.

Additionally, this combination is safe and well tolerated by these cirrhotic patients. Moreover, there was a marginal improvement in liver functions observed 12 weeks after the end of therapy. Therefore, based on the results of this real-world study, this combination is not only highly effective and safe, but also the cheapest combination among currently available regimens in Egypt and this makes it a very suitable regimen for a developing country like ours and this will help make the end of HCV in the nearby future in Egypt a reality.

Recommendations:

Since the combination of SOF plus DCV with or without RBV for only 12 weeks is cheap, highly effective & safe, in cirrhotic GT4 patients, it should be among the first line options for treatment of this group of patients in our country. The safety and tolerability of this regimen in cirrhotic GT4 patients recommends a further study for it's use in the treatment of decompensated GT4 cirrhosis. The development of HCC in one (2.5%) of our patients 3 months after achieving a SVR warrants continous surveillance for HCC in cirrhotic patients even after achieving a SVR.

Acknowledgements:

We would like to thank all participants who helped during this study.

Conflict of interest: None declared.

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تقييم فعالية وسلامة الدكلاتاسفير والسوفوسبفير لعلاج المرضى المصريين الذين يعانون من الإلتهاب الكبدى الفيروسى المزمن سى النمط الجينى الرابع وتليف الكبد

عدوى فيروس الإلتهاب الكبدى الوبائى (سى) هى السبب الرئيسى لمرض الكبد المزمن وزراعة الكبد، والنمط الجينى ٤ مسؤول عن حوالى ١٣٪ من حالات الإصابة به على مستوى العالم. حديثاً، تعتبر الأدوية المضادة للفيروسات مباشرة عن طريق الفم العلاج الأفضل لإلتهاب الكبد المزمن سى.

الهدف من البحث: تقييم فعالية وسلامة الدكلاتاسفير والسوفوسبفير لعلاج المرضى المصريين الذين يعانون من الإلتهاب الكبدى الفيروسى المزمن سى النمط الجينى الرابع وتليف الكبد.

البحث: أجريت هذه الدراسة على ٥٠ شخص مصابين بتليف الكبد نتيجة الإصابة بفيروس سى النمط الجينى ٤. وقد تم إجراء الآتى: التاريخ المرضى الكامل والفحص الإكلينيكى الشامل والفحوصات المعملية وتشمل: صورة دم كاملة ودلالات فيروسات كبدية (فيروس بى وسى) ووظائف كبد كاملة (إنزيمات كبد ونسبة ألبيومين بالدم ومستوى الصفراء بالدم وزمن ونشاط البروثرومبين). وتم عمل موجات صوتية على البطن والحوض. تم إعطاء مجموعة الدراسة سوفوسبفير ٤٠٠، دكلاتاسفير ٦٠ مع أو بدون ريبافيرين لمدة ١٢ إسبوعاً فقط.

النتائج: فيما يتعلق بفعالية الإستجابة المضادة للفيروسات، ومدى سلامة وآمان العلاج بالدكلاتاسفير والسوفوسبفير، تم حدوث إستجابة فيروسية مستدامة ١٢ إسبوعاً فى جميع المرضى المعالجين (١٠٠٪)، كل الأعراض الجانبية المصاحبة كانت بسيطة بدون حدوث مضاعفات خطيرة.

الخاتمة: يعتبر العلاج بالدكلاتاسفير والسوفوسبفير مع أو بدون ريبافيرين لمدة ١٢ إسبوعاً فقط فعالاً للغاية فى علاج مرضى التليف الكبدى المصابين بإلتهاب الكبد الفيروسى سى النمط الجينى الرابع.