Impact of direct-acting antiviral therapy in Egyptian patients with chronic hepatitis C and liver cirrhosis

Mohammed H. Elnadry[a], Sherif A. Abdel-Aziz[a], Mohammed Ghareb[a], Ali A. Ahamad[b], Nagah M. Abu-Mohammed[c], Marwan M. Tayel[a]

Background and aims In Egypt, ~14.7% of the population has hepatitis C infection and genotype 4 infection accounts for more than 90% of the hepatitis C virus infections. Available data with newer all-oral regimens in the treatment of genotype 4 infection suggest that sustained virological response (SVR) 12 rates in treatment-naïve cirrhotic and noncirrhotic patients are greater than 95%.
The study aimed to evaluate the virological response 12 weeks after treatment (SVR12), change in the model for end-stage liver disease score, and adverse clinical events during the study period.

Patients and methods This prospective study included 451 patients with chronic hepatitis C and liver cirrhosis over a 3-month period started at January 2017. And the study was ethically approved by the Medical Research Ethics Committee, Faculty of Medicine, Al-Azhar University. The enrolled patients were classified into three groups: group I included 162 patients with chronic hepatitis C and liver cirrhosis subjected to direct-acting antivirals (DAAs) therapy (100/162 compensated cirrhosis and 62/162 decompensated cirrhosis), group II included 234 patients known to have chronic hepatitis C without liver cirrhosis subjected to DAAs therapy, and group III included 55 patients with chronic hepatitis C and liver cirrhosis not subjected to DAAs therapy according to the national protocol of therapy (as a control group). Treatment was administered for 12 weeks that included variable regimens of DAAs according to the Egyptian Ministry of Health protocol.

Results We included 451 patients with chronic hepatitis C infection and liver cirrhosis; 47.8% of the patients were male, 84.4% were treatment naive, and 54.9% had cirrhosis. Of the study participants, 150 patients in group I and 53 patients in group II received sofosbuvir+daclatasvir+ribavirin, 183 patients received daclatasvir+sofosbuvir (group II), seven patients in group II received sofosbuvir+ledipasvir, five patients received sofosbuvir+ledipasvir+ribavirin (in group I), and seven patients in group I and nine patients in group II received ombitasvir/paritaprevir/ritonavir+ribavirin. Twelve weeks after end of treatment (SVR12) were 91.3% and 96.5% observed in group I and group II, respectively irrespective of the regimen of therapy. Treated patients in group I had a mean negative change in model for end-stage liver disease (–0.722; SD, 2.603) representing an improvement in liver function, whereas untreated patients in group III showed a minimal mean positive change (0.00; SD, 2.92) representing a deterioration in liver function ($P<0.001$). Improvements were observed in the Child-score (Child–Pugh–Turcotte) in group I versus untreated patients in group III. Hepatic encephalopathy was evident in 6.1% of patients in group I after treatment versus 38.1% in untreated patients (group III), and ascites developed in 30.2% of patients after treatment (group I) versus 65.4% in untreated patients (group III).

Conclusion Oral regimens of DAAs are effective in the treatment of hepatitis C virus infection even in patients with liver cirrhosis, leading to improvements in liver functions.
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Keywords: Child, Pugh score, direct-acting antivirals, hepatitis C Egypt, hepatitis C-related liver cirrhosis, model for end-stage liver disease score, sustained virological response

Departments of, [a]Tropical M., [b]Pharmacology, [c]Clinical Pathology, Al Azhar University, Cairo, Egypt

Correspondence to Marwan Mohammed Tayel, MBBCh, Ahmad Maher Teaching Hospital, 29 Ahmed Maher St. from Manshiet ElTahrir, 18511, Cairo, Egypt. Tel:+201063128684;
e-mail: marwantayel22@gmail.com

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Introduction

Egypt has the highest prevalence of hepatitis C virus (HCV) worldwide; it is estimated to be 14.7% among a representative sample of Egyptian population aged 15–59 years. Where it bears the highest prevalence rate in the world. Estimates for prevalence are based on data reported from the 2008 and 2015 Egypt Demographic Health Surveys (WHO, 2015). The Ministry of Health introduced the national plan and program for managing HCV, which has been successful so far in treating a large number of patients, with the aim of achieving disease control and eventual elimination of HCV in Egypt (WHO, 2015).

The aim of this study was to evaluate the virological response 12 weeks after treatment [sustained virological response 12 (SVR12)], change in the model for end-stage liver disease (MELD) score, and adverse clinical events during the study period.

Patients and methods

A prospective case–control study was carried out on 451 patients who fulfilled the designed inclusion criteria during 3-month period starting from January 2017. The study was carried out as a collaboration between Tropical Medicine Department, Al Azhar

University, and Viral Hepatitis Unit-Ahmed Maher Teaching Hospital, the National Committee for Control of Viral Hepatitis, Cairo, Egypt.

On the basis of the aim of this study, Egyptian patients who presented with HCV infection and liver cirrhosis over a 3-month period at the outpatient clinic of Viral Hepatitis Unit, Ahmed Maher Teaching Hospital were included in the study. Patients were recruited according to the following inclusion criteria: (HCV-RNA positivity, age 18–75 years, and treatment-naïve or treatment-experienced cirrhotic patients) and were excluded if they had any of the following: extra-hepatic malignancy except after 2 years of a disease-free interval, patients who had received a liver transplant just before the study period, patients with a severe form of extra-hepatic manifestation, pregnancy, or inability to use effective contraception, and inadequately controlled diabetes mellitus (HbA1c<9%), patients with serum albumin less than 2.8 g/dl, patients with total bilirubin more than 3 mg/dl, patients with international normalized ratio more than 1.7, patients with platelet count less than 50 000/mcL, or patients with hepatitis B virus infection. All patients were subjected to a full assessment of medical history, clinical examination, and laboratory investigations including HCV antibodies using the ELISA technique, HCV-RNA quantitative PCR [before treatment, follow-up at the end of treatment and at 12 weeks after the end of treatment, HBsAg, liver function tests (serum albumin, total and direct serum bilirubin, aspartate aminotransferase, alanine aminotransferase, prothrombin time, and international normalized ratio), alpha fetoprotein, complete blood count, fasting blood glucose, and HbA1c (in diabetic patients), serum creatinine, pregnancy test for females in the child-bearing period, and pelvi-abdominal ultrasonography.

Treatment was selected by the prescribing clinician according to the treatment protocols of the national committee for control of viral hepatitis and the international guidelines. Five groups of direct-acting antivirals (DAAs) were used in the management of the patients in this study; these included sofosbuvir +daclatasvir and sofosbuvir+ledipasvir, both with or without ribavirin, and ombitasvir/paritaprevir/ritonavir (qurevo)+ribavirin. Written informed consent was obtained from all patients before their participation in this study.

Statistical analysis

Data were coded, entered, and processed on a computer using statistical packaged for the social science (version 22, 2013; IBM SPSS, IBM Software Package for Statistical analysis, SPSS). *P* value less than or equal to 0.05 was considered the cut-off value for significance.

Results

The current study included 451 patients, who were classified into three groups: group I included 162 patients with chronic hepatitis C and liver cirrhosis subjected to DAAs therapy. This group was subdivided into two subgroups (100 compensated patients, group Ia, and 62 decompensated patients, group Ib). Group II included 234 patients known to have chronic hepatitis C without liver cirrhosis subjected to DAAs therapy (included to assess SVR12). Group III included 55 patients (as a control group) with HCV-related liver cirrhosis not eligible for DAAs therapy.

Table 1 shows that the mean age of the patients in group Ia was 53.6 years, 55.4 years in group Ib, 47.1 years in group II, and 53.8 years in group III. The table also shows that the male : female ratio was 59 : 41% in group Ia, 62.9 : 37.1% in group Ib, 43.6 : 46.4% in group II, and 47.3 : 52.7% in group III.

Table 2 shows that there was no statistically significant difference between group I and group III in serum bilirubin, alanine aminotransferase, serum albumin, platelets count, and MELD score at week 0 (before starting the treatment).

Table 3 shows that there was no statistically significant difference between group I and group III in the Child–Pugh score at week 0 (before starting the treatment).

Table 1 Demographic characteristics of the groups studied

Groups	Total	Age (mean±SD) (year)	Sex		Viral load (in million) (mean±SD)
			Male [*n* (%)]	Female [*n* (%)]	
Group I					
Compensated group Ia	100	53.6±1.44	59 (59)	41 (41)	2.2±1.2
Decompensated group Ib	62	55.4±2.6	39 (62.9)	23 (37.1)	1.6±0.9
Group II	234	47.1±2.9	102 (43.6)	132 (46.4)	1.5±0.8
Group III	55	53.8±3.2	26 (47.3)	29 (52.7)	1.9±1.1

Table 2 Comparison between (group I) and (group III) in terms of liver/renal status

Liver/renal status	Groups	*N*	Mean±SD	*t*	*P* value
Bilirubin (mg/dl)	Group I	162	1.5075±0.82216	0.43273	0.66565
	Group III	55	1.4564±0.51163		
ALT (U/l)	Group I	162	56.0994±36.67104	−0.54132	0.58885
	Group III	55	58.9091±19.81140		
Albumin (g/dl)	Group I	162	3.2950±0.36380	1.43812	0.15186
	Group III	55	3.2164±0.30657		
Creatinine (mg/dl)	Group I	162	0.7739±0.10519	−0.79720	0.42622
	Group III	55	0.7855±0.03558		
Platelets (×109/l)	Group I	162	115 487.6±53 657.9	−0.41388	0.67937
		55	118 709.09±36 330.1		
MELD score	Group III	162	9.9503±2.12956	−0.42113	0.67408
		55	10.0727±0.53936		

ALT, alanine aminotransferase; MELD, model for end-stage liver disease.

Table 3 Comparison of treated cirrhotic patients (group I) and untreated cirrhotic patients (group III) in terms of the Child–Pugh score at week 0 (before starting the treatment)

Groups	Total	Child–Pugh at week 0			*P* value
		Child A	Child B	Child C	
Cirrhotic groups (group I and group III)					0.654
Treated cirrhotic (group Ia and Ib) [*n* (%)]	162 (100)	100 (61.7)	50 (30.9)	12 (7.4)	
Untreated cirrhotic group III [*n* (%)]	55 (100)	31 (56.4)	18 (32.7)	6 (10.9)	
Total[*n* (%)]	217 100()	131 (60.4)	68 (31.3)	18 (8.3)	

Table 4 Sustained virological response 12 in the different regimens of direct-acting antivirals

	PCR at week 12 (SVR12)			
Treatment regimen	Positive	Negative	Total	χ^2
Sofosbuvir+daclatasvir [*n* (%)]	7 (2.4)	280 (97.6)	287 (100.0)	1.715
Sofosbuvir+daclatasvir+ribavirin [*n* (%)]	1 (2.3)	42 (97.7)	43 (100.0)	
Sofosbuvir+ledipasvir [*n* (%)]	2 (5.3)	36 (94.7)	38 (100.0)	
Sofosbuvir+ledipasvir+ribavirin [*n* (%)]	1 (5.3)	18 (94.7)	19 (100.0)	
Qurevo+ribavirin [*n* (%)]	0 (0)	9 (100.0)	9 (100.0)	
Total [*n* (%)]	11 (2.8)	385 (97.2)	396 (100.0)	

SVR, sustained virological response.

Table 5 Child–Pugh score at week 12 after treatment in treated cirrhotic patients (group I) and the untreated group (group III)

	Total	Child class at week 12			*P* value
		A	B	C	
Cirrhotic groups					0.015
Treated (group I a and b) [*n* (%)]	162 (100.0)	100 (61.7)	48 (29.6)	8 (4.9)	
Untreated group (group III) [*n* (%)]	55 (100.0)	28 (50.9)	18 (32.7)	9 (16.4)	
Total [*n* (%)]	217 (100.0)	134 (61.8)	66 (30.4)	17 (7.8)	

Table 4 shows that 97.2% of all treated patients under different regimens of DAAs achieved SVR12 and only 2.8% were HCV-RNA positive at 12 weeks after the end of treatment.

Table 5 shows that there was a statistically significant difference between group I and group III in the Child–Pugh score at week 12 (P=0.015).

Table 6 shows that in terms of the MELD score at week 0, there was no statistically significant difference between group I and group III, but there was a highly significant difference at week 12 and at week 12 after treatment between the treated and the untreated groups.

Table 7 shows that there was no statistically significant difference between the Child–Pugh score

Table 6 Model for end-stage liver disease score at week 0 (before starting treatment), week 12 (at the end of treatment), and at week 12 after treatment in treated cirrhotic patients (group I) and the untreated group (group III)

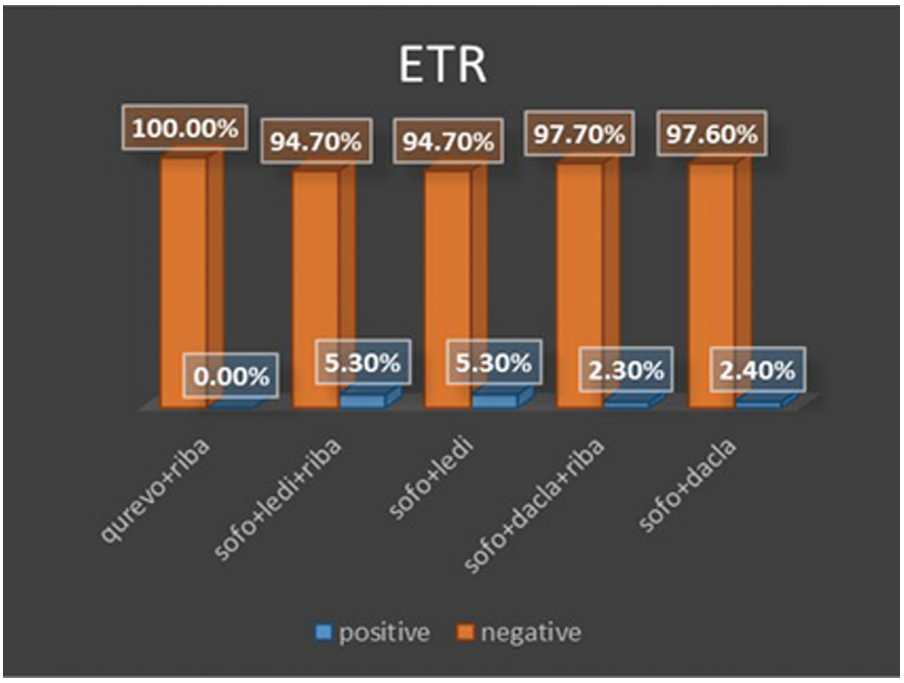
	Groups	*N*	Mean±SD	*P* value
MELD at week 0	Group I	162	9.95±2.12	0.674
	Group III	55	10.07±.539	
MELD at week 12	Group I	162	10.28±2.67	0.000
	Group III	55	12.80±2.45	
MELD at week 12 after treatment	Group I	162	9.95±2.40	0.000
	Group III	55	13.60±3.11	

MELD, model for end-stage liver disease.

Table 7 Comparison of the Child–Pugh score in the cirrhotic groups

Child-score	Cirrhotic group I (group Ia and Ib)	Control group (group III)	*P* value
At week 0			
Range	5–9	6–10	0.0610
Mean±SD	6.315±1.353	7.982±2.70	
At week 12 after treatment			
Range	5-11	6-12	0.020
Mean±SD	6.383±1.627	8.10±2.89	
Difference between week 0–12 after treatment			
Differences	–0.068±1.175	–0.255±1.109	
Paired test	0.463	0.095	

Figure 1



PCR at the end of treatment (ETR) with different regimens of DAAs. DAA, direct-acting antivirals.

in group I and group III at week 0, but there was a highly significant difference between the groups at weeks 12 and 12 after treatment (*P*=0.02).

Table 8 shows that there was no statistically significant difference in the MELD score in group I and group III at week 0 (*P*=0.07), but there was a highly significant difference between the groups at weeks 12 and 12 after treatment (*P*=0.01).

Table 9 shows that there was a highly statistical significant difference in the Child–Pugh score at week 0 and at week 12 after treatment in decompensated group Ib of patients.

Table 8 Comparison of the model for end-stage liver disease score in cirrhotic groups

MELD	Groups		ANOVA
	Cirrhotic group I (group Ia and Ib)	Control group	*P* value
At week 0			
Range	6–18	10–13	0.07
Mean±SD	11.019±3.165	10.4±1.4	
At week 12 and 12 after treatment			
Range	6–19	10–20	0.01
Mean±SD	10.296±2.677	13.055±2.460	
Difference between week 0–12 after treatment			
Differences	0.722±2.603	0.000±2.925	
Paired test	0.001*	1.000	

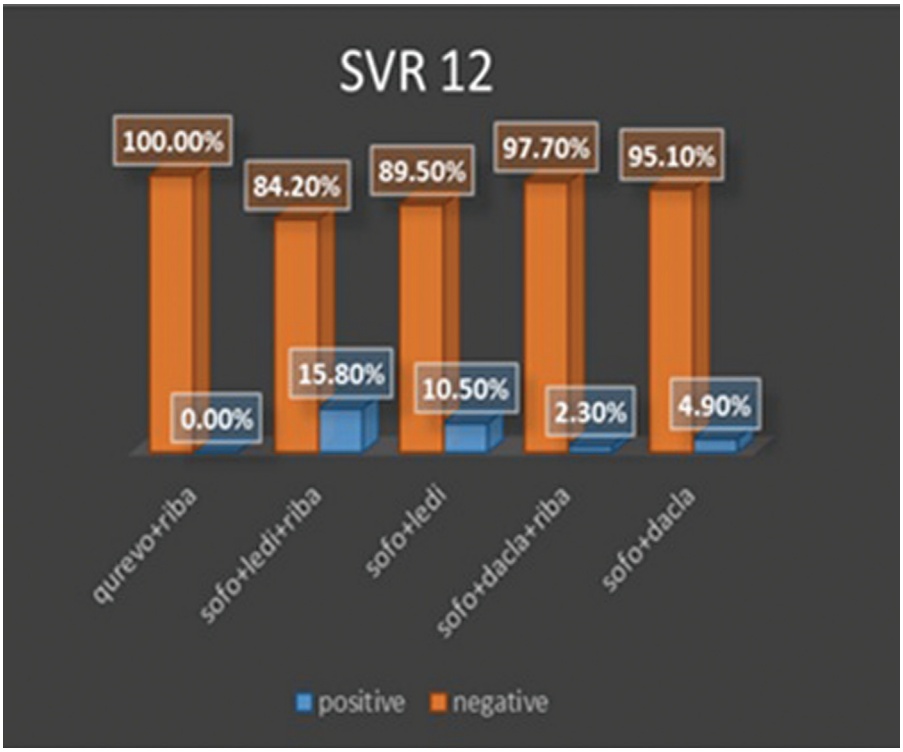
ANOVA, analysis of variance; MELD, model for end-stage liver disease; Ia, compensated cirrhotic subgroup of group I.

Table 9 Child–Pugh score in the decompensated cirrhotic group (group Ib) at week 0 and at week 12 after treatment

CP	Mean	*N*	SD	*t*	*P* value
CP at week 0	8.8871	62	1.1460	5.2447	0.000
CP at week 12 after treatment	8.3387	62	1.3172		

CP, Child–Pugh.

Figure 2



PCR at week 12 after treatment (SVR12). SVR, sustained virological response.

Table 10 shows that there was a highly significant difference in the MELD score at week 0, week 12, and week 12 after treatment in the decompensated cirrhotic group of patients.

Table 11 shows that there was a statistically significant difference in the MELD score and the Child–Pugh score at week 0 and week 12 after treatment in group III.

Table 12 shows that there was no significant difference between group I and group III in liver-related death, liver failure, and hepatocellular carcinoma (HCC) (Figs 1 and 2).

Discussion

The availability of highly effective all-oral, interferon-free, DAA medications for patients with chronic HCV

Table 10 Model for end-stage liver disease score in the decompensated cirrhotic group (G Ib) at weeks 0, 12, and 12 after treatment

	Mean	*N*	SD	*t*	*P* value
MELD					
MELD at week 0	10.6613	62	0.86732	10.2912	0.0000
MELD at week 12	9.2742	62	0.70523		
MELD at week 0	10.6613	62	0.86732	11.5760	0.0000
MELD score at week 12 after treatment	9.0000	62	0.72429		

MELD, model for end-stage liver disease.

Table 11 Model for end-stage liver disease score and Child–Pugh score in the untreated (control group) at week 0 and at week 12 after treatment of follow up

	Mean	*N*	SD	*t*	*P* value
MELD score					
MELD at week 0	10.4000	55	1.46059	–5.11827	0.00000
MELD at week 12 after treatment	11.6545	55	1.05792		
CP score					
CP at week 0	7.9273	55	2.70702	–3.46410	0.00105
CP at week 12 after treatment	8.1091	55	2.89746		

CP, Child–Pugh; MELD, model for end-stage liver disease.

Table 12 Outcome at the last visit (week 12 after the end of treatment)

	Outcome at last visit (week 12 after treatment)				*P* value
	Liver-related death	Liver failure	HCC	Clinical improvement	
Cirrhotic groups					
Treated cirrhotics (*N*=162) [*n* (%)]	3 (1.9)	29 (17.9)	9 (5.6)	121 (74.7)	0.000
Untreated cirrhotics (*N*=55) [*n* (%)]	4 (7.3)	24 (43.6)	3 (5.5)	24 (43.6)	
Total [*n* (%)]	7 (3.2)	53 (24.4)	12 (5.5)	145 (66.8)	217 (100)

HCC, hepatocellular carcinoma.

infection has transformed the treatment options for infected patients and most patients can now achieve viral clearance.

Our aim in the current prospective study was to evaluate the potential risks and benefits of DAA therapy in patients with chronic HCV infection and liver cirrhosis; therefore, we examined outcomes and reported serious adverse events in the studied groups carefully and therefore we believe that our dataset is likely to be accurate and complete with minimal errors from reporting or attendance failure.

The study was carried out at Viral Hepatitis Unit-Ahmed Maher Teaching Hospital under supervision of the National Committee for Control of Viral Hepatitis, Cairo, Egypt, and the Tropical Medicine Department, El-Hussein University Hospital.

A total of 451 individuals were included in this study. They were classified into three groups: group I included 162 patients with liver cirrhosis (100/162 compensated group Ia and 62/162 decompensated group Ib) subjected to DAAs therapy, group II included 234 persons known to have chronic HCV infection without liver cirrhosis subjected to DAAs therapy, and group III included 55 patients with chronic HCV infection and liver cirrhosis not subjected to DAAs therapy as a control group.

The sex distribution (male to female ratio in each group)in the current study showed no statistically significant difference between the studied groups (*P*=0.078); the results were in not in agreement with (Rosinska *et al.*, 2017), who reported that HCV infection accounted for 51% in men and 34.4% in women.

The mean age of patients in the cirrhotic group Ia and group Ib was 53.6 and 55.4 years, respectively, and in group II 47.1 years and in untreated cirrhotic group III was 53.8 years. The results are not in agreement with those reported by [1] in the Egyptian Demographic Health Survey, that HCV still affects a considerable proportion of the Egyptian population. It is estimated

that, in the 1–59-year age group, 5.3 million individuals are positive for HCV antibodies and, of these, ~3.7 million (69.5%) are HCV-RNA positive. The explanation for this disagreement in the sex distribution may be the difference in the number of patients included in each study.

The SVR12 in our study was more than 97% in groups of patient with Child–Pugh–Turcotte (CPT) A and B. Who received sofosbuvir+daclatasvir and sofosbuvir +daclatasvir+ribavirin and more than 94% in groups of patients CPT C receiving sofosbuvir+ledipasvir and sofosbuvir+ledipasvir+ribavirin and 100% response rate in groups receiving ombitasvir +paritaprevir+ritonavir (qurevo). The results are in agreement with those of Abdel-Razek and Waked [2]; they reported that the combination of SOF-LDV in a single oral daily fixed dose resulted in an SVR in more than 93% of patients after 8 weeks in HCV treatment-naïve patients and more than 97% after 12 weeks, and resulted in SVR rates more than 93% after 12 weeks in previous nonresponders with or without RBV [3,4]. This combination is also evaluated when administered for 12 weeks to 20 patients with HCV infection (including 40% of treatment-experienced patients and 40% of patients with advanced fibrosis) resulted in complete on-treatment viral suppression and SVR in all, except one noncompliant patient, for up to 12 weeks after the end of therapy [5]. The combination of SOF with the NS5A inhibitor administered for 12 weeks to 154 patients resulted in an overall SVR rate more than 95%, including 13/14 HCV patients [6]. An all-oral combination of ritonavir boosted paritaprevir and the NS5A inhibitor ombitasvir for 12 weeks in HCV patients without cirrhosis resulted in SVR12 rates of 100% with RBV and 91% without RBV in treatment-naïve patients, and 100% SVR in experienced patients.

Also Verna [7] reported that the approval of safe and effective (DAA) agents has markedly changed the care of patients with HCV infection. This may be particularly true for traditionally difficult-to-treat populations, including those with advanced liver disease. Remarkably, increasing availability of safe and effective treatment may have already led to a decline in liver transplant wait listing for HCV-related decompensated liver disease [8].

However, although SVR rates in the general population currently exceed 90–95% with first-line regimens [9], for those who have already developed CPT class B and C liver disease, the SVR rates remain suboptimal. In addition, controversy remains on the impact of viral eradication on the clinical course of these patients and the optimal timing of treatment in the context of anticipated liver transplantation.

An improvement has been observed in the Child-score (CPT) in group I versus untreated patients in group III. Also, treated patients in group I showed a mean negative change in MELD (-0.722; SD, 2.603) representing an improvement in liver function, whereas untreated patients in group III showed a minimal mean positive change (0.00; SD, 2.92) representing deterioration in liver function ($P<0.001$). The results are in agreement with those of Michael [10], who reported that the improved SVR rates and safety profiles of all oral-DAA have led to the treatment of some patients who would not have received widespread treatment in the IFN era. One such group is the decompensated cirrhotic patients, who have a poor prognosis, have limited treatment options, and make up a large proportion of those awaiting liver transplant [11]. Several open-label clinical trials of DAA in decompensated HCV patients have recently shown SVR rates above 80% and improvements have been observed in the CPT and/or MELD scores in a significant proportion of patients after a relatively short follow-up [12–17]. These improvements are largely attributable to changes in the biochemical parameters of serum bilirubin and albumin. The results for SVR observed in these studies are indeed impressive, given that the majority of these patients had several characteristics that would predict a poor response.

We have now seen multiple reports that DAAs are highly efficacious in a population of patients in most need of viral eradication. Viral eradication results in improvements in MELD and CPT scores, denoting improvement in liver function in studies of short-term follow-up. It appears that these regimens are relatively safe, with most adverse events caused by the underlying disease process. However, a proportion of patients do not seem to gain immediate benefit from DAA therapy. Determination of whether these patients are slower to improve or will continue to have decompensated liver disease and are at risk of further complications requires longer follow-up studies [10].The outcomes in the current study after the follow-up period (24 weeks) showed a clinical improvement in the treated cirrhotic cohort (47.7%) versus untreated cirrhotic cohorts (63.6%). However, there were no significant differences in the reported cases of HCC [nine (5.6%) patients in the treated cirrhotic group versus three (5.5%) patients in the untreated cirrhotic]. Although no definite conclusions can be drawn from the current study, our findings suggest that in patients with cirrhosis, a close monitoring for HCC development should be continued even after HCV

eradication. However, more data are needed on the possible influence of DAAs on the onset of new HCC and recurrences. Longitudinal evaluation of larger cohorts followed for a longer follow-up period could help to clarify the rationale for treating HCV patients with advanced liver diseases. Furthermore, given the complexity of the clinical scenario, there is a need for a multidisciplinary approach. Hepatologists, hepatobiliary/transplant surgeons, oncologists, radiologists, infectious disease specialists, and pathologists should be involved to define tailored interventions after HCV eradication on the basis of the severity of liver disease [18].

Conclusion

This study suggests that newer all-oral regimens of DAAs are effective in the treatment of HCV infection and in patients with liver cirrhosis, leading to prolonged improvement in liver function.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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