Original Article

Medical Journal of Viral Hepatitis (MJVH)

Incidence of hepatocellular carcinoma one year after direct acting antiviral therapy for treatment of HCV infection in patients with decompensated liver cirrhosis; A multicenter study

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Abstract

Background: Data on the occurrence of hepatocellular carcinoma (HCC) in decompensated cirrhosis following direct-acting antiviral agents (DAAs) remains insufficient. This study aimed to establish the incidence of HCC in patients with sustained virologic response (SVR) following DAA therapy in chronic hepatitis C (CHC) related decompensated cirrhosis.

Materials and methods: This prospective multicenter observational cohort study included 305 HCV patients with decompensated liver cirrhosis without HCC. Patients were divided into two groups. The treatment group included 216 patients who received DAAs while the non-treatment group included 89 patients who refused antiviral therapy. Patients were followed up for at least one year after achieving SVR. In the present study, 230 patients (176 in treated group and 54 in non-treated group) continued the study follow-up period of at least one year. SVR was achieved in 90% of patients.

Results: Nine patients (5.1%) in the treatment group and 6 patients (11.11%) in non-treatment group developed HCC during the one-year follow-up period after SVR. DAAs therapy was shown to had no significant effect on reducing of incidence of HCC when compared to non-treated patients (p=0.118), although the treatment group showed significant improvement regarding liver function, INR, creatinine, Child-Turcott-Pugh and MELD scores, variceal bleeding, hepatic encephalopathy and ascites when compared to the non-treatment group at one-year post-treatment.

Conclusions: treatment of HCV-related decompensated liver cirrhosis with DAA therapy does not reduce the incidence of HCC after one year of follow-up in spite of patients achieving excellent SVR response and showing significant reduction in cirrhosis-related complications.

Introduction

Hepatocellular carcinoma (HCC) currently accounts for 7% of all cancers, making it one the most common causes of cancer-related deaths worldwide1 [1]. Demonstrating a 2%–8% annual risk and a 30% 5-year cumulative risk of developing HCC in chronic hepatitis C (CHC)-related cirrhosis [2,3], chronic HCV infection has been established as a primary risk factor for the development of HCC [4].

Chronic HCV infection therapy that reaches sustained virological response (SVR) resulting in eradication of the virus is associated with reduced incidence of life-threatening complications and risk of developing HCC with subsequent improved survival rate of cirrhotic patients [5,6]. Use of direct-acting antiviral agents (DAAs) for treatment of chronic HCV infection has been established as the recommended line of therapy due to their excellent safety profiles and promising clinical outcomes [7-9]. Nevertheless, a large number of studies have suggested the occurrence of unexpectedly high rates of HCC incidence either during or following completion of the DAA regimens in cirrhotic patients, an observation not supported by other study groups [10,11]. However, it is worth noting that most of these reports were from retrospective single-center studies based on early DAA treatment regimens used mainly on small cohorts of patients usually presenting with more advanced cirrhosis when compared with patients included in clinical trials using IFN-based regimens [12]. Studies demonstrated that patients with decompensated liver cirrhosis had lower response rates than patients with compensated cirrhosis, with safety issues arising with regards to use of DAAs in patients with the most advanced liver disease [13]. While there remains controversy about the incidence of HCV-related HCC following DAA therapy in compensated liver cirrhosis, little data exists about the incidence of HCC in decompensated liver cirrhosis post-DAA treatment. Therefore, the aim of the current study was to determine the incidence of HCC in chronic HCV-related decompensated liver cirrhotic patients who achieved SVR following DAA therapy.

Materials and methods

This prospective multicenter observational cohort study included 305 adults with HCV infection (diagnosed by positive anti-HCV antibodies and PCR for HCV RNA) decompensated cirrhotic patients free from hepatocellular

Keywords: Hepatocellular carcinoma, hepatitis C virus, direct-acting antiviral agents, sustained virologic response, ascites, alpha fetoprotein.
Received: 1-3-2022; Accepted: 25-4-2022
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carcinoma who were candidates for treatment with DAAs. The patients were followed up at the Gastroenterology and Hepatology Department of Damietta Cardiology and Gastroenterology Center, Tropical Medicine Department and Internal Medicine Department, Mansoura University and Tropical Medicine, Menoufia University, Menoufia, Egypt, during the period from February 2019 to May 2021. Patients were divided into 2 groups, namely the treatment group, including 216 patients who received DAAs, and non-treatment group, including 89 patients who refused antiviral therapy. Complete medical history and physical examination were performed before administration of antiviral therapy for included patients. All patients had virological, hematological, and biochemical laboratory testing performed, in addition to abdominal ultrasonographic examination and triphasic MSCT where indicated. Child- Pugh-Turcotte and MELD scores were calculated. For one year after completion of the treatment regimen, patients were followed up every three months after reaching SVR or on regular scheduled outpatient clinic visits by laboratory and radiological investigations including triphasic MSCT if indicated. The study was ethically approved by the Medical Research Ethics Committee of Damietta Cardiology and Gastroenterology Center. A written informed consent was obtained from all patients after giving full explanation on the objective of the research.

Inclusion criteria: Patients 18 years or older with decompensated HCV liver cirrhosis having no history of past or current HCC who were eligible for DAAs therapy.

Exclusion criteria: Patients excluded where those who had not achieved SVR, those who had relapsed, or those who had died during the follow up period due to causes unrelated to HCC. In addition, patients with either hepatitis B virus (HBV) or HIV co-infection, and those having undergone previous IFN-treatment or previously ablated or active HCC, as well as patients having liver transplantation, renal impairment and other malignancies were also excluded.

Diagnosis and staging of HCC: HCC was suspected upon detection of a focal hepatic lesion by ultrasound or with elevated AFP level. Diagnosis was confirmed by triphasic MSCT based on the characteristic arterial enhancement and early washout in the delayed phase [14].

Diagnosis of liver decompensation: Liver decompensation in a compensated patient depended on the presence of at least one episode of overt ascites (or pleural effusion with increased SAAG (> 1.1 g/dL), overt hepatic encephalopathy and variceal bleeding [15].

Antiviral treatment: Patients in the treatment group were further divided into two groups, the first receiving sofosbuvir (SOF) and daclatasvir (DAC) for 24 weeks (Group I; 158 patients) and the second receiving sofosbuvir, daclatasvir and ribavirin for 12 weeks (Group II; 58 patients). Treatment choice was based on the decision of a local multidisciplinary conference of experienced clinicians.

Endpoints of the study: Primary end point: Follow up of the patients up to 48 weeks after the end of treatment or until the appearance of de novo HCC. Secondary end point: Any serious adverse events that led to discontinuation of follow up and/or death not related to HCC as the primary cause.

Statistical analysis

Data were entered and analyzed using IBM-SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Frequency and percentage were used to express qualitative data. Kolmogorov-Smirnov and Shapiro-Wilk's test were initially used to test for normality of quantitative data. P>0.050 indicated data was normally distributed. Extreme values (significant outliers) were tested for by examination of boxplots. Mean ± standard deviation (SD) was used to express quantitative data that was normally distributed, while median and interquartile range (IQR) were used if not normally distributed. To adjust p values when comparing column proportions, Chi-square test with Bonferroni method was used, as was Monte Carlo significance when appropriate. For normally distributed data in all groups without significant outliers, one-way ANOVA test was used; alternatively, the non-parametric Kruskal-Wallis H test was used. For normally distributed data in all measurements with no significant outliers, repeated-measures ANOVA test was used; alternatively, the non-parametric Friedman's test was used. results were considered as statistically significant if p value ≤ 0.050 for any of the used tests.

Results

A total of 305 consecutive HCV decompensated cirrhotic patients were included in this study to be divided into two groups, namely the treatment group including 216 patients receiving DAA therapy and had achieved SVR and the non-treatment group including 89 patients who refused therapy. Of the studied patients, 75 subjects were excluded, including 40 patients from the treatment group (28 patients missed follow-up appointments and 12 patients died) and 35 patients from the non-treatment group (19 missed follow-up and 16 died). The remaining 230 patients (176 in treated group and 54 in non-treated group) continued the study follow-up period of at least one year.

Table 1 shows the baseline data of the studied groups. There was no statistically significant difference between studied groups regarding age, gender, DM, hypertension, complications such ascites and variceal bleeding, and laboratory indices such as hemoglobin level, platelets, bilirubin, ALT, and AST. However, a significant increase was found in non-treatment group versus the treatment group with regards to serum albumin, creatinine, and AFP level.

Table 2 shows the laboratory data at baseline and at 48 weeks following completion of treatment among the studied groups. Compared to baseline values, a statistically significant improvement in levels of hemoglobin, platelets, ALT, AST, total bilirubin, albumin, INR, and creatinine was detected in the treatment group at 48 weeks post-treatment, although no significant change was found with regards to APF level. The non-treatment group similarly

demonstrated no statistically significant changes regarding these parameters with the exception of a significant decrease in serum albumin and significant increase in AFP level.

Table 3 shows a statistically significant decrease in both MELD and Child scores in the treated group of patients at 48 weeks post-treatment compared to baseline, while patients who did not undergo treatment demonstrated statistically significant increase in these scores over this same period of time.

Table 4 shows a statistically significant decrease in complications such as ascites, variceal bleeding and hepatic encephalopathy in the treatment group compared to non-treatment group with no statistically significant difference noted between groups regarding hepatocellular carcinoma.

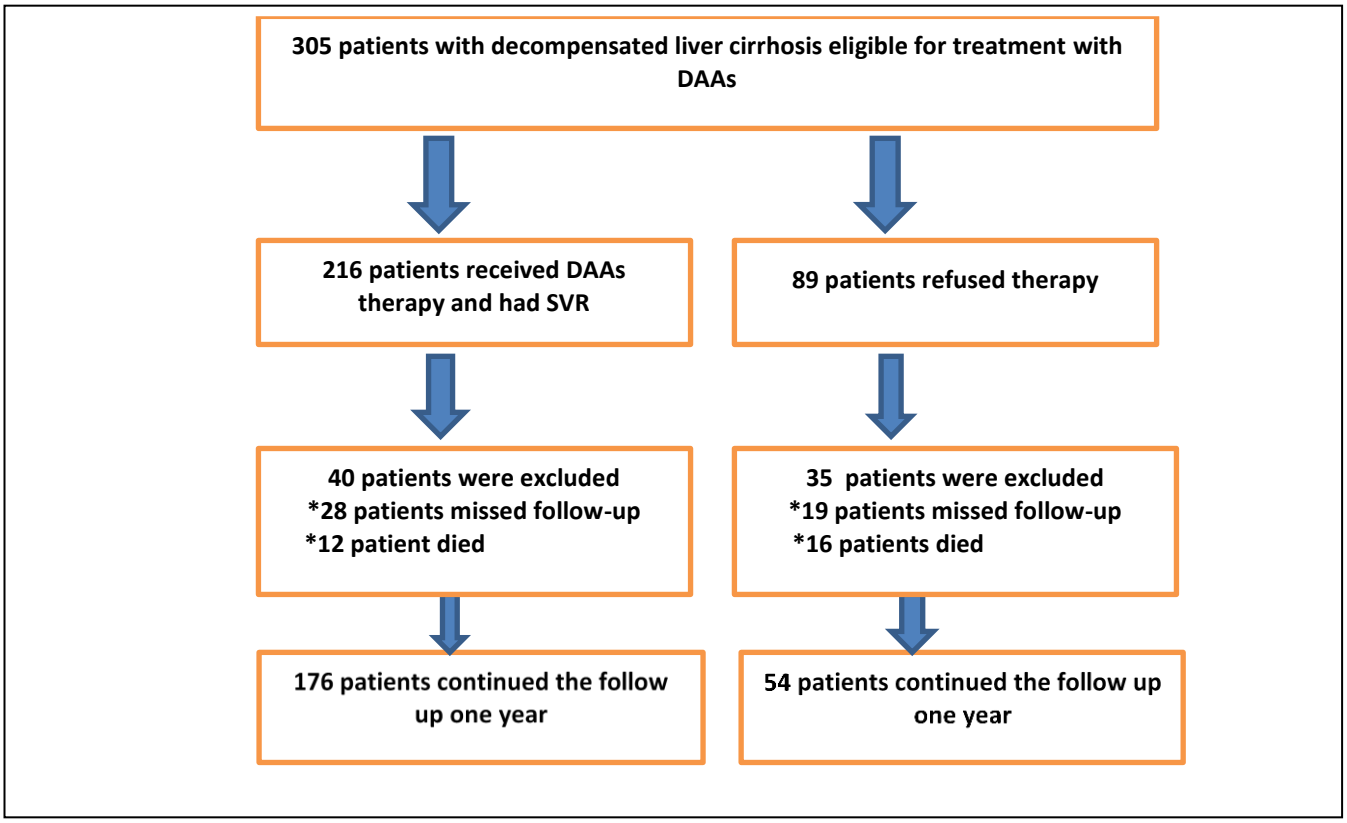

Figure 1: Flow chart of patients in the study

Table 1. Baseline clinical and laboratory data among the studied groups.

Variable	Group I (N= 176)	Group II (N= 54)	P value
Age	57.81±3.1	56.69±6.1	0.9633
Gender: M/F	94/82	36/18	0 .085
DM: N/%	78/44.3	30/ 55.6	0.147
hypertension	48/27.27	18/33.33	0.475
Ascites: N/%	118/67.04	34/62.96	0.579
HE: N/%	16/9.09	18/33.3	0. 001
Variceal bleeding: N/%	18/10.22	6/11.1	0.852
Hemoglobin (gm/dl)	11.48±1.32	11.03±0.93	0.997
Platelet count (/ccm3)	77.0 (62.25-105.0)	80.0 (64.097.0)	0.451
ALT (IU/L)	38.0 (28.75-50.25)	37(37-39)	0.845
AST (IU/L)	41.5 (35-56.25)	46.0 (42.0-65.0)	0.367
Serum bilirubin (mg/dl)	2.78±0.66	2.73±0.53	0.69

Serum albumin (gm/dl)	2.98±0.34	3.07±0.2	0.5
INR	1.54±0.26	1.59±0.176	0.093
AFP (ng/ml)	11.5 (7.88-18.0)	12.3 (7.30-89.6)	0.001
Creatinine (mg/dl)	0.94±0.34	1.23±0.26	0.001

HE, hepatic Encephalopathy; ALT, alanine transaminase; AST, aspartate transaminase; AFP, alfa fetoprotein.

Table 2. Parasitic infection incidence in HCV cases and control group.

	Group I N=176		**Group II N=54**		
Parameter	**Baseline**	**48week-post-treatment**	**Baseline**	**48week-post-treatment**	**P value**
HB (gm/dl)	**11.48±1.32**	**11.90±1.21**	**11.03±0.93**	**10.86±0.87**	**P1:0.002 P2: .328**
Platelets (109/l)	**77.0 (62.25-105.0)**	**78.0 (66.5-109.25)**	**80.0 (64.0-97.0)**	**83.0 (76.0-89.0)**	**P1:<0.001 P2: 0.135**
ALT (IU/l)	**38.0 (28.75-50.25)**	**33.0 (27.0-38.0)**	**37 (37-39)**	**35.0 (29.0-48.0)**	**P1: <0.001 P2: 0.23**
AST (IU/l)	**41.5 (35-56.25)**	**38.5(35-46)**	**46.0 (42.0-65.0)**	**51(40-57)**	**P1:<0.001 P2: 0.922**
Total bilirubin (mg/dl)	**2.78±0.66**	**2.14±0.56**	**2.73±0.53**	**2.81±0.64**	**P1:0.002 P2: 0.480**
Serum albumin (gm/dl)	**2.98 ± 0.34**	**3.1 ± 0.36**	**3.07 ± 0.2**	**2.84 ± 0.162**	**P1:0.001 P2: 0.001**
INR	**1.54±0.26**	**1.42±0.213**	**1.590±0.176**	**1.602±0.162**	**P1:0.001 P2:0.924**
AFP (ng/ml)	**11.5 (7.88-18.0)**	**10.5 (5.35-15.5)**	**12.3 (7.30-89.6)**	**13.6(7.3-93.0)**	**P1:0.060 P2:0.049**
Serum creatinine (mg/dl)	**0.94±0.34**	**0.86±0.246**	**1.23±0.26**	**1.27± 0.23**	**P1:0.006 P2:0.201**

HB, hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase; AFP, alfa fetoprotein; p1, group A before and after therapy; p2, group B before and after therapy.

Table 3. MELD score and Child-Pugh Score at baseline and 48 weeks post-treatment among the studied groups.

Child-Pugh Score			
Group	**Baseline**	**Post-treatment (48-weeks)**	**P value**
Treatment group	**8.1±1.14**	**7.56±1.27**	**P<0.001**
Non-treatment group	**8.22±1.42**	**8.66±1.47**	**0.023**
MELD score			
Group	**Baseline**	**Post-treatment (48-weeks)**	**P value**
Treatment group	**17.56±1.69**	**15.19 ±0.75**	**<0.001**
Non-treatment group	**17.41±1.76**	**18.1±2.212**	**0.03**

Table 4. Clinical outcomes and complications 48 weeks post-treatment among the studied groups.

Variable	**Group I (N=176)**	**Group II (N=54)**	**P value**
Ascites: N/%	**34/ 28.6%**	**44/ 81.48**	**0.001**
Variceal bleeding: N/%	**7/ 3.97%**	**12/ 22.22**	**0.0002**
Hepatic Encephalopathy: N/%	**4/ 2.27%**	**26/ 48**	**0.0001**
Hepatocellular carcinoma: N/%	**9/ 5.1%**	**6/ 11.11**	**0.118**

Discussion

The incidence of hepatocellular carcinoma in decompensated liver cirrhosis following direct acting antiviral therapy for chronic hepatitis C virus infection remains obscure, a fact that prompted the induction of the current study. This study showed that treatment of HCV-related decompensated liver cirrhosis by DAAs did not reduce the incidence of HCC after one year of reaching sustained virological response (SVR) in spite of an excellent SVR and a significant reduction in cirrhosis-related complications. Nine patients (5.1%) of those treated by DAAs developed hepatocellular carcinoma compared to six untreated patients (11.1%) over a follow-up period of one-year post-SVR, an insignificant difference between both groups.

While several studies have suggested that cirrhotic patients who undertake DAA regimens and achieve SVR may have an increased likelihood of new or recurrent liver malignancy [16,17], other reports have shown that DAA therapy was associated with decreased risk of HCC in cirrhotic HCV patients [18-20]. However, it should be noted that these studies were all conducted on chronic HCV patients with compensated liver cirrhosis.

In a study on a large group of English HCV patients with advanced liver disease treated with DAAs, Cheung et al noted that patients with decompensated cirrhosis demonstrated extensively improved liver function profile without evidence of adverse effects or increased HCC when compared to untreated patients [21]. Patients with decompensated liver cirrhosis in the present study had an overall SVR of 91%, this being 89.3% in patients who received six months of sofosbuvir and daclatasvir and 92.3% in patients who received sofosbuvir, daclatasvir and ribavirin for three months, with no significant difference detected between both treated groups.

Guidelines by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) confirm that different DAA regimens used in patients with decompensated cirrhosis are associated with essentially similar or slightly lower SVR rates than those of patients with compensated cirrhosis [22,23]. Indeed, vast numbers of HCV-infected decompensated cirrhotic patients who received DAA therapy had SVR rates that were only marginally lower than their compensated counterparts, with SVR revealed from both clinical trials and real-world reports to be around 80% following DAA therapy in patients with present or past decompensation [24,25]. A remarkable overall 95.1% SVR in chronic decompensated cirrhotic HCV infection was even reported by Omar et al [26].

Analysis of patients with decompensated liver cirrhosis who responded to DAA therapy showed significant improvement in both (model for end-stage liver disease) MELD score as well as Child-Pugh-Turcotte score. The current study demonstrated that direct acting antiviral (DAA) treatment in decompensated cirrhotic patients was associated with improvement in liver function profile as well as MELD and Child-Pugh scores. In accordance with these findings, several other studies also found improvement of liver function after achieving DAA-associated SVR in decompensated liver cirrhosis [27]. Furthermore, integrated analysis of data from four sofosbuvir-based clinical trials on decompensated cirrhotic patients who reached SVR showed that 31.6% and 12.3% of patients with baseline Child-Pugh scores B and C, respectively, regressed to Child-Pugh score A by week 36 of initiating HCV treatment [28]. Decompensated cirrhotic patients undergoing treatment also demonstrated a significant improvement in baseline laboratory parameters, as reported by Hanafy et al [29]. Additionally, a relatively short period of follow up post-SVR was associated with significantly improved Child-Pugh-Turcotte and/or MELD scores in various open-label clinical trials of DAA therapy administered to decompensated HCV cirrhotic patients [30,31].

The current study demonstrated significant improvement in cirrhosis-associated complications such as ascites, hepatic encephalopathy, and gastrointestinal bleeding at one-year post-SVR in treated patients when compared to those who were untreated. These results are in accordance with those of Hanafy et al who similarly demonstrated a statistically significant improvement in hepatic encephalopathy and gastrointestinal bleeding in treated versus untreated patients [29].

Conclusion

Treatment of chronic HCV related decompensated cirrhosis with DAA therapy does not reduce the incidence of HCC at one-year post-SVR despite excellent SVR and improvement of the clinical outcomes such as ascites and hepatic encephalopathy.

Acknowledgements

The authors would like to express their appreciation for all staff in Tropical and Internal Medicine Departments, Mansoura University and Damietta Cardiology and Gastroenterology Center. Tropical Medicine, Menoufia University.

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