Occurrence and Recurrence of Hepatocellular Carcinoma after Direct Acting Antivirals in Compensated Chronic Hepatitis (C) Cirrhotic Egyptian Patients

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ABSTRACT

Background: Egypt had been vexed by the highest load of chronic hepatitis C in the world. It represents a vast market of the new direct-acting anti-viral drugs (DAAs); effectively treating chronic hepatitis C virus (HCV) infection.
Objectives: The aim of this study is to detect the occurrence and recurrence of hepatocellular carcinoma (HCC) during the follow-up after antiviral treatment with direct acting antiviral therapy in patients with chronic HCV infection and in patient with chronic HCV prior history of treated hepatocellular carcinoma who achieved complete response.
Subjects and methods: This was prospective study including 150 patients with compensated chronic hepatitis C virus infection and 150 patients with compensated chronic hepatitis C virus infection prior history of treated hepatocellular carcinoma. The patients were attending Aswan university hospital and viral hepatitis unit in addition to Viral Hepatitis Unit and were prospectively collected at the end of December 2019. The patients were divided into two groups: Group (A): patients with chronic HCV infection who were treated with direct acting antivirals. Group (B): patients with chronic HCV infection prior history of treated hepatocellular carcinoma who were treated with direct acting antivirals.
Results: The results of the study revealed that there was no significant difference between the studied groups as regard time needed for HCC to occur after DAA.
Conclusion: Surveillance programs should be widely endorsed during and after DAAs therapy for patients at HCC risk, even for those who had been achieved HCV cure.
Keywords: Chronic hepatitis C, Direct acting antiviral, Egypt, Hepatocellular carcinoma.
Conflicts of interest: no conflicts of interest were encountered.
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INTRODUCTION

Hepatitis C virus (HCV) is a major global healthcare problem. The WHO estimated that up to 3% of the world's population were infected with the virus, equating to more than 170 million individuals worldwide, with significant associated morbidity and mortality **(1).**

Egypt has the highest prevalence rate of hepatitis C virus (HCV) in the world, making it the most challenging public health problem facing the country **(2)**. Studies show that 14.7% of the Egyptian population carries HCV antibodies and 9.8% have an active infection **(3).**

In 2015, Egypt Health Issues Survey showed that 10% of Egyptians between 15 – 59 years of age had been infected with HCV infection, while 7% were chronic active hepatitis C patients **(4).**

A mathematical model was used to estimate the 2014 prevalence in Egypt. Assuming that 65,000 patients were treated annually with pegylated (PEG) interferon and ribavirin (RBV) with a sustained virologic response (SVR) rate of 50%, that 32,000 patients were cured, that an estimated 150,000 new infections occur annually leading to 100,000 chronic HCV infections and that 150,000 persons with HCV die (120,000 of causes other than liver disease and 30,000 of HCV-related complications), seroprevalence was modeled to 10.6% and viremic prevalence to 7.3% in 2014 **(5).**

Hepatocellular carcinoma (HCC) is one of the most dreadful sequels of hepatitis C virus (HCV)-related cirrhosis. New direct-acting antivirals (DAA) have successfully created a new era of HCV elimination **(6).** However, their role in moderating the incidence of HCC in those patients is still questionable.

During the previous decades, pegylated interferon (PEG-IFN) plus ribavirin therapy for patients with chronic hepatitis C (CHC) cured hepatic C virus (HCV) infection in approximately 50% of treated patients **(7)**. Emerging treatments with IFN-free direct-acting antiviral agents (DAA) for patients with chronic CHC directly target HCV replication and have been widely used globally since 2014. Compared to conventional IFN-therapy, the sustained virological response (SVR) rate is higher and the side effects are reduced with DAA therapy **(8).**

In recent years, a dramatic improvement in HCV therapy followed the introduction of oral medicines that directly inhibited the replication cycle of HCV. These medicines, called direct-acting antivirals (DAAs), target three important regions within the HCV genome: NS3/4A protease, NS5A and NS5B RNA-dependent polymerase. These medicines have led to higher sustained virological responses (SVRs) than interferon-based regimens, are shorter in treatment duration, are orally administered and have fewer side effects. Individual DAAs vary in

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therapeutic efficacy, genotypic efficacy, adverse events and drug–drug interactions (DDIs), and must be used in combination with at least one other DAA [9].

AIM OF THE WORK

The aim of this study is to detect the occurrence and recurrence of hepatocellular carcinoma (HCC) during the follow-up after antiviral treatment with direct acting antiviral therapy in patients with chronic HCV infection and in patient with chronic HCV prior history of treated hepatocellular carcinoma who achieved complete response.

Hypothesis: Chronic hepatitis C infection is associated with hepatocellular carcinoma in some patients as a complication of the virus. Once the virus is eradicated, the possibilities of occurrence and recurrence of HCC are increased according to some studies or the possibilities may be decreased according to other studies. Also, know what is happening in Egyptian patients.

PATIENTS AND METHODS

Technical design:

Study design: This study is a prospective study

Setting: This study was carried out at Aswan University Hospital and Viral Hepatitis Unit.

Time of the study: from December 2017 to December 2019.

Target population: 150 patients with compensated chronic hepatitis C virus infection who were treated with direct acting antivirals (Groip A) and 150 patients with compensated chronic hepatitis C virus infection prior history of treated hepatocellular carcinoma by ablation, resection, chemoembolization or liver transplantation, who were treated with direct acting antivirals (Group B**)**.

Sampling technique: This study was performed on systematic random sampling.

Methods:

1. Clinical assessment: **(a) History:** complete history taking: age, sex, residency, occupation, smoking, presenting complaint, jaundice, itching, abdominal pain, weight loss, history of previous hepatic encephalopathy, history of previous antiviral treatment, history of previous bilharziasis or antibilharzial treatment and presence of comorbidities, such as diabetes mellitus or hypertension were evaluated. **(b) Clinical examination:** General examination and abdominal examination.

2. Laboratory assessment: 1. Complete blood count. 2. Liver function tests. 3. Kidney function tests. 4. Prothrombin time, prothrombin concentration and INR. 5. Viral hepatitis markers (HBV surface antigen, HCV antibody). 6. Alpha fetoprotein (AFP). 7. Quantitative HCV-RNA detection using real-time polymerase chain reaction (PCR).

3. Radiological assessment: (1) Abdominal ultrasonography (US). (2) Abdominal contrast-enhanced "Triphasic" computed tomography (CT) scan in HCC patients.

Diagnosis of HCC was made on presence of nodular lesion with arterial enhancement in the arterial phase and rapid washout in the portal phase. According to American Association for the Study of Liver Disease (AASLD), every suspicious lesion in high-risk patients with suggestive US findings for HCC was evaluated. Furthermore, by multidetector CT scan or dynamic MRI with contrast, lesions that had the typical characters of HCC were identified, and the diagnosis of HCC was confirmed. Biopsy was not necessary for the diagnosis of HCC in a nodule greater than 2 cm at initial diagnosis, and was compatible with HCC after one dynamic study.

A Pilot study was carried out on (10% of study sample) to test feasibility, applicability and clarity of methods.

Ethical Consideration:

We confirm that the present study ran in concordance with international ethical standards and applicable local regulatory guidelines. The study didn't have any physical, psychological, social, legal, economic, or any other anticipated risks to study's participants. The study conserved participants' privacy. Investigators were responsible for keeping the security of the data. We also confirm that the participants' data were not used for any other purpose outside this study. Personal data (e.g. Name, Contact info) were not entered in our data entry software to conserve the participants' privacy, however, each subject got a unique identifier code. Participants in the targeted institutions were informed about the study objectives, methodology, risk, and benefit. A written informed consent was obtained from each eligible patients prior to study's enrollment. **The study's protocol was reviewed and approved by Ethics Committee or Audit Department of Internal Medicine Department, Faculty of Medicine, Aswan University.**

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean±standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means. Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following: P-value <0.05 was considered significant. P-value <0.001 was considered as highly significant. P-value >0.05 was considered insignificant.

RESULTS

Table (1): Studying of demographic data in between the studied groups:

Variable	Group (A) (n=150)		Group (B) (n=150)		P value
Mean ± SD Range	47.4±14.4 (19-71)		51.45±14.9 (19-72)		>0.05
Mean ± SD Range	26.3±1.3 (23.4 – 29.6)		26.0±1.4 (23.6 – 28.7)		>0.05
	No.	**%**	**No.**	**%**	**P value**
Female Male	50 100	33.3 66.7	55 95	36.7 63.3	>0.05

This table shows that there is no statistical significant difference between the two studied groups as regard age, BMI or gender.

Table (2): Previous treatment lines of HCC in the HCC studied group:

Variable	Group (B) (n=150)	
	No.	**%**
Previous treatment:		
Surgical resection RFA TACE LT	50 70 20 10	33.3 46.7 13.3 6.7

TACE: transcatheter arterial chemo-embolization, LT: liver transplantation, RFA Radiofrequency ablation.

This table shows that 33.3% of HCC had a history of treatment with surgical resection, 46.7% had a history of RFA, 13.3% had a history of TACE and 6.7% had a history of LT.

Table (3): HCC occurrence or recurrence among the studied groups:

Variable	Group (A) (n=150)		Group (B) (n=150)		p-value
	No.	**%**	**No.**	**%**	
Yes No	2 148	1.3 98.7	5 145	3.3 96.7	>0.05

This table shows that there is no significant difference between the studied groups as regard HCC occurrence or recurrence.

Table (4): Time needed for HCC to occur after DAA treatment in between the studied groups:

Variable	Group (A) (n=2)	Group (B) (n=5)	P value
Mean ± SD Range	15.2±2.4 (2.2-28.2)	15.1±2.0 (2.1-20.2)	>0.05

This table shows that there is no significant difference between the studied groups as regard time needed for HCC to occur after DAA

Table (5): Relation between type of DAA and HCC development:

Variable	Cases developed HCC N=7		Cases didn't develop HCC N=293		p-value
	No.	**%**	**No.**	**%**	
Yes No	1 6	14.3 85.7	101 192	34.4 65.6	>0.05
Yes No	2 5	28.6 71.4	110 183	37.5 62.5	>0.05
Yes No	2 5	28.6 71.4	47 246	16.0 84.0	>0.05
Yes No	2 5	28.6 71.4	36 257	12.3 87.7	>0.05

This table shows that there is no significant relation between type of DAA and HCC development.

DISCUSSION

There is no statistically significant difference between the two studied groups as regard age, BMI or gender.

Our results are in agreement with study of **Nahon *et al.*** [10] as they reported that there was no statistically significant difference between the studied groups as regard age, BMI or gender.

Kozbial *et al.* [11] found that there was no statistically significant difference between the studied groups as regard age or gender.

The present study shows that 33.3% of HCC had history of treatment with surgical resection, 46.7% had history of RFA, 13.3% of TACE and 6.7% with liver transplantation. There was high significant difference between the two studied groups as regard ALT, total bilirubin and creatinine levels; also there was significant difference between the studied groups as regard AFP while there was no significant difference between the two studied groups as regard albumin, INR, platelets, total protein and WBCs.

Our results are in line with study of **Nahon *et al.*** [10] as they reported that there was highly significant difference between the studied groups as regard ALT, AST and total bilirubin.

The increasingly widespread use of direct-acting antiviral agents (DAAs) constituted a major breakthrough in the treatment of hepatitis C virus (HCV) infection, because of the high rates of sustained virologic response (SVR) achieved and an excellent safety profile [12].

In the study in our hands, there was no significant difference between the studied groups as regard HCC occurrence or recurrence. There was no significant difference between the studied groups as regard time needed for HCC to occur after DAA. There was no significant relation between type of DAA and HCC development.

Prenner and colleagues performed a retrospective study from 2014 to 2015 and compared patients treated with DAA therapy who either had active HCC on initiation or had previously received curative treatment for HCC with patients who had no history of HCC. Approximately 21% of patients with HCC failed to achieve SVR, which was significantly greater than the rate in those without HCC (12%). After multivariate analysis, the authors concluded that patients with active HCC upon initiation of DAA therapy were almost 6 times more likely to fail treatment, whereas those who had already received curative treatments for HCC showed SVR by 24 weeks after completion of DAA treatment. These findings led to further speculation as to whether the HCV/HCC interaction may have a more significant role than previously recognized [13].

Pretransplant patients receiving DAA therapy had higher recurrences of HCC, but such data may be limited because of sample size and selection bias [14].

Other studies showed the opposite effect on HCC recurrence after DAA therapy, with decreased occurrence or recurrence rates. **Affronti and colleagues** analyzed outcomes, including HCC, death, and transplantation, in HCV patients with advanced cirrhosis who received DAA therapy. Over the course of 82 weeks and after adjustment for confounders, the authors noted a significantly greater HCC-free survival rate in patients who achieved SVR compared to those who did not [15].

Although many studies have highlighted HCC recurrence after DAA therapy, some studies have suggested that there may be insufficient evidence for such a claim. The European studies that postulated an association between HCC recurrence and DAA therapy were noted to be mostly observational and were not randomized, controlled trials, which thereby allowed for possible confounding variables [16].

Additionally, HCC rates in some of these data sets were higher than expected and could not be reproduced in the US population, suggesting possible selection bias [17]. Further analyses continued to cast doubt on the evidence at hand. A retrospective analysis of the ANRS (France Recherche Nord & Sud Sida-HIV Hépatites) study in France could not confirm an increased risk of HCC recurrence in a cohort study of over 6000 patients, noting that the 6-month recurrence rate (10.6%) in patients treated with DAA agents was lower than that of patients who did not receive DAA therapy (18.7%). This finding suggests that DAA therapy in patients with cirrhosis may decrease the risk of HCC development, similar to what was reported in patients treated with interferon [18].

Cheung *et al.* [19] performed a prospective study on patients with HCV infection and decompensated cirrhosis and noted a decreased HCC incidence with SVR obtained by DAA agent, compared to patients who did not achieve SVR despite DAA therapy. The authors noted that patients treated with DAA agents experienced fewer adverse events, including decompensation and MELD deterioration, compared to patients not treated with DAA agents, but did not show increased rates of mortality, liver transplantation, or HCC occurrence.

According to **Nahon *et al.*** [10], there was increase in HCC incidence observed in patients with cirrhosis treated with DAAs compared with patients who achieved SVR following an IFN therapy. This could be explained by patient characteristics (age, diabetes, reduced liver function) and lower screening intensity.

D'Ambrosio *et al.* [20] investigated a cohort of 38 histological cirrhotic patients who had been prospectively followed for 10 years after achieving a SVR with IFN treatment. During a median follow-up of 86 months after a liver biopsy, no patients developed clinical decompensation, while 5 patients (13%) developed HCC. The 8-year cumulative probability of HCC was thus 17% regardless of the cirrhosis

regression, while the 8-year cumulative survival probability was 97% regardless of the cirrhosis regression (96% vs 100%, P = 1.0) or HCC development (100% vs 97%, P = 1.0).

Furthermore, **Bielen *et al.*** [21] did not find higher-than-expected early occurrence rates of HCC in patients treated with DAA regimens (1.1%; 4/355) compared to patients treated with IFN regimens (1.7%; 1/59). These rates were comparable to the estimated 1% per year frequency of HCC that is observed in patients with an SVR who were treated with IFN and ribavirin dual therapy.

Kobayashi *et al.* [22] demonstrated that the impact of DAA treatment was similar to that of IFN treatment with regard to HCC risk reduction in patients who achieved a SVR. The 3- and 5-year cumulative HCC development rates were 1.30% and 3.03%, respectively, in the DAA group, and 1.02% and 2.19% in the IFN group, respectively.

Treatment of HCV is costly. Given the size of the problem in Egypt, it is being addressed as a national health priority. However, budget limitations remain the main barrier to expanding treatment. The National Committee for the Control of Viral Hepatitis was established in 2006 with the mandate of developing a National Control Strategy for Viral Hepatitis. Treatment was based on pegylated interferon (peg-INF) in combination with ribavirin (RBV) according to Egyptian National Control Strategy for Viral Hepatitis in 2012 [23].

Treatment will be provided through 26 designated government centers, to be increased to reach 40 centers. The cost of treatment is expected to be distributed among several entities, including patient co-payment: 38% by Ministry of Health (MOH), 51% by the Health Insurance Organization (HIO), 3% by the private payments and 8% by cash payments at the centers [24].

The treatment program will cover 50,000 patients in its first phase, launched in October 2014. In December 2014, the MOH expects 100,000 more treatment courses to be delivered. The target is to ultimately treat 300,000 patients annually [24].

CONCLUSION

The recommendations for evaluation and management of patients with HCV infection remain unchanged. All HCV patients with cirrhosis should continue to have at least standard HCV surveillance biannually, and those who are deemed at high risk may benefit with closer follow-up.

RECOMMENDATIONS

1. Further studies on large geographical scale and on larger sample size to emphasize our conclusion.
2. For the time being, risk assessment for HCC should be rigorously undertaken before DAAs, and those at risk should have attentive surveillance during treatment and afterward.
3. For people at risk, it is noteworthy to explain the importance of continued surveillance after HCV eradication.
4. Also, physicians in the outreach clinics should know by heart that in HCV-positive patients, the risk of HCC is reaching higher figures compared with those eliminated the virus, yet sustained responders having advanced fibrosis are still at high HCC risk.
5.

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