Hepatitis C virus treatment by direct-acting antivirals in successfully treated hepatocellular carcinoma and possible mutual impact

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Background and aims Treatment of hepatitis C virus (HCV) after successfully treated hepatocellular carcinoma (HCC) becomes possible with the introduction of direct-acting antivirals because of their favorable efficacy, safety, and short period of treatment. Few data are available on the results of treatment using different direct-acting antiviral regimens in successfully treated HCC and a lot of debate about its role in tumor recurrence.

Methods Sixty-two HCV-related HCC patients were enrolled in the study after successfully treated HCC; the studied population included either Child–Pugh 'A' or 'B7'. The patients were subcategorized to receive one of the following regimens: group 1: sofosbuvir (SOF) + ribavirin (RBV) for 24 weeks, group 2: SOF + simeprevir for 12 weeks, group 3: SOF + daclatasvir for 24 weeks, and group 4: SOF + daclatasvir + RBV for 12 weeks. The overall median follow-up period is 12 months after treatment initiation (ClinicalTrials.gov no: NCT02771405).

Results All treatment regimens were tolerable for all patients, with no reported major adverse events during treatment. The overall sustained virologic response rate was 64.5%, with the highest result in group 4 and the lowest result in group 1; 87.5 and 26.7%, respectively. HCC recurrence was observed in 42% of patients; 80.7% of these patients developed recurrence within 6 months of treatment initiation.

Conclusion Treatment of HCV in successfully treated HCC is feasible, with the best results achieved using multiple direct-acting antivirals and RBV; a high rate of HCC recurrence was observed, especially within the first 6 months of treatment initiation. Eur J Gastroenterol Hepatol 00:000–000

Background

Egypt has one of the highest prevalence rates of hepatitis C globally [1]. In 2008, a demographic health survey (DHS) documented the prevalence of chronic hepatitis C viremia among 10% of the population between 15 and 59 years of age [2]; however, the prevalence decreased in the following DHS in 2015, with only 7% of viremic patients among the same age group [3]. Genotype 4 is the major infecting genotype in Egypt, representing more than 90% of those with chronic hepatitis C virus (HCV) [4,5].

HCC is the fifth most common cancer worldwide and the third leading cause of death among cancer mortalities. HCV represents a major cause of HCC development in HCV-related cirrhotic patients [6]. Before the introduction of HCV direct-acting antiviral drugs (DAAs), pegylated interferon (PegIFN) and ribavirin (RBV) were the cornerstone and standard of care therapy for HCV; yet, its use was limited to a certain groups of patients with compensated liver functions and could not be used safely for decompensated patients or those who have HCC, except under certain conditions. The use of pegylated interferon for HCV treatment in that era had a positive impact in reducing the incidence of HCC in patients who achieved a sustained virologic response (SVR) [7,8].

Treatment of HCV in patients with advanced liver disease becomes available with DAAs under the umbrella of its safety, efficacy, and short duration of therapy; to this extent, inclusion of HCC patients within the treatment groups becomes realistic, with a high efficacy, reaching 90% SVR 12 [9].

Recurrence of HCC after a radiological complete response may be either early or remote recurrence; there are conflicting data on the clear cut-off period for differentiating the early recurrence, which could be related to inadequate tumor treatment, poor differentiation, or vascular invasion from late recurrence, which could be related to the underlying liver disease. Yamamoto *et al.* [10] defined 17 months as a cut-off period to differentiate between early and remote recurrence in HCC patients treated with hepatectomy, whereas Poon [11] described a

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longer duration of up to 24 months. Tumor recurrence was described in different studies based on the modality used for HCC management; in hepatic resection, tumor recurrence varies from 51% of patients after 34 months [12] and 83.6% [13] and 82.8% [14] after 36 months. In radiofrequency ablation (RFA), recurrence was observed in 20% [15] and 28% [16] after 36 months, and 26% after 52 months [17], whereas in transarterial chemoembolization (TACE), recurrence was observed in 72.6% [13] and 68.9% [14] after 36 months.

An important alarm was raised about the unexpected high HCC recurrence rates after HCV treatment using DAAs [18] followed by a strong wave of contradictory data.

In the current study, we describe the results of treatment of 62 chronic HCV patients with successfully managed HCC and their follow-up after treatment.

Objective

The aim of this study was to explore the results of HCV treatment with DAAs in HCC patients who achieved a complete radiological response and the possible mutual impact.

Methods

Study design

The study was reviewed and approved by an independent ethics committee and carried out in accordance with the Declaration of Helsinki and good clinical practice guidelines (ClinicalTrials.gov no.: NCT02771405). All authors had access to the study data, and reviewed and approved the final manuscript. All enrolled patients provided written, informed consent before the start of the study. This was a prospective nonrandomized open-label study that enrolled 62 patients with genotype 4 HCV after successfully managed HCC; all enrolled patients had confirmed chronic HCV by positivity of HCV antibodies and viral RNA by PCR for more than 6 months.

HCC was diagnosed by the presence of neoplastic criteria (arterial enhancement and delayed wash out) in either a multiphase multislice spiral computed tomography scan or a dynamic contrast-enhanced MRI examination with or without α-feto protein (AFP) elevation.

Tumor staging and selection of the treatment modality were performed according to the Barcelona Clinic of Liver Cancer classification [19].

The patients were treated primarily for HCC (for the first time and no history of HCC previous treatment) using one of the following modalities:

(1) Percutaneous ethanol injection (PEI).
(2) Thermal ablation, by RFA or microwave ablation (MWA).
(3) Hepatic resection.
(4) TACE.

After successful management of HCC (achievement of a complete radiological response defined as the absence of tumor enhancement in all phases of computed tomography/MRI examinations, normalization of AFP (for those who showed elevated baseline levels), the patients received one of the following DAAs regimens for HCV treatment:

(1) Group 1: received sofosbuvir (SOF) + RBV for 24 weeks.
(2) Group 2: received SOF + simeprevir (SIM) for 12 weeks.
(3) Group 3: received SOF + daclatasvir (DAC) for 24 weeks.
(4) Group 4: received SOF + DAC + RBV for 12 weeks.

The patients were enrolled on the basis of the following inclusion criteria:

(1) Age between 18 and 70 years.
(2) Child 'A' or 'B7' liver cirrhosis.
(3) Controlled diabetes mellitus defined by HBA1C level of up to 8%, controlled hypertension, stable cardiac condition, no other malignancies, and no combined HIV or HBV infection.

The treatment regimens were allocated on the basis of the waves of availability of DAAs in Egypt through the national treatment program of HCV (the first wave was 12 weeks of PegIFN/RBV + SOF for PegIFN-eligible patients or 24 weeks of SOF + RBV for those who were not ineligible for PegIFN, the second wave comprised of 12 weeks of SOF + SIM, and the third wave included 12 weeks of SOF + DAC + RBV or 24 weeks of SOF + DAC for RBV-ineligible patients).

Safety and efficacy assessment for hepatocellular carcinoma status

After HCC management, the patients were subjected to a review of their clinical condition and laboratory parameters, and were tested for the tumor response to treatment (defined as the absence of neoplastic enhancement in dynamic studies and normalization of AFP levels) after 4 weeks of intervention; then, reassessment was repeated every 3 months. Tumor recurrence was detected by the reappearance of tumor enhancement/washout pattern and/or AFP progressive elevation. Local recurrence is defined as the reappearance of the radiological enhancement/washout inside the previously managed tumor; de-novo recurrence is defined as the development of new (1–3) lesion(s) with/without radiological enhancement/washout inside the previously managed tumor; and multicentric recurrence is defined as the development of new multiple (>3) lesions with/without radiological enhancement/washout inside the previously managed tumor; metastatic recurrence is the appearance of either lymphatic, vascular, or extrahepatic tumor spread with/without radiological enhancement/washout inside the previously managed tumor.

Safety and efficacy assessment for hepatitis C virus treatment

After initiation of DAAs treatment, the patients had regular follow-up visits to ensure treatment compliance and review any complaint, physical abnormalities, and laboratory deviations; these visits were every 4 weeks until completion of the treatment regimen. After 12 weeks of treatment stoppage, the patients were tested for either SVR (defined by negative HCV RNA by PCR) or viral relapse (defined by recurrence of HCV RNA by PCR after treatment stoppage and achieving negative HCV RNA until the end of treatment).

Statistical analysis

Analysis of data was carried out using SPSS 21 for Windows (SPSS Inc., Chicago, Illinois, USA). A description of variables is presented as follows:

(1) Numerical variables were described in the form of mean, SD, median, 25th and 75th percentiles.
(2) Categorical variables were described in the form of numbers and percents.

Numerical data were not normally distributed. Accordingly, nonparametric tests were used for comparison. This was carried out using the Mann–Whitney *U*-test when comparing between two groups of independent variables. The Kruskal–Wallis test was used when comparing between more than two groups of independent variables. Results were expressed in the form of *P* values.

Comparison between categorical variables was carried out using χ^2. Fisher exact test was used instead of the χ^2-test when one expected cell or more were up to 5.

The relative risk with a 95% confidence interval was calculated for 2×2 cross tables of categorical variables.

The significance of the results was assessed in the form of *P*-value, which was differentiated as follows:

(1) Nonsignificant when the *P*-value was more than 0.05.
(2) Significant when the *P*-value was up to 0.05.

Results

The baseline characteristic data of the study patients, and methods for HCV and HCC treatment are described in Table 1.

Table 1. Baseline data of study patients

Age (mean ± SD) (years)	60.31 ± 7.17
Sex (males/females) [*n* (%)]	42 (67.7)/20 (23.3)
Diabetics/nondiabetics [*n* (%)]	26 (41.9)/36 (58.1)
Smoker/nonsmokers [*n* (%)]	18 (29)/44 (71)
BCLC stage 0/A [*n* (%)]	10 (16.2)/52 (83.8)
Tumor maximum diameter (mean ± SD) (cm)	2.58 ± 0.81
Child–Pugh A/B [*n* (%)]	58 (93.5)/4 (6.5)
AST (mean ± SD) (IU/l)	70.37 ± 29.08
ALT (mean ± SD) (IU/l)	64.02 ± 32.84
Bilirubin (mean ± SD) (mg/dl)	1.12 ± 0.56
Albumin (mean ± SD) (g/dl)	3.44 ± 0.49
INR (mean ± SD)	1.17 ± 0.18
Hemoglobin (mean ± SD) (g/dl)	12.87 ± 1.61
WBCs (mean ± SD) (10^9/l)	5.03 ± 2.07
Platelets (mean ± SD) (10^9/l)	124.44 ± 48.06
BUN (mean ± SD) (mg/dl)	26.70 ± 11.89
Creatinine (mean ± SD) (mg/dl)	0.89 ± 0.25
HBA1c (mean ± SD) (%)	5.19 ± 1.52
AFP (mean ± SD) (ng/ml)	14.21 ± 2.03
HCV RNA (mean ± SD) (IU/ml)	5.9 $\log_{10}$ ± 6.15 $\log_{10}$
Naive/PegIFN experienced [*n* (%)]	54 (87.1)/8 (12.9)
Period between HCC management and DAAs initiation/ months (mean ± SD)	9.40 ± 11.15
Treatment regimen [*n* (%)]	
Group 1 SOF/RBV 24 weeks	15 (24.2)
Group 2 SOF/SIM 12 weeks	13 (21)
Group 3 SOF/DAC 24 weeks	2 (3.2)
Group 4 SOF/DAC/RBV 12 weeks	32 (51.6)
HCC treatment strategy [*n* (%)]	
RFA	31 (50)
MWA	10 (16.1)
PEI	6 (9.7)
TACE	6 (9.7)
Resection	4 (6.5)
Combined techniques	5 (8.1)

AFP, α-feto protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic of Liver Cancer; BUN, blood urea nitrogen; DAA, direct-acting antivirals; DAC, daclatasvir; HBA1c, hemoglobin A1c; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; MWA, microwave ablation; PegIFN, pegylated interferon; PEI, percutaneous ethanol injection; RBV, ribavirin; RFA, radiofrequency ablation; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TACE, transarterial chemoembolization; WBCs, white blood cells.

According to Barcelona Clinic of Liver Cancer, 10 cases were (stage 0) 52 (stage A) HCC. Eight patients were candidates for liver transplantation, but the decision was changed because of donor unavailability and they were shifted to other procedures. Forty-one patients were treated using a single session of thermal ablative procedures (RFA/MWA), six patients were treated using PEI (five sessions, once/week), six patients were treated by TACE because pf difficult tumor localization under sonographic guidance, and five patients underwent two sessions of thermal ablation (RFA, followed by MWA) because of residual tumor activity after the first session (combined technique).

After HCC treatment by the above-mentioned methods, HCV treatment was not applicable for such group in Egypt using PegIFN and RBV, until introduction of DAAs; for this reason, the first group (SOF/RBV) in this study had a longer interval between HCC treatment and initiation of DAAs, 17.8 ± 14.6 months, followed by the second group (SOF/SIM), 7.8 ± 8.2 months, and then finally, for the current wave of treatment with SOF/DAC/RBV, SOF/DAC, it was 7.8 ± 7.6 months, 3 ± 0, respectively, with an overall mean interval of 9.40 ± 11.15 and an overall median follow-up duration after the initiation of treatment with DAAs of 12 months (3–14 months) at the time of this analysis.

All studied patients showed 100% treatment adherence and compliance, with no dropouts or missed doses; the side effects reported during the period of treatment were abdominal discomfort, headache, nausea, dizziness, itching, anemia, and dyspnea. All the side effects reported were mild and did not necessitate dose reductions or treatment discontinuation. Low overall treatment response to different DAAs was observed in this cohort, with the highest SVR achieved with the SOF/DAC/RBV regimen for 12 weeks being 87.5% and the lowest with 24 weeks of SOF/RBV being 26.7% as shown in Fig. 1 and Table 2.

The overall tumor recurrence was 42%, with the highest recurrence observed in those treated with TACE (66.7%) and the lowest in those treated with surgical resection or combined maneuvers (0% for both) ($P = 0.04$). None of the tested parameters had any relation with tumor recurrence, except higher levels of baseline aspartate aminotransferase and alanine aminotransferase, which are significantly related to tumor recurrence in our studied population ($P = 0.03$ and 0.01, respectively) as shown in Table 3.

Figure 2 and Table 4 show the cumulative incidence of HCC recurrence among all the patients studied; 3 months after HCV treatment initiation (end of the treatment point for those who underwent a 12-week regimen or mid-point of treatment for those who underwent a 24-week regimen), HCC recurrence was observed in six patients (23% of the group of patients who developed tumor recurrence).

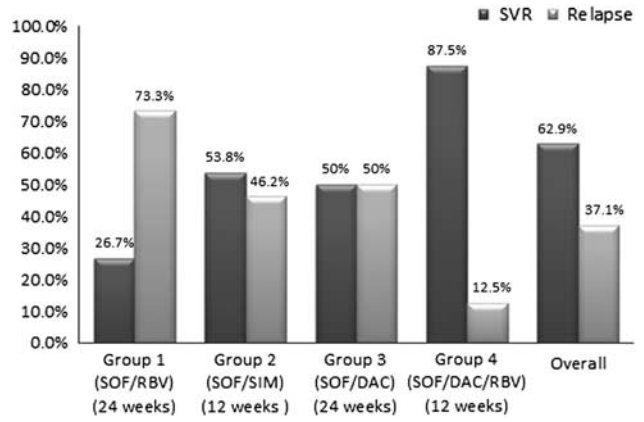

Fig. 1. Treatment response (SVR 12) to different DAAs regimens (intention-to-treat analysis). DAA, direct-acting antivirals; DAC, daclatasvir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

Table 2. Treatment response (sustained virologic response 12) to different direct-acting antivirals regimens (intention-to-treat analysis)

	SVR [*n* (%)]	Relapse [*n* (%)]	*P*.value
Group 1 (SOF/RBV) 24 weeks	4 (26.7)	11 (73.3)	0.001
Group 2 (SOF/SIM) 12 weeks	7 (53.8)	6 (46.2)	
Group 3 (SOF/DAC) 24 weeks	1 (50)	1 (50)	
Group 4 (SOF/DAC/RBV) 12 weeks	28 (87.5)	4 (12.5)	
Overall treatment response	40 (64.5)	22 (35.5)	

DAC, daclatasvir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

Table 3. Follow-up of hepatocellular carcinoma status

	n (%)/mean ± SD	*P* value
Incidence of recurrence		
No recurrence	36 (58)	–
Local recurrence	5 (8.1)	
De-novo recurrence	11 (17.8)	
Multicentric recurrence	7 (11.3)	
Metastasis	3 (4.8)	
Overall recurrence	26 (42)	
New BCLC evaluation after recurrence (0/A/B/C/D)	0/11/12/1/2	
Relation between HCC recurrence and method of HCC management (no recurrence/recurrence)		
RFA	15 (48.4)/16 (51.6)	0.04
MWA	7 (70)/3 (30)	
PEI	3 (50)/3 (50)	
TACE	2 (33.3)/4 (66.7)	
Resection	4 (100)/0	
Combined techniques	5 (100)/0	
Relation between HCC recurrence and laboratory parameters (no recurrence/recurrence)		
AST	64.1 ± 29.1/79.6 ± 26.9	0.03
ALT	54.1 ± 25.3/78.6 ± 37.4	0.01
Relation between HCC recurrence and treatment outcome (no recurrence/recurrence)		
SVR	25 (64.1)/14 (35.9)	0.4
Relapse	12 (54.5)/10 (45.5)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic of Liver Cancer; HCC, hepatocellular carcinoma; MWA, microwave ablation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; SVR, sustained virologic response; TACE, transarterial chemoembolization.

Another 15 patients with tumor recurrence were discovered between 3 and 6 months (57.7% of the group of patients who developed tumor recurrence). The subsequent intervals showed fewer number of patients with tumor recurrence: four

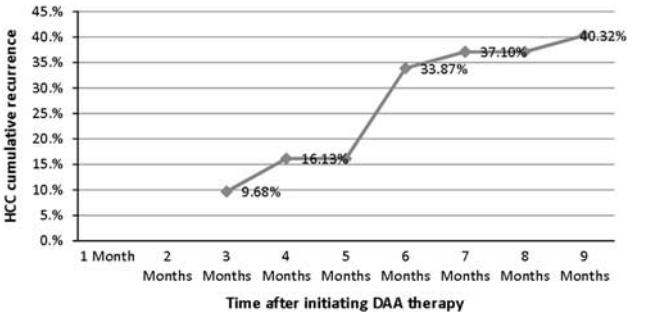

Fig. 2. Cumulative incidence of hepatocellular carcinoma (HCC) recurrence.

(15.5%), zero (0%), and one (3.8%) for intervals of 6–9, 9–12, and 12–14 months, respectively. Tumor recurrence usually developed within the first 6 months after the initiation of DAAs treatment, representing 33.87% of all the patients studied (80.7% of the group of patients who developed tumor recurrence). No recurrence was observed during HCV treatment periods either for the 60 patients who were treated with the 12-week regimen or for the two patients who were treated with the 24-week regimen.

One mortality was reported among the studied cases as a sequel of rapid liver decompensation, and occurred 10 weeks after completion of the treatment course (group 3) and before reaching the SVR assessment point; the patient was included in the statistical analysis and considered to have tumor recurrence and relapser to HCV therapy.

Discussion

Treatment of HCV-related HCC patients became feasible with the introduction of DAAS, particularly in Egypt, which has a heavy HCC burden exceeding 7% of chronic liver disease patients because of the high prevalence of chronic viral hepatitis, especially HCV [20]. Multiple DAAs regimens are available through the HCV national treatment program in Egypt, with overall satisfactory results exceeding 90% SVR in most regimens either in real-life data [21] or through different HCV G4 clinical trials conducted in Egypt [22–24].

In the current study, an overall SVR of 64.5% was achieved, with the highest treatment response observed in group 4 (87.5%) and the lowest response observed in group 1 (26.7%); these treatment outcomes were much lower than those observed by Conti *et al.* [9] in 59 HCC patients (72% of these patients were genotype 1) who received different DAAs regimens, with an overall SVR of 89.8%. In 3 French cohorts of HCC patients (HEPATHER cohort of 267 patients), CIRVIR cohort of 79 patients, and CUPILT cohort of 314 patients, very high SVR results were achieved, 91.9, 100, and 96.8%, respectively, with more than 65% of the patients included in these cohorts were genotype 1 [25], In a recently published retrospective cohort, failure to achive SVR was observed in 21% of patients with HCC in comparison with 12% non-HCC patients, confirming the negative impact of HCC on HCV treatment outcome [26], which may explain the low response to HCV treatment also within this cohort; 24.2% of the studied population received SOF and RBV for 24 weeks, which yielded the lowest result in the Egyptian national treatment program of HCV [21].

Table 4. Overall cumulative/time interval recurrence

	3 months	6 months	9 months	12 months	14 months
Cumulative recurrence [*n* (%)]	6 (23)	21 (80.7)	25 (96.2)	25 (96.2)	26 (100)
	3 months	3–6 months	6–9 months	9–12 months	12–14 months
Recurrence [*n* (%)]	6 (23)	15 (57.7)	4 (15.5)	0 (0)	1 (3.8)

Table 5. Comparison model between recurrence in the current study/ published studies

Method of HCC treatment	Recurrence (this study) (%)	Recurrence
RFA	51.6	6.8 [31]
MWA	30	11.8 [32]
PEI	50	26 [33]
TACE	66.7	34.3 [34]
Resection	0	61.5 [35]
Combined maneuvers	0	19 [36]

HCC, hepatocellular carcinoma; MWA, microwave ablation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

The first spark of HCC-DAAs possible interrelationship was declared by Reig *et al.* [18], who observed an unexpectedly high rate of HCC recurrence (27.6%) in 58 cured HCC patients who had received different DAAs regimens, which is in agreement with Conti *et al.* [9], who reported a high incidence of both HCC recurrence (28.8%) (17 out of 59 treated HCC patients) and HCC de-novo occurrence (3.1%) (nine out of 285 treated cirrhotic patients without HCC) in HCV patients who received DAAs. Kozbial *et al.* [27] emphasis on the same hypothesis and reported HCC recurrence in 8.1% (16 out of 198 treated HCC patients).

This cumulative data obtained by Reig and colleagues, Conti and colleagues, and Kozbial and colleagues or even our data comes in contrary with the data of the 3 French cohorts in which no increased risk of HCC recurrence with DAAs treatment was observed and a similar risk was found between treated and untreated groups (0.73 vs. 0.66) in the HEPATHER cohort (1.11 vs. 1.73) in the CIRVIR cohort, and in the CUPILT cohort (2.2%) of liver transplant recipients for HCC subsequently treated 70 months after liver transplantation [25]. The data of Reig and colleagues was faced by multiple criticizing reports, including concerns about the heterogeneity of the studied populations in the methods used for HCC treatment, the long interval between HCC cure and HCV treatment, and the presence of selection bias [28–30].

Table 5 describes the incidences of recurrence in the current study compared with previously published data for patients treated with the same methods, but did not receive antiviral therapy, and for similar tumor diameters and follow-up periods as in the current study. The choice of treatment modality affects the incidence of recurrence. TACE was considered for a long time as a palliative treatment for HCC management; even when used for the management of potentially treatable lesions, rapid and higher rates of recurrence occurred in our study for those treated with TACE compared to published data. The same results were also observed for those treated with PEI, RFA, and MWA; in contrast, no recurrence was observed in those treated with surgical resection and combined methods putting into consideration their relatively small sample size (14.6%) compared to the rest of patients treated with other modalities.

The antiproliferative effect of pegylated interferon together with the modest reduction in HCV viral load may explain the positive effect of this treatment in reducing the progression to HCC in cirrhotic patients who achieved an SVR compared with those who failed to achieve SVR [37]; meanwhile, the sharp, rapid decline of HCV RNA, which is associated with marked and rapid normalization of the patient biochemical profile and reduction of hepatocyte inflammation may be the triggering factor for HCC development as noted in the current study. The group who showed greater baseline elevation in aspartate aminotransferase and alanine aminotransferase showed higher incidence of HCC recurrence.

Similar to this theory, treatment of combined HCV, HBV cases using DAAs showed flare of HBV early after HCV elimination and disappearance of HCV RNA [38,39], and yet, for the applicability of this theory, more genetic and pharmacological studies on the possible actions of DAAs in both HCV and host genomes are needed.

Conclusion

HCV treatment in successfully managed HCC patients is possible, with the best results for regimens containing multiple DAAs + RBV; recurrence of HCC after DAAs treatment is not an uncommon finding and more controlled trials are needed to clarify or deny the possible relationship. Till then, an adequate interval between HCC management and DAAs initiation could help in the detection of early tumor recurrence.

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Conflicts of interest

Gamal Esmat: speaker; advisory board member and investigator for Gilead, BMS. Aisha Elsharkawy: Investigator;

Gilead, Janssen. Mohamed Hassany: Investigator; Gilead, Janssen, Abbvie. For the remaining authors there are no conflicts of interest.

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