DOI: 10.26717/BJSTR.2018.04.001106
Ken Sato. Biomed J Sci & Tech Res

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574-1241

Review Article Open Access

The Risk of Hepatocellular Carcinoma is increased in Hepatitis C Virus Patients Treated with Interferon-free Direct-acting Antiviral-based Therapy: True or False?

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Received: May 13, 2018; **Published:** May 24, 2018

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Abstract

Hepatitis C virus (HCV) infection is a major leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). The recent development of new direct-acting antivirals (DAAs) that are highly effective and well-tolerated has facilitated the achievement of sustained virological response rates in more than 90% of patients with HCV infection, regardless of the stage of liver fibrosis, and is expected to reduce the rate of progression to HCC or risk of waitlist dropout among liver transplant candidates with HCC. However, several studies have raised concerns about the risk of HCC in HCV patients treated with interferon (IFN)-free DAA-based therapy, although other studies have failed to obtain findings supporting these results. These conflicting results prompted us to search for further reliable studies to draw a conclusion about this pivotal issue. This article focuses on the current situation regarding the occurrence and recurrence of HCC in HCV patients treated with IFN-free DAA-based therapy.

Keywords: Hepatocellular carcinoma; Hepatitis C virus; Direct-acting antivirals; Sustained virological response; Occurrence; Recurrence

Abbreviations: AHR: Adjusted Hazard Ratio; CI: Confidential Interval; CT: Computed Tomography; CXCL: (C–X–C motif) Ligand; DAA: Direct-Acting Antiviral; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; HR: Hazard Ratio; IFN: Interferon; ISGs: Interferon-Stimulated Genes; MRI: Magnetic Resonance Imaging; RFA: Radiofrequency Ablation; RR: Relative Risk; SVR: Sustained Virological Response; TACE: Transcatheter Arterial Chemoembolization; TRAIL: Tumor Necrosis Factor-Related Apoptosis Inducing Ligand; VEGF: Vascular Endothelial Growth Factor

Introduction

Overview of Concerns Regarding the Risk of Hepatocellular Carcinoma Induced by Interferon-free Direct-acting Antiviral-based Therapy Liver cancer is the fourth leading cause of cancer death and the sixth-most frequent cancer worldwide [1]. Hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer globally [1]. Hepatitis C virus (HCV) was responsible for 21% of liver cancer mortality as the global level in 2015 [2]. In Japan, HCV infection was the factor contributing most frequently to liver cancer mortality, at 69% [1]. The recent development of new direct-acting antivirals (DAAs) that are highly effective and well-tolerated has helped achieve sustained virological response (SVR) rates in more than 90% of patients with HCV infection, regardless of the stage of liver fibrosis and is expected to reduce the progression to HCC or risk of waitlist dropout among liver transplant candidates with HCC. Interferon (IFN)-based therapy, which has been mostly replaced by IFN-free DAA-based therapy, reduced the risk of HCC in patients with cirrhosis [3-5]. Regarding IFN-free DAA-based therapy, however, a report by Reig et al. [6] suggesting an unexpectedly high rate of early tumor recurrence in patients with HCV-related HCC undergoing IFN-free DAA-based therapy has raised great concern, although a number of other studies failed to obtain similar findings. Thus, the association between the risk of HCC and IFN-free DAA-based therapy is controversial and uncertain. We performed a systematic review of studies regarding the association between the risk of HCC and IFN-free DAA-based therapy.

Occurrence of HCC Following In-Free Data-Based Therapy

Several studies [7-9] have reported an increase in the occurrence of HCC following IFN-free DAA-based therapy. Cardoso et al. [7] reported that 7.4% of patients were newly diagnosed among 54 HCV-infected cirrhotic patients after a median follow-up of 12.0 months, compared to annual incidence rates of 1.2% to 1.4% in patients who achieved SVR following IFN-based therapy [10,11].

However, the study was a retrospective cohort study performed at a single center, and the number of subjects who received DAA-based therapy was only 54. Kozial et al. [8] reported an HCC occurrence rate of 6.6% (13/195) in patients with advanced liver disease who completed 48 weeks of follow-up, compared to the estimated 1%/year frequency of HCC in patients with SVR treated with IFN/ribavirin dual therapy [12-15].

That study was also a retrospective cohort study without a control cohort and comprised of a small number of subjects. Of further note: ultrasound was used to exclude HCC in some of the subjects. Computed tomography (CT) and magnetic resonance imaging (MRI) are less likely to overlook space-occupying lesions than ultrasound and may therefore be more suitable for HCC screening just before starting DAA therapy. Gas or air disrupts ultrasound waves and thus the ultrasound is not suitable for especially the parts of the liver near the bowel or pleural cavity. Ravi et al. [9] reported that 6 patients (9.1%) developed HCC either during or within 6 months of treatment among 66 cirrhotic patients, compared to an HCC incidence rate of 3%-5% per year in patients with HCV cirrhosis [16]. That study was also a retrospective cohort study without a control cohort and comprised of a small number of subjects. Furthermore, four of six HCC patients in that study were screened by ultrasound before starting IFN-free DAA-based therapy. Patients who developed HCC were counted regardless of the achievement of SVR.

Other studies [17-29] disagreed with the increase in the occurrence of HCC following IFN-free DAA-based therapy. Conti et al. [17] reported that HCC was detected in 9 of 285 patients (3.16%, 95% confidence interval [CI]: 1.45-5.9) during the 24-week post-treatment evaluation and compared their findings to those of a historic population of similar untreated cirrhotic patients previously followed at their centers (1-year cumulative HCC occurrence rate: 3.2%). That study was also a retrospective cohort study, and the follow-up period was short. Cheung et al. [18] reported a liver cancer incidence of 10/406 (2.5%) for months 6-15 and 17/406 (4%) for months 0-6 in IFN-free DAA-based therapy-treated patients vs. 11/261 (4%) in untreated patients. This was a prospective study with untreated patients as a control group and the HCC incidence analyzed over two different periods. The authors mentioned that the study was limited by their use of untreated patients with decompensated cirrhosis as control subjects and no matching with treated patients except for the patients being subjected to the same inclusion criteria and obtained from the same registry.

However, the incidence of HCC in this study included both the occurrence and the recurrence, so these results must be interpreted with caution. Foster et al. [19] reported that HCC was developed in 25 of 409 decompensated patients (6.1%) who received IFN-free DAA-based therapy and 21 of 261 decompensated patients (8.0%) who did not receive IFN-free DAA-based therapy. This was a retrospective, multicenter, observational study with a relatively large study population. However, the follow-up period was three months on therapy and three months post therapy, making this a very short study. Ioannou et al. [20] reported that the HCC incidence per 100 patient-years was higher after DAA-only treatment than after DAA+IFN or IFN-only treatment, although there was no significant association between the treatment regimen and the HCC risk after adjusting for important confounders: DAA-only (adjusted hazard ratio [AHR] 1.12; 95% CI 0.95-1.32) and DAA+IFN (AHR 1.04; 95% CI 0.87-1.26) when the AHR of IFN-only was set as 1.00.

The authors analyzed the risk factors for HCC, as cirrhosis, advanced age, diabetes, low platelet count, and a low serum albumin level were prevalent in the DAA-only group. They showed similar results exclusively in cirrhotic patients. Although this was a retrospective study, the number of subjects was large, and the study included 35,871 patients receiving IFN-only, 4,535 receiving DAA+IFN, and 21,948 receiving DAA-only. Innes et al. [21] reported that IFN-free therapy was associated with a significantly increased risk of HCC (HR: 2.48; p = 0.021) in a univariate analysis, but the association between IFN-free therapy and the occurrence of HCC disappeared after multivariate adjustment for baseline factors (AHR: 1.15, p =0.744). The number of study subjects was relatively large, and the study included 272 patients who received an IFN-free regimen and 585 who received an IFN-containing regimen. Although the median duration of follow-up was relatively long at 2.4 years overall, it varied markedly by treatment regimen (1.7 and 3.5 years for patients who received an IFN-free regimen and an IFN-containing regimen, respectively).

Kanwal et al. [22] reported that 271 cases of HCC occurrence were observed during 22,963 person-years of follow-up, with an annual HCC incidence rate of 1.18 per 100 person-years (OR 1.18%, 95% CI, 1.04%-1.32%). Patients with SVR had a significantly reduced risk of HCC (0.90 vs. 3.45 HCC/100 person-years; AHR, 0.28, 95% CI = 0.22-0.36). They did not observe any findings to suggest that DAAs promote HCC. This was a retrospective cohort study, but the number of study subjects was large (N =22, 500). The authors described several limitations associated with their study as follows: 1) the study subjects were limited to veterans with HCV; 2) untreated patients and patients who achieved SVR with IFN-based therapy were not included; and 3) the average follow-up period was short. Calleja et al. [23] reported that the occurrence of HCC was confirmed in 30/3233 (0.93%) patients within 18 months of starting DAA therapy. The authors did not mention the risk of the occurrence of HCC, but the rate was not numerically higher than the annual incidence rates of patients who achieved SVR following IFN-based therapy [10,11], the estimated 1%/year frequency of HCC in patients with SVR treated with IFN/ribavirin dual therapy [12-15], or the HCC incidence rate of 3%-5% per year in patients with HCV cirrhosis [16].

Furthermore, the number of study subjects was relatively large. However, 46.7% of the subjects in that study were cirrhotic patients, and there was no routine surveillance monitoring protocol in place. Thus, the ratio of the occurrence of HCC may have been reduced and must be interpreted with caution. Reddy et al. [24] reported they noted no increased risk for HCC occurrence in patients with more advance disease treated with DAA-only regimens. HCC occurrence and recurrence were detected in 23 patients treated with DAA-only (n = 18) or IFN-containing regimens (n = 5); the median time from the parent study end-of-treatment to the diagnosis of HCC was 70 (range, 0.4-206) weeks.

HCC occurrence and recurrence (n = 23, 2%) developed infrequently, with no significant difference between the responders (n = 20/1,329, 2%) and non-responders (n =3/160, 2%). They compared their findings with the incidences in a similar population in an Italian study (3%) [17] and the population of a Japanese study with responders treated with DAAs (2.6%) or peg-IFN/ribavirin (2.3%) [30]. This study was a large, multi-national study, and the follow-up period was relatively long (144 weeks). However, the diagnosis and detection of HCC was made by ultrasonography, even in cirrhotic patients. This may have led to the underestimation of the HCC occurrence and recurrence, as mentioned above. Ogata et al. [25] reported that the estimated annual incidence of HCC for the first 2 years in patients treated with all DAA regimens was 0.9%, which was not markedly different from that in patients who achieved SVR [30,31].

This study was a large-scale study (n =1170) and used the propensity score to confirm the HCC occurrence between all DAA-based regimens and IFN-based regimens (p = 0.155). The authors described several limitations associated with their study as follows:

a. the timing of the imaging studies was not uniform;

b. the follow-up period was short;

c. the study subjects were all Japanese patients infected with HCV genotype 1b. Furthermore, the study was a single-center experience, the follow-up imaging was performed by ultrasonography, and the frequency of liver cirrhosis was not available. Waziry et al. [26] reported that DAA therapy was not associated with an increased rate of HCC occurrence (relative risk [RR] 0.68; 95% CI 0.18-2.55; p =0.55) in a meta-regression analysis adjusted for the study follow-up and age. This was a systematic review including meta-analyses and meta-regression.

The authors mentioned several limitations associated with their study as follows:

a) the number of studies was relatively small, and the studies were largely observational, including many retrospective studies;

b) substantial geographical variation existed among the studies within the groupings;

c) the collection of key demographic and clinical characteristics varied across studies, and key variables were not collected sufficiently;

d) details on the "aggressiveness" of HCC recurrence events in the IFN- and DAA-based studies were lacking. Darrick et al. [27] reported that the HCC occurrence rate was significantly higher in untreated patients with cirrhosis (45.3 per 1000 person years; p = 0.03) than in those treated with either IFN or DAAs, while there was no significant difference in the HCC occurrence rate between the DAA- and IFN-treated groups (22.8 vs. 21.2 per 1,000 person years; p = 0.78). The number of studies was large, and the review included 3,534, 5,834, and 8,468 patients in IFN-treated, DAA-treated, and untreated groups, respectively. The authors described several limitations associated with their study as follows:

e) the follow-up period was relatively short;

f) the study cohort comprised veterans with marked differences from the general population (male predominance and higher rates of smoking and alcohol use);

g) this was a retrospective cohort study;

h) to diagnose cirrhosis, they used a clinical score rather than a liver biopsy;

i) data on the surveillance practices to detect HCC were unavailable; and

j) The calendar time confounded the treatment time, as IFN was generally used before the advent of DAAs.

Calvaruso et al. [28] reported that HCC occurrence was observed in 2.1% and 7.8% of patients with SVR and 6.6% and 12.4% of patients with non-SVR in Child-Pugh class A and B, respectively, at 1 year after the start of DAA ($p < 0.001$ by log-rank test). The mean interval from the start of DAA to an HCC diagnosis was similar between the patients with and without an SVR (p = 0.11). They concluded that SVR achievement by DAA treatment reduced the HCC occurrence over a mean follow-up of 14 months. This was a multi-center, large-scale, prospective study focused on patients with HCV cirrhosis with separate analyses performed based on the Child-Pugh classification. The authors described several limitations associated with their study as follows:

a. The observation time was short, and

b. The competence in the diagnosis of HCC among participating clinical centers might have varied. In addition, ultrasound was used to exclude HCC before the start of DAA.

Faillaci et al. [29] reported the proangiogenic liver microenvironment in 244 DAAs-treated chronic hepatitis C patients with advanced fibrosis and the factors associated with de novo HCC in 257 patients with cirrhosis of different etiologies. While no patients without liver cirrhosis developed HCC, 14/28 (50.0%) cirrhotic patients with prior HCC developed HCC recurrence. The mean interval from HCC curative treatment to DAA initiation was 16.0±11.5 months (median 11 months, range 3-33 months). Although the occurrence rate was markedly high, the authors concluded that DAA therapy was not per se able to predict the occurrence of HCC; DAAs only encouraged HCC in predisposed patients, i.e. those with severe fibrosis and splanchnic collateralization. This study included patients with significantly advanced cirrhosis, such as Child-Pugh B/C, and those with esophageal varices that were likely to develop HCC. Furthermore, the screening method was ultrasound performed on a six-month basis, which is not always sufficient before DAA treatment. HCC occurrence was detected after a mean period of 3.3±5.3 months after stopping DAAs, and the duration was very short, so precancerous lesions that were not detected or were unlikely to be detected might have existed before DAA therapy [30,31].

The Recurrence of HCC Following IFN-Free DAA-Based Therapy

Several studies [6,17,32,33] have reported an increase in the recurrence of HCC following IFN-free DAA-based therapy. Reig et al. [6] reported 16 (27.6%) cases of radiological HCC recurrence in 58 patients with prior HCC who received DAAs and 7 (41.2%) cases of radiological HCC recurrence in 17 patients in which DAA treatment was started with a 'time between HCC treatment and last assessment of complete response by imaging' of less than 4 months. They observed an HCC recurrence rate of 41.2% compared to 21.5% according to the independent assessment and 17.6% according to investigator assessment in STORM [34]. This was a retrospective study without a control cohort, and the number of study cohorts was small with a very short overall median follow-up period after DAA (5.7 months). Furthermore, the rate of cirrhotic patients was unclear. Conti et al. [17] reported that 17 of 59 cirrhotic patients (28.81%; 95% CI: 17.76-42.07) experienced HCC recurrence during 24-week follow-up after DAA treatment.

They observed a recurrence rate of 28.81% in patients with a median disease-free interval of 376 days in their study that included transcatheter arterial chemoembolization (TACE) before DAA treatment compared with an expected HCC recurrence of approximately 20% at l year after surgical resection or radiofrequency ablation (RFA) [35]; the authors concluded that the HCC recurrence rate was not unexpected. However, they postulated that DAA therapy in cirrhotic patients with a history of HCC may increase the risk of liver cancer, given that sudden and simultaneous HCC recurrence was observed within a few months after starting DAA treatment in 17 patients. As mentioned above, this study was also conducted in a retrospective cohort, and the follow-up period was short. Furthermore, TACE is inferior to RFA or surgical resection from the perspective of achieving a radical cure and is therefore not always a suitable treatment modality for achieving a complete radical response before DAA initiation. Yang et al. [32] reported a numerically but not statistically significantly higher risk of HCC recurrence (5/18, 27.8%) in patients who received DAA following liver transplantation compared to the risk in untreated patients (6/63, 9.5%).

The authors stated several limitations associated with their study, such as the small sample size and risk for selection bias. Three of 5 recurrence cases received TACE as a bridging treatment. Kassas et al. [33] reported that DAA treatment significantly increased the risk of HCC recurrence to 3.82 (95% CI: 2.00-7.30) after adjusting for time since achieving an HCC complete radiological response, sex, age, Child-Pugh score, and history of gastroesophageal varices using inverse probability of treatment weighting. Although the study cohort was small, the authors excluded TACE, which is considered as a palliative therapy for HCC, and any patients with early recurrence within three months since achieving a complete radiological response. They also performed their analysis excluding non-SVR12 patients and obtained similar results. In addition, they performed a propensity scored comparative time-dependent analysis and advocated that DAA treatment be avoided within two years after achieving an HCC complete radiological response.

However, other studies [24,26,29,36-41] disagree with the increase in the occurrence of HCC following IFN-free DAA-based therapy. Pol et al. [36] reported that an increased risk of HCC recurrence following DAA treatment was not observed in three different prospective cohorts. In the ANRS CO22 "Therapeutic options for hepatitis B and C: A French cohort" (HEPATHER) cohort, in which the inclusion period was August 2012 to September 2014, the HCC recurrence rates were 0.73/100 and 0.66/100 person-months in 189 patients who received DAA and 78 patients who did not. In the ANRS CO12 "Cirrhosis Virale" (Cirvir) cohort, in which the inclusion period was 2006 to 2012 and all subjects had cirrhosis, the HCC recurrence rates were 1.11/100 and 1.73/100 person-months in 13 patients who received DAA and 66 patients who did not. In the ANRS CO23 "Compassionate use of Protease Inhibitors" (CULPILT) Cohort in which the inclusion period was October 2013 to December 2015 and all subjects were liver transplant recipients for HCC and treated DAA, HCC recurrence rates were 7/314 (2.2%) after a median time of 70.3 months after liver transplantation. They concluded that in the CULPILT cohort, the HCC recurrence rate of 2.2% was lower than the rate expected based on previous studies with an IFN regimen. These were prospective studies, and the follow-up periods were relatively long. Minami et al. [37] reported that the cumulative recurrence rates at 1 and 2 years were 21.1% and 29.8%, respectively, in the DAA group (N = 27), 26.3% and 52.9%, respectively, in the IFN group (N = 38) and 30.5% and 61.0%, respectively, in the control group (N = 861).

DAA treatment was not significantly associated with early tumor recurrence (DAA group vs. control: HR 0.57, p = 0.12; DAA group vs. IFN group: HR 0.65, p = 0.28). As the number of study subjects, especially those in the DAA and IFN groups, was very small, the criteria of "only the use of RFA as radical treatment for HCC" and "less than two years' interval between HCC treatment and the start of antiviral therapy" were set to decrease the selection bias. Cabibbo et al. [38] reported that the 6-, 12-, and 18-month HCC recurrence rates in the overall cohort were 12%, 26.6%, and 29.1%, respectively. They found no increased risk of HCC recurrence during or after DAA-based treatment. While the number of study subjects was not very large, this was a prospective study that showed a unique point of view in which HCC recurrence rates with prior recurrence history were numerically higher than those without a history of recurrence. The authors described several limitations associated with their study as follows:

a) the follow-up period was short (median 8.7 months, range 3-19 months) with a relatively small number of events;

b) the accuracy of the area under receiver operating characteristic curve that they used was insufficient to predict HCC early recurrence at the individual patient level; and

c) some potential risk factors of HCC recurrence were not available. Reddy et al. [24] reported they found no increased risk for HCC recurrence in patients with more advance disease treated with DAA-only regimens.

The pros and cons of this study have already been mentioned above. Waziry et al. [26] reported that DAA therapy was not associated with increased HCC recurrence (RR 0.62; 95% CI 0.11-3.45; p = 0.56) in a meta-regression analysis with adjustment for the duration of study follow-up and age. This was a systematic review,

meta-analysis, and meta-regression. The authors mentioned several limitations associated with their study, as described above. Adhoute et al. [39] reported that radiologic HCC recurrence was detected in 41% of cirrhotic patients who received DAAs (N = 22) and 35% of cirrhotic patients who did not (N = 49) (p = 0.7904), with no significant difference in the time to progression between the patients who received DAAs and those who did not (12 [9-16] months vs. 14 [8-21] months, p = 0.7688). Although this was a retrospective cohort study and the number of study subjects was small, they used controls matched by propensity score for the age, sex, liver function, HCC stage, and treatment. However, they advised that DAA treatment be discouraged for at least 12 months after achieving an HCC cure because they found an association between HCC recurrence and a short time interval between cancer treatment and DAA initiation. Zavaglia et al. [40] reported only 1 case (3.2%) of HCC recurrence in their series of 31 consecutive patients with HCV-related cirrhosis and HCC cured after locoregional treatment or resection who received DAAs. The median time between the last HCC treatment and start of DAA was 19.3 months (25th-75th percentile: 12.6-36.9). The median time from the last radiological complete response before starting antiviral therapy and the start of DAA therapy was 1.7 months (25th-75th percentile: 1.05-2.4). The overall follow-up period after the start of DAA therapy was 8 months (25th-75th percentile: 5-10.9). Interestingly, despite using the same inclusion criteria as Reig et al. [6], they did not confirm the findings of the previous results [6,17]; they suggested that the reason for this discrepancy was their longer interval between the HCC treatment and the start of DAA therapy (median 19.3 months in their series and 11.2 months in that of Reig et al. [6]. Unfortunately, the number of study subject was very small. Huang et al. [41] reported that the cumulative HCC recurrence was similar in the DAA group (N = 62) and the non-DAA group (N = 87) (HR 0.91, 95% CI 0.58-1.42, p =0.67) using liver transplant candidates with HCC. In addition, patients in the DAA group had a lower risk of waitlist dropout due to tumor progression and death than those in no DAA group (HR 0.30, 95% CI 0.13-0.69, p = 0.005). The authors pointed out several limitations associated with their study as follows:

a. This was a retrospective, single-center, observational study; and

b. This was not a randomized study regarding the assignment of DAA therapy. Although the study population was relatively small, they used weighted propensity score modeling to adjust for a competing risk analysis.

Faillaci et al. [29] observed HCC recurrence in 14/28 (50.0%) patients. Although the recurrence rate was considerably high, the authors concluded that DAA therapy was not per se able to predict the recurrence of HCC. The study subjects were likely to develop HCC as mentioned above in the section regarding "HCC occurrence". The mean recurrence time was 3.9±3.8 months after stopping DAAs, which was quite short. Ultrasound was used for screening before DAAs therapy despite the patients having advanced cirrhosis. This suggests that precancerous lesions that were not detected or were unlikely to be detected might have already existed before DAA therapy was initiated, as mentioned above in the section regarding "HCC occurrence".

Discussion

Based on the findings of meta-analyses, prospective studies, large cohort studies and cohorts with adjustment for significant risk factors for HCC, HCV patients treated with IFN-free DAA-based therapy are unlikely to be at an increased risk of HCC occurrence or recurrence at present, with contradictory findings noted in only one study [33]. The conflicting results among the previous studies may be explained by several reasons. Cabibbo et al. [38] suggested the influence of potential biases among studies with different designs, numbers of study subjects, inclusion or exclusion criteria, definitions of HCC early recurrence, methods and timing of imaging follow-up, types of curative HCC treatment, intervals between tumor cure and the start of DAA therapy, and intervals between the last assessment of the tumor response and the start of DAA therapy.

Given the results of previous studies, the risk of HCC recurrence may be more open to debate than that of HCC occurrence. The studies of Reig et al. [6] and Conti et al. [17], which were retrospective studies without controls, were most likely to produce these potential biases. Furthermore, we believe in the importance of the interval between tumor eradication and the start of DAA therapy, and the interval between the last assessment of the tumor response and the start of DAA therapy. Camma et al. [42] reported that probability of HCC recurrence was lower in case of more than 6 months between HCC treatment and last assessment of HCC complete response than in case of equal to or less than 6 months between them if the time of starting DAAs was used as the origin of the Kaplan-Meier curve. In this regard, the median time from HCC treatment to the start of DAA therapy based on the results of Reig et al. [6] was only 11.2 months. Thus, comparing HCC recurrence based on the time from the confirmation of a complete response and the day of starting DAA therapy may be crucial for resolving the contradictory issues regarding HCC recurrence.

In the context of altered immune immunological surveillance, the comparison of HCC recurrence between SVR and non-SVR patients is also important, as is the selection of a control group, as studies using control groups adjusted for critical subject characteristics were unlikely to show any evidence of an increased HCC recurrence in patients treated with IFN-free DAA-based therapy. The selection of the subjects themselves is also critical; the subjects in previous studies have ranged from those with chronic hepatitis to those with advanced cirrhosis. Some studies lacked information regarding the disease severity of study subjects, such as the rate of cirrhosis in the whole patient cohort. The risk of HCC occurrence or recurrence should be evaluated based on disease severity.

However, we cannot completely deny the possibility that DAAs themselves affect HCC development, especially in patients predisposed to HCC. The DAA-induced sudden interruption in immune surveillance through the rapid elimination of HCV might affect tumor progression [29,43,44], possibly by the following mechanism:

a) low numbers [45] and a reduced activation of NK cells that produce IFN-γ as a protective agent against tumorigenesis [46] in patients with hepatocellular carcinoma may decrease the surveillance pathways for HCC, leading to the HCC development [44];

b) reduced levels of the IFN-stimulated gene (ISG) products (C–X–C motif) ligand (CXCL)10 and CXCL11 may lead to a loss of intrahepatic immune activation [47] as elevated ISG levels reflect an increased activation of innate immune cells that respond to type I IFN [47], causing the HCC development;

c) a decrease in tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-receptor-2 expression may lead to anti-apoptotic conditions advantageous to HCC development, as TRAIL mediates apoptotic signaling and can cause apoptosis in tumor cells [44];

d) a rapid decline in the HCV-specific and non-specific T cells from the liver and a reduced return of leukocytes to the liver may reduce the ability to surveil the residual cancer cells and subsequently cause rapid development of HCC [44];

e) DAAs may affect HCC development directly [43]

f) DAAs may exacerbate the already increased circulating levels of vascular endothelial growth factor (VEGF) and activate angiopoietin-2 expression in the livers of patients predisposed to HCC, such as those with severe fibrosis and elevated microvascular shear stress in those with cirrhosis with splanchnic collateralization due to portal hypertension, thereby leading to HCC development [29].

Potential key predictors of HCC occurrence or recurrence after DAAs, such as liver angiopoetin-2, were suggested as mentioned above [29]. Future studies should explore such key predictors of HCC occurrence or recurrence and try to identify patients predisposed to HCC after DAA therapy using liver tissue or blood samples.

Conclusion

At present, there is no clear evidence supporting an increased risk of HCC occurrence or recurrence in HCV patients treated with DAAs. However, the timing of DAA intervention after confirming an HCC cure to minimize HCC recurrence, the potential key predictors of HCC occurrence or recurrence, and the patients susceptible to HCC after DAAs should be explored in future studies. A sophisticated randomized controlled study is ideal but not realistic due to ethical issues. A prospective, multicenter large study designed to minimize potential biases, such as with propensity score modeling, and to explore potential key predictors of HCC occurrence or recurrence is definitely needed.

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