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## Association between direct-acting antiviral agents in hepatitis C virus treatment and hepatocellular carcinoma occurrence and recurrence: The endless debate

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### Abstract

Since direct-acting antiviral agents (DAAs) have been introduced into hepatitis C virus treatment, the sustained viral response (SVR) rate has significantly increased to more than 95%. Scientific evidence supports the idea that SVR after interferon therapy has beneficial effects related to cirrhosis progression, resulting in a reduction in the incidence of hepatocellular carcinoma (HCC). However, a significant debate exists related to DAA impact on HCC development. We reviewed the current literature highlighting the controversial data related to DAA association with *de novo* HCC occurrence or recurrence and possible pathophysiology of HCC related to DAAs. After a review of the published literature, we believe that the current evidence does not confirm or repudiate a higher rate of *de novo* HCC occurrence or recurrence related to DAA therapy. More trials are needed to determine if there is an association between HCC occurrence or recurrence and DAA or if it is related to preexisting liver cirrhosis.

**Key Words:** Hepatitis C virus; Sustained virologic response; Direct-acting antiviral drugs; Hepatocellular carcinoma; Liver cirrhosis

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**Core Tip:** Present evidence does not confirm or repudiate a higher rate of *de novo* hepatocellular carcinoma (HCC) occurrence or recurrence related to direct-acting antiviral agent (DAA) therapy. More trials are required to determine whether there is an association between HCC occurrence or recurrence and DAA or if it is mainly related to preexisting liver cirrhosis.

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## INTRODUCTION

Hepatitis C virus (HCV) is an enveloped single-stranded ribonucleic acid (RNA) virus. It is mainly transmitted through infected blood, after which it identifies the target cell through multiple molecules; it enters the host cells by clathrin-mediated endocytosis. In the cell, the viral capsid is disrupted and the RNA genome is released to be translated into a single polyprotein precursor that is later cleaved into multiple mature products[1]. Co- and post-translational cleavage steps are mediated by different viral proteins, including proteins (nonstructural protein 3 [NS3], NS4A, NS5A, and NS5B proteins) that are targets for direct-acting antiviral agents (DAAs)[2]. Hepatocellular carcinoma (HCC) occurrence reflects the integration of different host, viral, and environmental factors over many years[2]. HCV-mediated liver inflammation with subsequent tissue necrosis, fibrosis, and cellular regeneration lead to genetic mutations that lead to neoplastic transformation[2]. HCV proteins themselves are carcinogenic[2]. NS5B has a role in cell cycle disruption and accordingly HCC development, through binding to retinoblastoma protein – that controls cell proliferation – and promoting its degradation, which sequentially stimulates cell cycle progression. Other products E2, NS3, and NS5A result in aggressive HCC development through disrupting RAF/mitogen-activated protein kinase/extracellular signal-regulated kinase-regulated pathways. Some products, such as NS2 NS3, and NS5A inhibit p53, resulting in abnormal cell cycle and apoptosis[3].

The annual HCC occurrence rate in untreated HCV patients is 2%-8%[4]. HCC recurrence rates after curative treatments, namely surgical management and thermal ablation, differ between trials. A meta-analysis that included 11 studies evaluated the recurrence rates of HCC in patients who did not receive HCV treatment post radiofrequency ablation (RFA) or surgical intervention for the HCC < 3 cm in size. The 6-mo recurrence rates were between 0% and 12.5%, recurrence at 1-year was between 4.9% and 62.5%, and recurrence at 2 years was between 31.8% and 100%. Probabilities of recurrence from this meta-analysis were 7.4% at 6 mo, 20% at 1 year, and 47% at 2 years[5].

Antiviral therapy against hepatitis B virus (HBV) reduces the risk of HCC development and recurrence[6]. In HCV, the impact of HCV eradication using pegylated interferon (IFN) on HCC occurrence and recurrence has also been studied[6,7]. The studies found a decrease in HCC occurrence and recurrence over time due to turning off the necro-inflammatory process with antiviral treatment. Yet, there is still a significant risk in cirrhotic patients, and therefore, long-term surveillance for HCC is necessary[8].

HCV eradication is now better achieved using DAAs but may be lower in HCC patients. Beste *et al*[9] reported sustained virologic response (SVR) after different DAA regimens in 74% of HCC patients; it was 91% in non-HCC patients. Another study reported higher viral relapse after oral anti-HCV regimens in patients with active or treated HCC compared to patients without HCC history (21% vs 12%) with significantly higher relapse rates among those with active HCC[10]. In another study, ledipasvir/sofosbuvir showed lower 12-wk SVR (SVR12) among HCC patients compared with non-HCC patients. SVR rates were 94.1% and 98.7% in HCC and non-HCC groups, respectively[11]. An Egyptian cohort compared SVR rates in those with successfully managed HCC with sofosbuvir combined with ribavirin alone or sofosbuvir combined with daclatasvir or simeprevir. Overall rates of SVR12 in this cohort were 64.5%. SVR rate was highest (87.5%) in treated HCV patients with a combination of sofosbuvir, daclatasvir, and ribavirin, which indicate a significant benefit of ribavirin addition to a sofosbuvir-daclatasvir regimen in HCC patients treated with ablation[12].

Another Egyptian study reported an overall SVR12 rate among patients with ablated HCC treated sofosbuvir in addition to daclatasvir with or without ribavirin was 68%, and 85.7% after sofosbuvir/ledipasvir treatment[13].

In HCC patients, lower SVR rates may be explained by decreased delivery of the drug to the cancerous hepatocytes leaving these cells as a reservoir for HCV. Again, immune and inflammatory changes in patients with HCC can explain the somewhat unfavorable response after DAAs[10,14].

IFN therapy can decrease the risk of *de novo* HCC development in cirrhotic patients with an adjusted relative risk of 0.54 (95% confidence interval [CI]: 0.33-0.89) compared to untreated patients. The effect is more evident in patients who achieve SVR with a relative risk of 0.05 (95%CI: 0.006-0.34) compared to untreated patients[15]. Also, IFN-based therapy has a significant impact on the reduction of all-cause mortality in chronic HCV patients[16-18]. The incidence of HCC was estimated to be 1% approximately per year in patients with SVR treated with IFN-based therapy[19,20]. Again, it was estimated that IFN-based therapy decreases HCC occurrence by 76%[19]. Unfortunately, such agreement is not present in the case of DAAs despite achieving more than 90% SVR in a 12-wk period[17,21].

A meta-analysis studied the role of IFN therapy for HCV after curative treatment for HCC showed that IFN reduced the HCC recurrence rates at 2, 3, and 5 years of follow-up in HCV patients, but no significant change was observed in the recurrence rate of HCC during the 1st year of follow-up[22].

Although higher SVR rates can be attained with DAAs, their effects on *de novo* HCC occurrence and recurrence are uncertain. Several papers have reported an increase in the incidence of HCC occurrence and/or recurrence after DAA administration. Tumorigenesis after DAAs can be attributed to an imbalance between cell apoptosis and pro-survival[2,23]. The direct and rapid viral eradication caused by DAAs without immune system involvement can disrupt the natural surveillance by the immune system with subsequent dormant tumor cells progression[23,24]. This fast viral eradication induces disruption of the innate immunity and reduction of IFN receptors II and III that regulate tumor angiogenesis and tumor anti-proliferative effects[24,25]. The rapid decline in natural killer cells has been linked to HCC progression[24,26]. Several immune mediators were identified and shown to be at higher levels before DAA initiation in patients who developed HCC thereafter[27]. Moreover, the level of tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) remained high after DAA completion in those who developed HCC thereafter but was decreased in subjects who did not develop HCC later. This suggests a role for persistent high TNF- $\alpha$  in HCC occurrence and recurrence after DAAs[27,28]. Vascular endothelial growth factor (VEGF) also increases during DAA therapy and persists at high levels for 3 mo[29]. In addition, higher levels of angiopoietin-2 in patients with HCC occurrence and recurrence after DAAs have been found, and the authors suggested that the increase in VEGF induced by DAAs stimulates neo-angiogenesis in the liver in patients with clinically significant portal hypertension[30]. Some studies also noted a significant reduction in microRNA 122 concentrations in serum levels in patients treated with DAAs, which has a central role in suppressing HCC development and hence that also might be implicated in tumor development[31,32].

## ASSOCIATION BETWEEN DAAS AND DE NOVO HCC

A few months after wide-scale implementation of DAAs in HCV management, many reports surprisingly reported higher rates of HCC recurrence and occurrence[33,34]. In a study done by Cardoso *et al*[35], 7.4% of the patients who achieved SVR on DAAs were diagnosed with HCC with a median time for HCC development of 8 mo.

Conti *et al*[34] reported that 3% of the patients treated with DAAs developed *de novo* HCC within a 6-mo follow-up and concluded that attaining SVR on DAAs does not seem to reduce the incidence of HCC occurrence. Moreover, multivariate analysis found that the risk of HCC development increased with a higher Child-Pugh score.

Kozbial *et al*[36] also reported that in patients with SVR on DAA therapy, there was a 5% incidence of *de novo* HCC development, which is significantly higher than that with IFN-based therapy as mentioned before.

In a retrospective study, Ravi *et al*[33] observed *de novo* HCC occurrence in about 9% of HCV-related cirrhosis patients during or within 6 mo of DAA therapy and another 3% developed new indeterminate lesions.

A French study that followed three separate cohorts with more than 6000 patients treated with DAAs concluded that recurrence of HCC is similar in treated and untreated patients[37]. Other studies reached a similar conclusion regarding *de novo* HCC occurrence after DAAs[21,38].

The same results were obtained in a British study. Also, this study concluded that DAAs were associated with improved liver function in patients with decompensated liver cirrhosis compared to placebo[39]. This indicates that in contrast to IFN-based therapy, DAAs do not reduce the incidence of HCC after achieving SVR, but at the same time do not increase its incidence.

Abdelaziz *et al*[40] in a small retrospective study that included 89 patients who developed HCC after DAAs (either occurrence or recurrence) found that the time until HCC development was significantly longer in the *de novo* group compared to the recurrence group.

Zeng *et al*[20] suggested that DAA treatment often includes advanced age groups and patients with advanced cirrhotic disease who cannot receive IFN-based therapy.

In response to such a theory, Calvaruso *et al*[41] studied HCC occurrence in patients treated with DAAs with Child-Pugh class A and B. In 1 year, HCC occurred in approximately 2% of patients with Child-Pugh class A and 8% in class B ( $P < 0.001$ ). Moreover, low serum albumin and thrombocytopenia were independently associated with increased risk of HCC.

A similar study that included about 4000 patients found that in a 1-year follow-up, the risk of HCC development was 0.46% (95%CI: 0.12-1.17) in patients with F3 class based on METAVIR fibrosis and activity score, 1.49% (1.03-2.08) in Child-Pugh A, and 3.61% (1.86-6.31) in Child-Pugh B patients[42].

In a large retrospective study that included more than 22000 patients, DAA-treated patients who achieved SVR had a significantly reduced HCC risk (0.90 *vs* 3.45 HCC/100 person-years; adjusted hazard ratio 0.28; 95%CI: 0.22-0.36). However, in patients with established cirrhosis who achieved SVR, the absolute HCC risk remained high, indicating that liver cirrhosis was the most significant risk factor for HCC development[43].

Finkelmeier *et al*[44] followed 819 patients for a median period of 263 d after DAA therapy and found that in 550 patients with no cirrhosis (F0-F3) none developed *de novo* HCC, while 9% of those with cirrhosis (F4) developed *de novo* HCC. In addition, HCC developed more in males, older patients, treated patients, patients with a lower SVR12 rate, and those with higher levels of liver inflammation markers. The study compared their cohort with an older cohort of IFN-treated patients and concluded that *de novo* HCC development is the same with DAAs and IFN.

Ioannou *et al*[45] found a higher HCC incidence with DAAs compared to IFN-based therapy, but after adjusting confounders, including age, cirrhosis severity, serum albumin, and platelet count, it was concluded that HCC risk reduction was achieved regardless of the regimen used to achieve SVR.

Mettke *et al*[38] found a similar finding. In a multivariate analysis, only a higher MELD-Score and  $\alpha$  fetoprotein (AFP)-levels were associated with a higher risk of HCC.

Tani *et al*[46] studied 1454 patients who received DAAs and found that the annual incidence of *de novo* HCC was 1.8%. This study identified age and AFP level after DAAs as independent factors risk factors for HCC development and proposed a novel scoring system (0-2 points) to predict HCC occurrence following DAAs. HCC incidence at 2 years was 0.3%, 6.27%, and 18.37% in 0-, 1-, and 2-point, groups, respectively. However, independent validation is required for this scoring system.

Shiha *et al*[47] studied 2400 patients in Egypt with advanced fibrosis (F3-F4) and found that the annual incidence of HCC was 2.3% (95%CI: 1.942-2.814) with a slightly higher incidence in patients with cirrhosis (2.9%, 95%CI: 2.407-3.535). Similar findings were reported from a prospective study in Latin America that reported an annual incidence of 2% in a cohort of 1400 patients; all the patients who developed HCC were classified as F3-F4 classes according to METAVIR fibrosis and activity score before initiating treatment with DAAs[48].

However, another study that included 400 patients in Egypt found that HCC occurrence rate was 7.6% in patients who received DAAs. All patients included had also cirrhosis and/or with fibrosis (class F3-F4)[49]. Similar findings were reported by Hassany *et al*[50] in a cohort of 350 Egyptian patients in which HCC occurrence after DAAs was 6.7% in patients with SVR and 23.8% in patients with non-SVR.

A meta-analysis that included 26 studies found that DAA therapy was not associated with higher HCC occurrence (RR 0.68, 95%CI: 0.18-2.55,  $P = 0.55$ ), and the authors concluded that there is no difference in HCC occurrence following SVR with DAAs compared to IFN-based therapy[51]. Another meta-analysis that included 138 studies found that the hazard ratio was 0.58 (95%CI: 0.20-1.07) for HCC occurrence and 0.59 (95%CI: 0.24-1.03) for HCC recurrence after DAA treatment compared to IFN-based treatment[52].

Furthermore, Abdelaziz *et al*[53] studied the differences in tumor behavior HCV-induced HCC in patients either treated with or without DAAs and concluded that HCC behavior was more aggressive in DAA-treated patients based on portal vein thrombosis, malignant lymphadenopathy, and HCC imaging characteristics.

El Fayoumie *et al*[54] assessed pattern changes in HCC after DAA treatment and demonstrated that HCC after DAA treatment may occur in less advanced liver disease. Infiltrative and multiple nodules patterns of HCC after DAA treatment were significantly more frequent than among HCC patients without DAA treatment. Also, HCC was still detected up to 4 years after starting DAA therapy.

However, most of the trials did not report the long-term incidence of HCC occurrence post-DAAs (*e.g.*, see Pecoraro *et al*[55]), and due to the relatively short period of DAA treatment, it is difficult to draw a solid conclusion regarding the relationship between DAAs and HCC. The summary of the studies is listed in [Table 1](#).

## ASSOCIATION BETWEEN HCC RECURRENCE AND DAAS

Regarding HCC recurrence after DAAs, in 2016 Reig *et al*[56] were the first to report high HCC recurrence rates at 28% with a 3.5-mo median time from initiating DAAs. They also reported a more aggressive HCC recurrence[57]. Another Italian study reported that the recurrence rate of HCC was also 28% 6 mo after DAA therapy[34]. HCC recurrence in 30% of cases within 1 year was reported in another study[58]. In 2017, a high HCC recurrence rate after DAAs was again reported by another multicenter study[59]. HCC recurrence rate after liver transplantation was also reportedly high in patients who received DAAs before surgery[60]. In contrast to this study, another study reported no HCC recurrence in a group managed by liver transplantation but high rates of recurrence among those treated with RFA or liver resection. In 2018, Elkassas *et al*[61] reported a non-randomized trial with a significantly

**Table 1 Summary of studies of the association between direct-acting antiviral agents and *de novo* hepatocellular carcinoma occurrence**

Ref.	Type of study	n (treated with DAAs)	Follow-up period	Incidence of HCC occurrence
Ravi <i>et al</i> [33]	Prospective	61	6 mo	9%
Conti <i>et al</i> [34]	Prospective	344	24 wk	3.16%
Cardoso <i>et al</i> [35]	Prospective	240	12 mo	7.4%
Mettke <i>et al</i> [38]	Prospective cohort treated with DAAs <i>vs</i> retrospective control matched group of untreated patients	158 in DAAs group <i>vs</i> 184 in the control group	440 d for DAAs group <i>vs</i> 592 d for the control group	2.9% <i>vs</i> 4.5%
Cheung <i>et al</i> [39]	Prospective cohort treated with DAAs <i>vs</i> retrospective control matched group of untreated patients	406 in each group	15 mo	4% in both groups
Calvaruso <i>et al</i> [40]	Prospective	2249	16 mo	3.5%
Romano <i>et al</i> [41]	Prospective	3917	536.2 + 197.6 d	1.4%
Kanwal <i>et al</i> [43]	Retrospective	22500	12 mo	1.18%
Finkelmeier <i>et al</i> [44]	Prospective	819	263 d	3.6% annually
Ioannou <i>et al</i> [45]	Retrospective	21948 treated with IFN free regimen	-	1.32% annually
Tani <i>et al</i> [46]	Retrospective	1088 (Patients with SVR)	4 yr	1.88% annually
Shiha <i>et al</i> [47]	Prospective	2372 patients with advanced liver fibrosis or cirrhosis with SVR	12 mo	2.3% annually
Pinero <i>et al</i> [48]	Prospective	1400	16 mo	2% annually
Lashen <i>et al</i> [49]	Retrospective	392 (F3-F4) patients	34 mo	7.6%
Hassany <i>et al</i> [50]	Prospective	350	2 yr after the end of treatment	6.7% in patients with SVR <i>vs</i> 23.8% in patients with non-SVR

DAAs: Direct-acting antiviral agents; HCC: Hepatocellular carcinoma; IFN: Interferon; SVR: Sustained viral response.

increased HCC recurrence rate after DAAs in Egyptian patients. More microvascular invasion in tumors after DAAs was reported in another study[62].

Data from the ANRS cohorts from France showed no significant difference in HCC recurrence between those who received DAAs and those who did not[37]. In 2017, Cabibbo *et al*[63] reported that the recurrence rates after DAAs at 6 and 1-year follow-up were comparable to those reported previously without HCV treatment (12% and 26.6%, respectively). In addition, another study also found no higher risk of HCC recurrence on DAAs[9]. A meta-analysis of papers published between 2000 and February 2017 found no increased risk of HCC recurrence after DAAs when compared to that after IFN[62].

In 2018, another multicenter study showed no increase in HCC recurrence on DAAs[64]. Another study reported that patients who received DAAs had a lower risk of dropping off the transplantation waiting list due to death or HCC growth. Huang *et al*[65] described HCC recurrence at a rate of 17% per year in their meta-analysis, and they concluded that there was no strong evidence of increased HCC recurrence risk after DAAs.

In 2019, a multicenter study with North American cohorts reported no link between DAAs and HCC recurrence[66]. A Japanese study compared the behavior and HCC recurrence risk and found no differences after IFN or DAA therapy[67]. A meta-analysis revealed no verification of increased probability of HCC recurrence post-DAA therapy with a rate of HCC recurrence after DAAs equals 16.76% per year[52]. Another study revealed better survival in patients with ablated HCC who received DAAs thereafter[68].

In a more recent international multicenter retrospective study published in 2020, there was no increase in the risk of HCC recurrence or the risk of mortality in patients with HCC waiting for liver transplantation[69]. Another group reported no difference in the behavior of HCC recurrence or mortality rates in patients who achieved SVR after either IFN or DAAs[70].

**Table 2 Summary of Studies of the association between direct-acting antiviral agents and hepatocellular carcinoma recurrence**

Ref.	Type of study	Number (treated with DAAs)	Median follow-up period	Incidence of HCC recurrence
Reig <i>et al</i> [56]	Retrospective	58	5.7 mo	27.6%
Conti <i>et al</i> [34]	Prospective	59	24 wk	28.81%
Calleja <i>et al</i> [58]	Retrospective	70	12 mo	30%
Elkassas <i>et al</i> [61]	Prospective	53 vs 63 untreated patients	16 mo vs 23 mo in the untreated group	37.7% vs 25.4%
ANRS study group[37]	Retrospective	(1) ANRS CO22 HEPATHER cohort: 189 vs 78 untreated patients	20.2 vs 26.2 mo	0.73 vs 0.66/100 person-mo
		(2) ANRS CO12 CirVir cohort: 13 patients received DAAs	79 mo	7.7%
Ogawa <i>et al</i> [64]	Prospective	152	1 yr	6.5% in non-cirrhotic and 23% in cirrhotic patients
Cabibbo <i>et al</i> [68]	Prospective	143	18 mo	29.1%
Huang <i>et al</i> [65]	Retrospective	62 receive DAAs vs 87 did not receive DAAs	12 mo	47% vs 49.8%
Singal <i>et al</i> [66]	Retrospective	304 received DAAs and 489 did not	365 d	17.1 vs 46.4%
Kinoshita <i>et al</i> [67]	Retrospective	147 received DAAs vs 156 received IFN	2 yr	60% vs 61%
Ikeda <i>et al</i> [71]	Prospective	89	2 yr	22.1%
Imai <i>et al</i> [72]	Retrospective	13 DAAs, 14 IFN, and 64 untreated groups	-	The 3-yr recurrence-free survival was 76.2% in DAAs group vs 69.2% in the IFN group and 22.4% in the untreated group
Gorgen <i>et al</i> [69]	Retrospective	875	-	the 5-yr recurrence-free survival was 93.4%, 84.8%, 73.9% for the pre-liver transplant DAA, IFN, and antiviral naïve groups
Tahata <i>et al</i> [70]	Retrospective	63 patients in each group	3 yr	43% in the DAAs vs 34% in the IFN group
Kamal <i>et al</i> [13]	Retrospective	52	2 yr	42.3%

DAAs: Direct-acting antiviral agents; HCC: Hepatocellular carcinoma; IFN: Interferon.

Kamal *et al*[13] reported 26.9% and 42.3% HCC recurrence rates at 1- and 2-year follow-up in a cohort that received DAAs. The authors concluded that DAAs do not increase overall HCC recurrence rates, similar to the rates in untreated HCV patients with ablated curable HCC although authors included lesions up to 5 cm in their cohort.

Zeng *et al*[20] described no recurrence in the HCC group after DAAs. Another study also described a significant decrease in HCC recurrence after DAAs[71]. A more recent study in 2020 also described the same finding[72].

Increasing the interval between HCC management and DAA initiation is suggested to decrease the risk of early HCC recurrence after DAAs. A Japanese study recommended that to reduce the risk of HCC recurrence, at least a 120-d interval between HCC management and initiation of DAA therapy [73]. Kamal *et al*[13] also observed higher 6-mo HCC recurrence in those who started DAAs within 12 wk from percutaneous tumor ablation with a higher incidence of multi-centric recurrence. But the recurrence rates were nearly equal in both groups by the end of the first and second years of follow-up and close to the recurrence rates reported after curative HCC management in HCV untreated patients although they have included lesions up to 5 cm, not only 3 cm, in their study. The summary of the studies is listed in Table 2.

## CONCLUSION

In conclusion, although DAAs are associated with increased SVR, there is still controversial data regarding the association between DAAs with *de novo* HCC occurrence, recurrence, and HCC morphologic and pathological behaviors. Also, when to initiate DAA treatment in patients with treated

HCC is still uncertain. Randomized trials are required to address these issues.

## FOOTNOTES

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