Review Article

Direct-acting antivirals and hepatocellular carcinoma recurrence

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Abstract: Hepatocellular carcinoma (HCC) is primarily caused by hepatitis C virus (HCV) infection, which is treated mainly by direct-acting antiviral agents (DAAs). Compared with interferon therapy, DAAs offer excellent results and tolerable side effects making them the preferred treatment for many groups of patients, especially old and cirrhotic patients. However, there is controversial data regarding HCC occurrence or recurrence following HCV eradication with DAAs, especially in patients with previously treated HCC. Most reports arise from studies restricted by various methodological limitations, thus hampering the interpretation of their results and preventing formulation of solid conclusions. These limitations include small sample size, exclusion of control arms, and inconsistent elimination of HCC or suspicious nodules before DAA treatment. Many of the studies were also not multi-centric, being mainly retrospective, observational studies consisting of a small number of patients and short follow-up time. As a result, the full picture on this issue remains unclear to date. This review evaluates literature data showing the effect of DAAs on HCC recurrence following successful treatment of the tumor. Despite initial negative reports demonstrating an increased risk of HCC recurrence after DAAs therapy, these data cannot be considered definitive and have not been confirmed by most subsequent studies which have shown no increase in HCC recurrence after DAA therapy.

Keywords: Hepatocellular carcinoma (HCC); direct-acting antiviral agents (DAAs); chronic hepatitis C virus

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Introduction

Hepatocellular carcinoma (HCC) is the most prevalent hepatic malignancy, accounting for 5.6% of all malignances and reported as the second most common cause of cancer deaths globally (1-5). In cirrhotic hepatitis C virus (HCV) patients, the annual risk of HCC is approximately 3–8% (6), with a 30% 5-year cumulative risk for the development of HCC in patients with cirrhosis, the highest risk being among cirrhotic HCV infected patients (7).

During the interferon (IFN) era, achieving a sustained virological response (SVR) resulted in decreased likelihood of developing HCC (8-10), but the wide accessibility of direct-acting antiviral agents (DAAs) associated with higher safety profiles and superior efficacy enables treatment of chronic HCV patients with advanced fibrosis and cirrhosis with significant SVR (11,12).

Evidence supporting HCC recurrence following DAAs therapy remains a matter of debate (13). While some studies have established an increased risk of HCC occurrence or recurrence in cirrhotic patients after DAA treatment (*Table 1*), others have not supported these observations (26,27). The authors felt that this ongoing controversy justifies the necessity to review the evidential literature regarding whether treatment with DAAs is linked with higher rates of HCC recurrence following DAAs therapy or not.

Table 1 Hepatocellular carcinoma recurrence after direct-acting antiviral agents treatment

Authors, year	Type of study	Number of patients treated with DAAs	Follow-up time (months)	Recurrent HCC incidence (%)
Reig *et al.*, 2016, (14)	Retrospective	58	Mean: 5.7	27.6
Conti *et al.*, 2016, (15)	Retrospective	59	Mean: 5.6	28.8
Nagata *et al.*, 2017, (16)	Retrospective	83	Mean: 21.6	45.1
Virlogeux *et al.*, 2017, (17)	Retrospective	23	Median: 13.0	47.8
Cabibbo *et al.*, 2017, (18)	Prospective	143	Mean: 8.7	20.3
Lin *et al.*, 2020, (19)	Retrospective	60	Median: 20	37.1
Singal *et al.*, 2019, (20)	Retrospective	304	Median: 10.4	42.1
ANRS CO22 HEPATHER, 2016, (21)	Prospective	189	Mean: 20.2	12.7
ANRS CO12 CirVir, 2016, (21)	Prospective	13	Median: 32	7.7
ANRS CO23 CUPILT, 2016, (22)	Prospective	314	Mean (after LT): 70.6	2.2
Bielen, *et al.*, 2017, (23)	Retrospective	41	Mean: 21	15
Ogawa *et al.*, 2018, (24)	Prospective	152	Median: 17	23.1
Ikeda *et al.*, 2017, (25)	Retrospective	89	Median: 20.7	34.5

DAAs, direct-acting antivirals; HCC, hepatocellular carcinoma.

Direct-acting antiviral therapies and HCC: the dilemma?

While successful treatment of chronic HCV by DAAs has been reported (28-30), some observational studies have reported a higher incidence of early HCC recurrence following DAAS therapy (14,15,31). Several large prospective studies incorporating lengthy follow-up periods and a substantial number of chronic HCV patients treated by DAAs recently demonstrated that DAA-treated patients may have lower rates of HCC recurrence than patients who do not achieve SVR or those who remain untreated (17,32,33).

Studies of increased HCC recurrence after DAA

Reig *et al.* (14) reported an unexpectedly high rate (27.6%) of early tumor recurrence after DAAs. However, this study included a small number of patients (58 patients) with a short interval between HCC treatment and DAA therapy (median follow-up of 6 months from DAA start). Similarly, Conti *et al.* also found that the recurrence rate of HCC after treatment with DAAs was 28.81% in a single-center cohort including 59 patients and had a short 24-week period of follow-up (15). However, these studies could not reach definitive conclusions on account of their limitations including the small number of study subjects and their retrospective nature, lack of an untreated control arm, heterogeneous research population and inconsistent methodology unaddressed by the authors, such as the combination of heterogeneous groups of patients receiving different treatments options, whether palliative and curative.

Cammà *et al.* (34) analyzed the data in the Reig study and suggested that the probability of HCC recurrence during the first 6 months following initiation of DAAs therapy was twice as high for patients with a shorter interval between their HCC treatment and their latest assessment of complete response compared with patients with longer intervals (<15%). This means that the high early tumor recurrence rate claimed by Reig was driven largely by cases started on DAAs shortly after being treated for HCC. A different case-control study conversely showed that HCV therapy with DAAs neither accelerated nor prevented early HCC recurrence when compared to untreated patients, both groups of patients showing similar recurrence rate, time to progression, and HCC pattern (35).

Interestingly, Jain *et al.* studied the rate of HCC recurrence in liver transplant (LTx) recipients treated with DAAs compared with non-treatment and observed that recurrence was significantly higher with non-SVR end-of-treatment response compared with patients who achieved SVR or those who were untreated (36). Furthermore, a

prospective multicenter study from Italy reported that the probability of HCC early recurrence in previously cured HCC patients remained high despite HCV cure by DAAs. The risk was similar, but not greater, than that observed in the DAA untreated patients (18).

A recent retrospective, multicenter cohort study enrolled 326 consecutive patients with chronic hepatitis C who required HCC treatment following sustained viral response by DAAs administration demonstrated that, during the follow-up after SVR, 171 patients (52.5%) had a recurrence of HCC. HCC recurrence within 6 months after SVR determination (early recurrence) was seen in 46 patients, whereas recurrence was beyond the early phase in 125 patients (37).

Studies of decreased HCC recurrence after DAA

A single-center study conducted by Lin *et al.* determined that out of the 107 HCC studied patients, 60 had received DAA therapy after ablation of HCC. At a median follow-up of 20 months, 37.1% patients had HCC recurrence after DAA therapy. There was no statistical difference in recurrence and free survival between patients receiving DAA treatment and those who had not, although anti-viral therapy improved the survival outcome of HCC patients with no increase in recurrent HCC after curative therapy (19).

A multicenter study by Singal *et al.* reported that in patients with complete response to HCC therapy (resection, local ablation, transarterial chemo- or radioembolization, or radiation therapy), DAA treatment was not associated with increased overall or early HCC recurrence, this being comparable in both treated and non-treated patients (20). Similar results by Kuo *et al.* established that DAA therapy did not appear to increase HCC recurrence when compared with non-treatment (38). A further study on 349 patients with HCV who underwent DAA treatment by Kogiso *et al.* also determined that DAA did not increase the rate of HCC. Interestingly, in this research, six liver transplant patients and one kidney transplant patient had HCC, but no HCC was detected after DAA therapy (39). Additionally, Nakamura reported a similar HCC recurrence rate in patients having undergone curative DAA treatment as before the DAA era, confirming the idea that DAA therapy is not related to HCC development (40).

However, Miuma *et al.* found a decreasing HCC recurrence rate after curative treatment for primary HCC in patients with chronic hepatitis, with DAA therapy decreasing the subsequent HCC recurrence rate after treatment for the first HCC. These findings suggest that with respect to the time interval between HCC curative treatment and DAA induction, DAA therapy was not associated with early-stage HCC recurrence after curative treatment (41). Furthermore, Preda *et al.* reported that DAA therapy significantly decreased the recurrence rate of HCC and improved survival in patients with treated HCV-associated HCC (21), while three additional large prospective French multicenter cohorts came to a similar conclusion that there was currently no evidence to suggest that DAAs heighten the risk of HCC recurrence, especially following curative HCC treatment, including liver transplantation (LT) (22).

Additionally, there was no evidence for HCC occurrence or recurrence risk following SVR from DAA and IFN-based therapy in a study by Waziry *et al.* (42). A meta-analysis of 24 studies on a total of 1,820 patients determined that HCC recurrence following DAA therapy ranged from 0% to 59%, with recurrence being associated with a history of previous HCC recurrence and a shorter interval between commencement of DAA therapy and HCC complete response. Moreover, no significant differences in HCC recurrence were found between prospective and retrospective studies or between studies with follow-up periods shorter or longer than 12 months (43). Another study by Nishibatake Kinoshita *et al.* (44) evaluated HCC recurrence rates from the induction of antiviral therapy in patients with completely ablated HCV-related HCC who received antiviral therapy with DAAs or with IFN-based therapy. Findings showed that at 1 and 2 years, respectively, the recurrence rates were 39% and 61% in the IFN group and 39% and 60% in the DAA group. No significant difference in early HCC recurrence rates and patterns was detected between both therapy arms.

A recent study by Lim *et al.* on the risk of HCC recurrence in patients with HCV-related HCC undergoing LT found that, pre-transplant DAA therapy was associated with a statistically insignificant but strong trend toward increased HCC recurrence when compared to viremic controls (45). Another recent large meta-analysis of 977 HCV-related HCC patients who achieved complete radiological response and underwent treatment with DAAs determined that the effects of DAAs therapy on HCC recurrence risk remain inconclusive (46).

Conclusions

There is mounting evidence that, viral clearance of HCV

using DAAs therapy is not associated with increased recurrence of HCC.

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Footnote

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