Review

Impact of direct-acting antivirals on the recurrence of hepatocellular carcinoma in chronic hepatitis C

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Abstract

Chronic hepatitis C virus (HCV) infection is estimated to affect 56.8 million individuals globally and is a major and independent risk factor for the development of hepatocellular carcinoma (HCC). After the introduction of safe and potent direct-acting antivirals (DAAs), capable of curing HCV infection also in patients with advanced liver disease at high risk of HCC, the beneficial effect on a *de novo* HCC development after viral clearance has been established. However, studies addressing the relationship between DAA-induced eradication and risk of HCC recurrence (i.e., reappearance of HCC treated before starting antivirals) have produced contradictory data, suggesting either an increase or a decrease of HCC recurrence rate, while some report no effect of these treatments. Thus, there seems to be an unclear benefit of viral clearance in patients with a history of HCC curative treatment, where the recurrence rate remains worryingly high. This short review aims to summarize current evidence on the impact of DAAs on HCC recurrence rates, the pathogenic mechanisms and characteristics of HCC recurrence after DAA treatment, the predictors of tumor recurrence, and the impact of DAAs on overall survival.

Keywords: Hepatitis C virus, hepatocellular carcinoma, liver oncogenesis, direct-acting antivirals, tumor recurrence

INTRODUCTION

Hepatocellular carcinoma (HCC) represents the most frequent primary liver malignancy[1]. Being the fourth most common cause of cancer-related death worldwide, with a 5-year survival rate of 18%, liver cancer is an

important global burden that is projected to cause more than one million deaths in 2030 according to the World Health Organization[2,3]. While HCC is the leading cause of mortality in patients with compensated cirrhosis, it rarely develops in those without an underlying chronic liver disease and advanced fibrosis[4]. Chronic hepatitis C virus (HCV) infection is estimated to affect 56.8 million individuals worldwide and is an independent risk factor for the development of HCC, through a complex mechanism that encompasses on the one hand chronic inflammation, fibrinogenesis, and eventually cirrhosis and on the other hand the direct carcinogenic effects of the virus[5]. Chronic HCV infection and the development of HCC often lack symptoms and physical signs, leading to a late diagnosis in advanced stages and a poor prognosis. Although there are many therapeutic options for HCC, the mainstay of curative treatment remains surgical resection of the liver, local ablation, and liver transplantation (LT). However, even after curative treatment, HCC presents a recurrence rate of up to 70%, which is unusually high compared to other malignant neoplasms[6]. Effective treatment of chronic HCV infection is believed to be the best strategy for the prevention of HCC occurrence in these patients. Until a few years ago, the mainstay of HCV treatments was interferon-alpha (IFN-α) and its long-acting form, pegylated IFN-α (Peg-IFN-α), in combination with ribavirin (RBV). These drugs were poorly tolerated, especially in patients with advanced liver disease, and achieved relatively low levels of sustained virologic response (SVR), defined as lack of detectable HCV RNA in serum 12-24 weeks after the end of therapy, which is tantamount to permanent viral clearance[7]. It was also nonetheless demonstrated that patients who had achieved SVR with IFN-α based treatments had a significantly reduced risk of developing HCC in comparison with the ones failing to do so[8]. Since the introduction of direct-acting antivirals (DAAs), the beneficial effect on *de novo* HCC has been further confirmed[9,10]. DAAs have been shown to have a better safety profile, shorter treatment period, and can be administered even in advanced liver disease stages including decompensated cirrhosis, achieving a markedly increased SVR rate of > 95%. Thus, since HCC represents a major complication of chronic hepatitis C, it is not surprising that the introduction of DAAs has been associated with high expectations of decreasing the risk of development of both occurent and recurrent HCC in patients with chronic HCV infection, thus improving their prognosis[11]. However, contradictory data have emerged from several studies evaluating the relationship of DAAs with the risk of HCC recurrence in the group of patients who have been previously cured for HCC[12-15]. On that account, some authors have suggested an increase, a decrease, or even no effect of DAA treatment on HCC recurrence[12-15]. Although meta-analyses have suggested that the risk of developing *de novo* HCC in patients without HCC at the start of antiviral therapy is decreased, there seems to be an unclear benefit in those with a history of treated HCC, where the recurrence rate remains worryingly high[7]. This short review aims to summarize current evidence on the impact of DAAs on HCC recurrence rates, the pathogenic mechanisms and characteristics of HCC recurrence after DAA treatment, the predictors of tumor recurrence, and the impact of DAAs on overall survival.

DAAS AND HCC RECURRENCE
Definition and categories of recurrence
Although the definition of HCC occurrence may be simple, HCC recurrence still lacks a widely accepted definition. One simple definition for HCC recurrence is the reappearance of HCC in patients who have been treated with radical and potentially curative procedures, with the most effective being surgical resection. However, it remains a heterogeneous term as it can vary in terms of spatial (intra-hepatic or local versus distal recurrence) and temporal (early versus late recurrence) features[16]. According to a meta-analysis of seven studies, the significant variability in reported HCC recurrence rates can be partially explained by the case definition[17]. There are currently many hypotheses around the mechanisms of intra-hepatic HCC recurrence after curative treatment. Several authors have divided HCC recurrence in "early" and "late", with two years from treatment serving as the cut-off. Considering the underlying mechanisms, "early recurrence" is thought to derive from microscopic (and therefore undetected) metastases of the primary tumor, while "late recurrence" is thought to be driven by the underlying liver cirrhosis and its

carcinogenic properties[18]. However, there are very few studies evaluating the difference in carcinogenic processes and prognosis between "early" and "late" recurrence, which explains the lack of consensus concerning these terms. A study that aimed to address this exact issue suggested that 17 months after curative HCC surgical resection might be a more suitable cut-off value between early and late recurrence. Additionally, the authors reported different independent risk factors for early [alpha-fetoprotein (AFP) level > 100 ng/mL, multiple HCC, serosal invasion, and microvascular invasion] and late recurrence (liver cirrhosis)[19].

Do DAAs Increase HCC recurrence rates?

Some of the earliest studies suggested that DAA treatment can increase the recurrence rate of HCV-related HCC in previously cured patients [Tables 1 and 2]. One of the first studies that demonstrated a negative impact of DAAs on the risk of HCC recurrence was a retrospective multicenter study from Spain by Reig *et al.* in 2016[12]. The study included 58 patients with a mean follow-up of 5.7 months and reported a recurrence rate of 27.6%. The recurrence risk was particularly high (41.2%) in patients receiving DAAs < 4 months post HCC treatment, suggesting that timing of DAAs administration after HCC treatment could have an impact on the recurrence rate. The authors reported for the first time an unexpectedly high recurrence rate of HCC in patients receiving DAA therapy and although based in a small number of patients this study raised concerns about the benefit of this treatment in this sub-group of patients[12]. An almost simultaneous single-center cohort study by Conti *et al.* reported a similar trend, with 17 out of 59 patients with previously treated HCC (28.8%) experiencing tumor recurrence within a 24-week follow-up[13]. Younger age and more advanced liver fibrosis were found to be significantly associated with high rates of HCC recurrence[13]. Additionally, a multicenter cohort study that included 47 patients treated for HCC with surgical resection, ablation, or trans-arterial chemo-embolization (TACE) from five European centers reported that 77% and 58% of the patients were recurrence-free after six months and one year post DAA treatment, respectively. The recurrence was significantly associated with the time interval between HCC treatment and DAAs initiation[20]. A prospective cohort study from Egypt also showed that DAA-exposed patients can have up to four times increased HCC recurrence incidence rate compared to non-DAA-exposed patients (recurrence rate 37.7% in DAA-exposed *vs.* 25.4% in non-DAA-exposed patients)[21].

Are HCV-Related HCC recurrence rates unaffected by DAAs?

Subsequent studies came to question this association between DAAs and HCC recurrence, reporting no effect of DAAs on HCC recurrence rates. Several studies suggested that patients who achieve SVR with IFN-α-based or DAA treatments have similar HCC recurrence risk[21,22,41]. A recent multicenter retrospective study from Japan that included 338 patients found no significant difference in cumulative HCC recurrence rates in 1-, 2-, and 3-year survival (20.6%, 27.4%, and 34.6% in the IFN group *vs.* 19.2%, 32.3%, and 43.0% in the DAA group, $P = 0.332$) and overall survival (OS) rates (OS rates in one, two, and three years: 100%, 98.3%, and 96.6% in the IFN-α group *vs.* 100%, 98.4%, and 96.4% in the DAA group, $P = 0.132$). The authors found a homogenous HCC recurrence pattern between the two groups that were distinguished by similar tumor characteristics and serum AFP levels at HCC recurrence[42]. A recent study from Taiwan suggested that DAAs cannot increase the risk for HCC recurrence and tumor progression. The authors compared a DAA and an IFN-α-treated arm, and they found no difference in median recurrence-free survival (RFS) counting from either antiviral (29.3 months *vs.* 39.2 months, $P = 0.764$) or curative HCC treatment (65.8 months *vs.* 44.0 months, $P = 0.130$)[40]. Another recent case–control study showed that DAA-treated patients had similar rates of recurrence (41% *vs.* 35%, $P = 0.7904$), time to progression (12[9-16] months G1 *vs.* 14[8-21] months G2, $P = 0.7688$), and HCC pattern at recurrence [assessed with Barcelona Clinic Liver Cancer Stage (BCLC)] compared to untreated patients. However, these authors suggested that the time interval between HCC treatment and antiviral therapy can have a significant role in HCC recurrence rate, discouraging DAA initiation < 12 months after HCC cure[43]. Additionally, in a prospective study, Cabibbo *et al.* compared a

Table 1. Retrospective studies on HCC recurrence after treatment of chronic hepatitis C with DAA

Author, year (reference)	n	HCC treatment	Median time (range) from HCC treatment to DAA (months)	SVR (%)	Median FU (range) (months)	HCC recurrence in DAA-exposed (%)	HCC recurrence in controls (%)	Cumulative HCC recurrence rate (%)	Median time from DAA treatment to HCC recurrence (months)
Reig *et al.*, 2016[12]	DAA: 58	surgical resection, ablation, TACE	11.2 (3.6-23.2)	97.5	5.7 (0.4-14.6)	27.6	NA	NR	3.5 (1.1–8)
Nagata *et al.*, 2017[14]	Total: 143, IFN: 60 *vs.* DAA 83	surgical resection, RFA	NR	IFN 65 *vs.* DAA 96	IFN: 81.6 (2.4-264) *vs.* DAA: 21.6 (1.2-92.4)	29	53	At 5 years: DAA 45.1 *vs.* IFN 54.2	NR
Mashiba *et al.*, 2018[22]	Total: 516, IFN 148 *vs.* DAA 368	NR	11.1 (0.5-167.9)	IFN: 52.7 *vs.* DAA 94.2	IFN 25.5 *vs.* DAA 7.7	NR	NR	NR	NR
Singal *et al.*, 2019[23]	Total: 797, DAA: 383 *vs.* no DAA: 414	surgical resection, RFA, TACE, other	7.7 (3.6-14.1)	DAA: 79.4	NR	54.6	50.7	NR	NR
Nakamura *et al.*, 2019[24]	DAA: 312	surgical resection, RFA	9.9	92.3	28.5	43.2	NA	1-, 2- and 3-year: 18.3, 38.8 and 55.4	NR
Zou *et al.*, 2019[25]	DAA: 264	liver transplant, surgical resection, ablation, TACE	22	92	23.3 ± 9.8	26.1	NA	1- and 2-year: 3.3 and 20.2	12.2 ± 8.0
Kuo *et al.*, 2020[26]	DAA 82 *vs.* IFN 80 *vs.* Untreated 160	surgical resection, RFA	30.7	NR	NR	26.8	IFN 56.8, untreated 58.8	3- and 6-months: DAA: 4.8 and 15.5	NR
Ogawa *et al.*, 2021[27]	DAA: 326	surgical resection, ablation, TACE, particle radiotherapy, PEIT, multimodal	14.4 (3.6-188.4)	NR	32.4 (0-64.8)	52.5	NA	3- and 5-year: curative treatment 40.8 and 51.4 *vs.* palliative treatment 66.5 and 73.7	NR
Elbaz *et al.*, 2021[28]	DAA: 523	Ablation	NR	83.7	5.3	20.1	NA	recurrence rate/100PY: 7.26	NR
Watanabe *et al.*, 2021[29]	DAA: 199	NR	20 ± 26	92	22	48.7	NA	4- and 6-month, 1-, 2- and 3-year: 9.0, 16.6, 29.8, 41.0, 53.4	10
Tani *et al.*, 2021[30]	DAA: 130	surgical resection, RFA, TACE, MTA	NR	NR	41 ± 13.9	63.8	NA	6-month, 1-, 2- and 3-year: 23.2, 32.5, 46.3, and 59.4	NR
Ochi *et al.*, 2021[31]	DAA 56 *vs.* no DAA 112	surgical resection, RFA	5.6 (1.6-11.4)	NR	48	36.7	66.7	1-, 2-, 3-, 4-year: DAA *vs.* no DAA: 12.5 *vs.* 22.7, 27.8 *vs.* 41.1, 36.7 *vs.* 54.3, and 36.7 *vs.* 66.7	NR
Ahn *et al.*, 2021[32]	DAA: 100	RFA, surgical resection, radiation therapy, TACE, multimodal	NR	88	15.8 (4.4-29.9)	37	NA	1-, 2-year: 28.4 and 61.3	NR

Table 2. Prospective studies on HCC recurrence after treatment of chronic hepatitis C with DAAs

Author, year	*n*	HCC treatment	Median time (range) from HCC treatment to DAA (months)	SVR (%)	Median FU (range) (months)	HCC recurrence in DAA-exposed (%)	HCC recurrence in controls (%)	Cumulative HCC recurrence rate (%)	Median time from DAA treatment to HCC recurrence (months)
Pol *et al.*, 2016[33]	Total: 267, DAA: 189 *vs.* no DAA 78	surgical resection, ablation, TACE	NR	DAA: 91.9	20,2	12.7	20.5	NR	NR
Cabibbo *et al.*, 2017[34]	DAA: 143	surgical resection, ablation, TACE	11 (1-126)	96	8.7 (3-19)	20.3	NA	6-, 12- and 18-month: 12, 26.6 and 29.1	NR
El Kassas *et al.*, 2018[21]	Total: 116, DAA: 53 *vs.* no DAA: 63	RFA, MWA, PEIT, surgical resection	NR	DAA: 77.4	DAA 16 *vs.* no DAA 23	37.7	25.4	recurrence rate/100PM: DAA 4,06 *vs.* no DAA 1,0	NR
Ogawa *et al.*, 2018[35]	DAA: 152	surgical resection, RFA, particle radiotherapy, multimodal	14.4	NR	17	17.1	NA	1-year: 6.5 non-cirrhosis *vs.* 23.1 cirrhosis	NR
Lleo *et al.*, 2018[36]	DAA: 161	surgical resection, ablation, liver transplant, TACE	NR	95	12	23.6	NA	6-, 12-, and 18-month: 8.5, 20.9, and 26.9	20.7
Nakano *et al.*, 2019[37]	DAA: 459	surgical resection, ablation	NR	NR	29.4 ± 6.8	47.2	NA	1 , 2 , and 3 year:27.1, 43.4, and 50.8	34
Cabibbo *et al.*, 2019[38]	DAA 163 *vs.* no DAA 328	surgical resection, ablation	2.1 (0.5-6)	DAA: 83	DAA 21.4 *vs.* no DAA: 17.5	27.5	37.3	6-month, 1-, 2- and 3-year: DAA *vs.* no DAA 6 *vs.* 9, 15 *vs.* 20, 27 *vs.* 40 and 70vs57	NR
Sangiovanni *et al.*, 2020[39]	DAA: 124	NR	11 (1-188)	95	15	32	NA	mean yearly incidence 29.9/100PY and 2-year: 42.9	NR
Chi *et al.*, 2021[40]	DAA: 199 DAA (127 prospective, 72 retrospective), DAA 107 *vs.* IFN 42	surgical resection, liver transplant, RFA, PEIT, TACE, Yttrium-90, target therapy	DAA 8.2 (0.1-133.3) *vs.* IFN 3.8 (0.1-33.5)	DAA 95 *vs.* IFN 64.3	DAA 26.9 (6.0-147.6) *vs.* IFN 64.4(13.0-126.6)	NR	40.3	NR	DAA 29.3 *vs.* IFN 39.2

DAA-exposed and a non-DAA-exposed group of patients and reported a similar HCC recurrence rate (HR = 0.70; 95%CI: 0.44–1.13, *P* = 0.15). Notably, they demonstrated that DAA-exposed patients had significantly reduced hepatic decompensation (HR = 0.32; 95%CI: 0.13–0.84, *P* = 0.02)[38]. In addition, Nakamura *et al.* reported one-, two-, and three-year HCC recurrence rates of 18.3%, 38.8%, and 55.4%, respectively, comparable to those reported before the advent of DAAs, suggesting that DAA therapy may not be associated with tumor development[24]. A systematic review, meta-analysis, and meta-regression that included 17 studies on HCC recurrence found no association between DAA therapy and HCC recurrence, after adjusting for study follow-up and age (RR = 0.62, 95%CI: 0.11–3.45, *P* = 0.56)[44]. Similarly, Sapena *et al.*, in a large meta-analysis of 21 studies of HCV-related cirrhosis and HCC that included 977 DAA-treated patients and 328 DAA-unexposed patients from the ITA.LI.CA cohort as controls, observed no significant difference in recurrence rate between DAA-exposed and DAA-unexposed patients

(RR = 0.64, 95%CI: 0.37-1.1; P = 0.1)[45].

Do DAAs decrease HCV-Related HCC recurrence rates?

Recently, several studies have supported that DAA therapy can even decrease the HCC-recurrence risk in patients who have previously undergone curative treatment. A study from Japan compared two patient cohorts with history of HCV-related HCC who were DAA-exposed or non-DAA-exposed, after matching for age, gender, and BCLC staging, and found that DAA therapy significantly decreased recurrence rate when it was performed after initial HCC therapy (one- and two- year recurrence rates of 18.1% and 25.0% in DAA *vs.* 21.8% and 46.5% in non-DAA, P = 0.003)[15]. Additionally, a multicenter retrospective study on Child–Pugh A class patients who fulfilled the Milan criteria reported a significantly lower recurrence rate in the DAA group compared to the non-DAA group (36.7% *vs.* 66.7%, HR = 0.46; 95%CI: 0.27-0.77, P = 0.003). DAA treatment was also shown to significantly improve survival rate and lower median albumin-bilirubin (ALBI) score[31]. A meta-analysis of six studies that included a total of 1105 patients exposed to DAAs versus 1912 controls who were either non-treated or treated with peg-IFN-α-based regimens, with a follow-up ranging from 1.25 to 4 years, found that DAA therapy decreased HCC recurrence by 64% compared to untreated controls (OR = 0.36, 95%CI: 0.27-0.47, P < 0.00001)[46].

Do DAAs affect the dropout rate from the liver transplant waiting list?

While HCV eradication after DAA treatment has been shown to improve MELD and Child-Pugh scores and lead to a delisting of almost one third of liver transplant candidates with chronic HCV without oncological complications[47,48], the effect of DAAs administration and timing on waitlisted patients with HCC history is not fully elucidated. A single center case–control study from Italy showed that the DAA-treated and control groups had similar drop-out rates due to tumor progression (8.7 *vs.* 4.3%, respectively, P = 0.9)[49]. Additionally, a retrospective study of 149 LT candidates with locally treated HCV-related HCC suggested that DAAs have no effect on HCC recurrence, while they can reduce the risk of delisting due to HCC progression[50]. Neutral results concerning the effect of DAA treatment on the waitlist drop-out due to tumor progression and post-LT HCC recurrence were also reported by Emamaullee *et al.*[51]. On the contrary, a retrospective cohort that compared DAA-treated, IFN-treated, and untreated groups of HCC patients awaiting LT showed that SVR achieved with DAAs before LT was associated with increased post-LT HCC recurrence, compared to no-treatment[52]. Undoubtedly, there is a need for optimization of DAA administration timing in HCV-related HCC patients awaiting LT in order to benefit from the positive effects of SVR on liver function preservation while avoiding any possible risk of tumor progression acceleration or recurrence that would induce a waitlist drop-out. A recent multicenter study that aimed to address this question suggested 0-3 months post-LT as the ideal time frame for DAA administration in patients with history of HCV-associated HCC[53].

TIME ASSOCIATION BETWEEN DAA TREATMENT AND HCC RECURRENCE

Several studies observed that there might be a time association between DAAs administration and HCC recurrence. In a large multicenter study, Singal *et al.* compared patients treated with DAAs to untreated controls and suggested that early tumor recurrence could be associated with the timing of DAA therapy[23]. Specifically, they reported that HCC recurred less in patients who delayed DAA treatment > 6 months after tumor complete response (CR) (HR = 0.56, 95%CI: 0.22-1.38), although this difference was not statistically significant[23]. Additionally, Warzyszyńska *et al.* suggested that patients with previously treated HCC may be at a higher risk of accelerated tumor relapse when receiving DAA therapy[54]. By recruiting 19 patients receiving DAAs after tumor and the non-DAA group had a recurrence rate of 42.1% and 65.6%, respectively (P = 0.058), with a recurrence time that was significantly shorter in DAA-treated patients (265 *vs.* 632 days after surgery, P = 0.033)[54]. In fact, several studies have reported that the time elapsing from HCC treatment to DAA exposure may significantly increase the risk of tumor relapse[20,25,32,35]. More specifically, patients

treated with DAAs less than 12 months following HCC treatment are shown to exhibit increased HCC recurrence rates[32,35].

PATHOGENIC MECHANISMS OF HCC RECURRENCE AFTER DAA TREATMENT

Different hypotheses have been suggested regarding the underlying mechanisms of HCC recurrence following HCV treatment with DAAs that imply immunological and epigenetic mechanisms.

The immunological surveillance theory

Even though the exact mechanism of action remains unclear, IFN-α is known to have immune-mediated anti-proliferative properties as well as anti-angiogenic effects. DAAs act in a different manner, by dramatically suppressing viral replication from the initial days of treatment. This may lead to a phenomenon that has been characterized as dysregulation in the surveillance of the immune system[55]. It is known that HCV-infected hepatocytes produce Type I, II, and III IFNs that act on tumor, immune, and endothelial cells and may decelerate cancer genesis and progression. Recent *in vitro* studies have demonstrated that effective DAA treatment rapidly downregulated IFN-stimulating gene expression and Type II and III IFN production, which could affect the risk of developing HCC occurrence or recurrence after therapy[56]. Natural killer (NK) cells are crucial components in microenvironment tumor surveillance and have a direct anti-tumor immune-mediated cytotoxic effect[57]. Chronic HCV infection is known to modify NK cells phenotype by causing them to produce fewer antiviral cytokines and exhibit an increased cytotoxic function. Several studies have suggested that DAAs alter NK cells' functional phenotype rapidly after administration by downregulating NK cell cytotoxicity receptors and impairing their cytotoxic anti-tumor function, which potentially enables hepatocarcinogenesis[58-60]. Moreover, DAA treatment modifies mucosal-associated invariant T (MAIT) liver cell function while inducing changes in macrophage-derived cytokines. MAIT cells are activated in chronic HCV infection and significantly decrease in situations of liver inflammation and fibrosis[61]. A recent report shows that DAA induced HCV eradication does not restore MAIT cell function, which further supports the persistent immune dysfunction after DAA treatment[62].

Epigenetic factors

Few epigenetic factors have been studied in the context of HCC development after DAA therapy. Highly activated neo-angiogenesis is demonstrated to play a significant role in hepatic tumor growth. Angiopoietin-2 and vascular endothelial growth factor, as angiogenesis pathway markers, can be present in higher concentrations in liver tissue of DAA-treated patients and are related to HCC occurrence and recurrence[63,64]. miR-122 is a serum biomarker that is involved in HCV replication and its loss has been associated with HCC development. Santangelo *et al.* observed that DAA-treated patients have a decreased level of liver-specific miR-122, which is potentially linked to a higher HCC recurrence risk[65]. Additionally, a recent study that explored the effect of sofosbuvir and daclatasvir in HCC-derived cell lines demonstrated possible off-target effects that ultimately lead to modulation of tumor cell proliferation and migration. These findings suggest that transcriptomic and epigenetic changes may justify reported cases of more aggressive recurrence[66]. Sofosbuvir, which is used as a backbone in DAA-based therapies, has also been shown to increase epidermal growth factor receptor expression and phosphorylation, leading to pro-survival reprogramming of hepatoma cells[67].

PREDICTORS OF HCC RECURRENCE

Many of the studies addressing HCC recurrence post DAAs aim to report predictors of that event [Table 3]. Nakamura *et al.* suggested that multiple HCC nodules at the first HCC treatment, history of multiple treatments for HCC, and *Lens culinaris* agglutinin A-reactive fraction of AFP (AFP-L3) ≥ 10% at the initiation of DAA therapy are positively associated with the risk HCC recurrent development after

Table 3. Predictors of HCC recurrence in DAA treated patients

Author, year	Predictors
Cabibbo *et al.*, 2017[34]	Main tumor size, history of prior HCC recurrence
Nagata *et al.*, 2017[14]	Pre-treatment AFP, post-treatment WFA + M2BP
El Kassas *et al.*, 2018[21]	Exposure to DAAs, Child-Pugh score, presence of gastroesophageal varices
Ogawa *et al.*, 2018[35]	Higher baseline AFP level, cirrhosis, time from previous HCC treatment to initiation of DAA, number of HCC nodules, therapeutic procedures
Mashiba *et al.*, 2018[22]	AFP at completion of antiviral therapy, duration between last HCC treatment to antiviral therapy, number of treatments
Lleo *et al.*, 2019[36]	Lack of SVR, AFP > 10 ng/dL
Nakamura *et al.*, 2019[24]	Multiple tumors at the first HCC treatment, a history of multiple treatments for HCC, AFP-L3 ≥ 10% at the initiation of DAA therapy
Nakano *et al.*, 2019[37]	AFP level before DAA therapy, number of curative treatments for HCC before DAA therapy
Zou *et al.*, 2019[25]	Non-curative HCC treatment, shorter duration between HCC treatment completion and DAA initiation, no SVR
Cabibbo *et al.*, 2019[38]	Lack of SVR
Sangiovanni *et al.*, 2020[39]	History of alcohol abuse, history of HCC recurrence
Watanabe *et al.*, 2021[29]	Male gender, no SVR, history of more > 2 treatments for HCC
Tani *et al.*, 2021[30]	Palliative treatment prior to DAA treatment, AFP at SVR
Ochi *et al.*, 2021[31]	DAA, tumor size
Ahn *et al.*, 2021[32]	Last HCC treatment durability (< 12 months)
Chi *et al.*, 2021[40]	no SVR
Sapena *et al.*, 2022[45]	AFP logarithm, HCC recurrence history pre-DAA initiation, performance status, tumor burden pre-HCC treatment
Ogawa *et al.*, 2022[27]	For late recurrence: cirrhosis, number of HCC nodules (≥ 2), previous palliative HCC treatment; For early recurrence: AFP > 7 ng/mL at 12 weeks after DAA administration, time from HCC CR to DAA initiation (< 1 year), number of HCC treatments necessary to achieve CR (≥ 2)

DAAs[24]. AFP level before DAA therapy (P = 0.0047) and the number of curative procedures for HCC before antiviral treatment (P < 0.0001) were also found to be associated with HCC recurrence in another large multicenter prospective study from Japan[37]. Interestingly, Mashiba *et al.* found in univariate analysis that duration from last HCC treatment to starting antiviral therapy was significantly associated with early recurrence of HCC in patients who achieved SVR, irrespectively of the type of antiviral therapy (IFN or DAA therapy)[22]. This finding was confirmed in a multivariate analysis[22]. In addition, El Kassas *et al.* demonstrated that HCC recurrence was associated with DAA exposure with an incidence rate ratio of 3.83 (95%CI: 2.02-7.25), while Child-Pugh score and the presence of gastroesophageal varices were predictors of that recurrence[21].

POST HCC DAA TREATMENT AND IMPACT ON OVERALL SURVIVAL

Although the hypothetical association between DAAs and HCC recurrence has been extensively studied, only a few studies aimed to assess their impact on overall survival. To investigate the predictors of HCC recurrence and the causes of mortality in this group of patients, more case–control studies recruiting untreated HCV patients as control arms would be necessary, raising major ethical objections. In a prospective observational study that recruited 328 patients with HCV-related cirrhosis and early-stage HCC who had completely responded to curative treatments, Cabibbo *et al.* demonstrated that hepatic decompensation was a stronger driver of mortality than HCC recurrence. Using a time-dependent Cox regression analysis, patients who had hepatic decompensation within 12 months of follow-up as first event had about 7.5 times higher risk of mortality (HR = 7.52, 95%CI: 1.23-13.48, P < 0.0001) in comparison with patients having early HCC recurrence as a first event that had only 2.5 (HR = 2.50, 95%CI: 1.23-5.05, P = 0.0110)[68]. The authors concluded that DAAs could improve overall survival (OS) of patients with HCV-related cirrhosis and successfully treated HCC by long-term preservation of liver function[68].

Additionally, a large multicenter cohort that included 797 patients with HCV-related HCC [304 (38.3%) DAA-treated *vs.* 489 (61.7%) untreated] from 31 hospitals demonstrated that patients that achieved SVR after DAA therapy had a significantly reduced death risk (HR = 0.29, 95%CI: 0.18-0.47). Interestingly, the same association was not present in DAA-treated patients without an SVR. The one- and two-year risk of mortality for DAA treated patients was 5.5% and 11.8%, respectively[23]. Kamp *et al.* retrospectively analyzed data from 969 HCC patients and reported similar results[69]. Specifically, patients who received DAAs had a significantly higher OS in comparison to the non-DAA group (71.8 months *vs.* 11.6 months, $P < 0.0001$), while patients who achieved SVR at 12 weeks (SVR12) after DAA treatment also significantly improved their survival compared to the ones who received DAAs but without reaching SVR12 (75.6 months *vs.* 26.7 months, $P < 0.0001$)[69]. Recently, Ochi *et al.* reported a higher survival rate at 48 months of follow-up in a DAA-treated group compared to the untreated group (91.0% *vs.* 68.7%, HR = 0.33, 95%CI: 0.13-0.84, $P = 0.021$)[31]. The above-mentioned results point to the direction that DAAs potentially improve the overall survival of HCV-related HCC patients.

HCC SURVEILLANCE IN PATIENTS WITH A HISTORY OF HCC AND DAA-INDUCED SVR

According to the recommendations of the European Association for the Study of the Liver (EASL), patients with complete response to HCC therapy should be treated for their HCV infection according to the same general recommendations as for patients without HCC. Furthermore, as patients with complete response to HCC therapy who achieve SVR have a continued risk of HCC recurrence, indefinite post SVR HCC surveillance is recommended[70]. Similarly, the American Association for the Study of Liver Diseases (AASLD) suggested that treating HCV infection with DAAs in patients with HCC history should be performed after HCC is completely treated with no evidence of recurrence after an observation period of 3-6 months. According to the guidance statements, SVR achieved after DAA treatment lowers the risk of HCC for cirrhotic HCV patients without reducing it to zero and therefore cirrhotic patients with treated HCV should continue to undergo surveillance. Surveillance should be performed with liver ultrasound (US) with or without AFP every six months[71]. On the contrary, the Asian Pacific Association for the Liver (APASL) clinical practice guidelines that were published in 2017 state that, in HCV-related HCC patients having received curative therapy, IFN-α-based regimes may decrease recurrence risk and improve survival rates, while there is no such evidence for DAA-induced SVR. These authors recommend surveillance at four-month intervals for HCC by US and tumor markers for SVR patients with previous HCC history[72,73].

CONCLUSIONS

Undoubtedly, the emergence of DAAs has revolutionized anti-HCV treatment, with more than 95% of patients achieving SVR regardless of genotype and liver disease severity, from low liver fibrosis stages to decompensated cirrhosis. This will eventually lead to large SVR cohorts of aging patients under surveillance programs with a persisting important risk of HCC development, despite viral eradication. While these treatments were initially expected to improve outcomes by decreasing both the development of *de novo* and recurrent liver malignancy, the first studies on the subject reported conflicting results. Nevertheless, recent studies and meta-analyses point to the direction that DAAs ultimately do not increase HCV-related HCC recurrence risk, leading to the conclusion that, to properly assess the impact of DAA treatment on HCC recurrence, methodological issues of previous published studies should be taken into account. Firstly, study design heterogeneity should be considered. Some studies are retrospective, some have a control group that could be untreated or IFN-treated, and some lack a control group. Simultaneously, baseline patient and tumor characteristics can differ among studies. Additionally, studies are characterized by heterogeneity when it comes to type and number of curative treatments, history of prior HCC recurrences, definition of HCC recurrence (in temporal and locoregional terms), and follow-up schedule. Radiological assessment of complete response after curative HCC treatment or HCC recurrence can also be a methodological issue as it

may be influenced by subjective observations. Another important fact is the lack of randomized control trials (RCTs) given the fact that DAAs represent nowadays the standard of care for HCV infected patients, and therefore these RCTs would be considered unethical. Ultimately, the poor understanding of the pathogenic mechanisms of HCC recurrence after DAA treatment contributes to the uncertainty of the issue. Conversely, it is known that DAA treatment and subsequent SVR reduces the risk of hepatic decompensation, which could eventually improve the overall survival. In fact, a recent study showed that hepatic decompensation is a stronger driver of mortality than HCC recurrence. In addition, the improvement of liver function could render early HCC curative treatments more feasible, resulting in prolonging overall survival. In conclusion, based on the lack of compelling evidence of negative effects of DAAs in patients with previously treated HCC and the benefit of preserving liver function on overall survival, the use of DAAs in these patients should be encouraged.

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