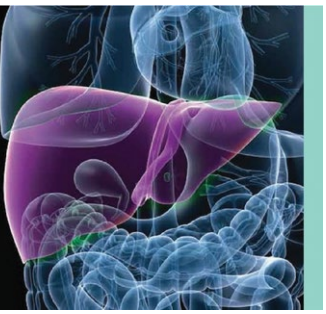

Hepatocellular Carcinoma Risk After Direct-Acting Antiviral Therapy

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Chronic hepatitis C virus (HCV) infection is a leading cause of hepatocellular carcinoma (HCC) worldwide. In the United States, HCV accounts for more than 60% of HCC cases.[1,2] The most important risk factor for HCC among patients with HCV is cirrhosis. Viral eradication is thought to reduce cancer risk by preventing cirrhosis and causing regression of fibrosis. Eliminating HCV also reverses other processes implicated in HCC pathogenesis, such as chronic inflammation and direct carcinogenic effects of the virus.

Direct-acting antivirals (DAAs) are well-tolerated agents that cure HCV in more than 95% of treated patients. A growing body of evidence suggests that DAA-induced sustained virological response (SVR) improves portal hypertension and fibrosis in patients with chronic HCV and may reduce mortality.[3] However, the question of whether DAAs prevent HCC has generated substantial controversy. In this review, we examine the impact of DAA therapy on the risk of *de novo* and recurrent HCC.

THE IMPACT OF DAAs ON *DE NOVO* HCC

A primary objective of antiviral therapy is to reduce the risk for HCC. This was indeed the case after interferon (IFN)-induced SVR. In two meta-analyses, patients with HCV who achieved SVR with IFN had significantly lower rates of HCC compared with nonresponders (relative risk [RR], 0.26; 95% confidence interval [CI], 0.18-0.31[4] versus RR, 0.34; 95% CI, 0.26-0.46[5]).

In contrast, initial studies in the DAA era produced less promising results. Conti et al.[6] described an Italian cohort of 285 patients with HCV-related cirrhosis who completed a course of DAAs, of whom 9 (3.16%) experienced development of *de novo* HCC in the first 24 weeks after treatment completion. Additional small studies reported even higher rates of HCC after DAA treatment. These rates compared unfavorably with historic HCC rates in untreated or IFN-treated patients. It was hypothesized that DAAs

Abbreviations: CI, confidence interval; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; SVR, sustained virological response; VA, US Department of Veterans Affairs.

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cause rapid viral suppression that disrupts cancer immune surveillance, thereby allowing malignant cells to escape immune regulation.

Comparison of crude HCC rates in DAA-treated patients with that of historic controls, however, fails to account for the higher baseline HCC risk of DAA-eligible patients because of older age and more advanced liver disease. In a retrospective cohort study of more than 60,000 US Department of Veterans Affairs (VA) patients with chronic HCV, DAA recipients tended to be older than IFN recipients, were more likely to have cirrhosis, and were more likely to have comorbid conditions, such as diabetes and alcohol abuse, that elevate the risk for HCC.[7] After adjusting for these confounders in multivariate analysis, the risks for HCC after DAA and IFN treatments were no different (adjusted hazard ratio [aHR], 1.12; 95% CI, 0.95-1.32). Other studies comparing DAA- and IFN-treated patients have come to similar conclusions.[8-11] (Table 1)

Large cohort studies also confirm that patients with DAA-induced SVR have a significantly lower risk for HCC compared with treatment failure or no treatment (Table 1). A study of more than 20,000 VA patients found that DAA recipients who achieved SVR had a more than 70% lower risk for HCC compared with nonresponders (aHR, 0.28; 95% CI, 0.22-0.36).[12] An Italian study of 2249 patients treated with DAAs reported a 2.6% cumulative incidence rate of HCC at 1 year among patients who achieved SVR and 8% among nonresponders, with treatment failure identified as an independent risk factor for HCC.[13] Using an administrative claims database, Singer et al.[8] demonstrated that DAA recipients have a lower risk for HCC compared with untreated controls (aHR, 0.84; 95% CI, 0.73-0.96).

Collectively, observational studies support the effectiveness of DAA therapy for primary prevention of HCC. However, achievement of SVR does not obviate the need for continued HCC surveillance in patients with cirrhosis.

TABLE 1. COHORT STUDIES EVALUATING THE ASSOCIATION BETWEEN DAA THERAPY AND *DE NOVO* HCC

First Author	Year	Study Design	Data Source	Patients	Start of Follow-up	Crude HCC Incidence Rate per 100 Person-Years (Total No. of Patients)		Adjusted HR of HCC* (95% CI)
DAA treatment with SVR versus DAA treatment without SVR						**SVR**	**No SVR**	
Kanwal[12]	2017	Retrospective cohort	VA	HCV	Antiviral completion	0.90 (19,518)	3.45 (2982)	0.28 (0.22-0.36)
Ioannou[7]	2018	Retrospective cohort	VA	HCV	180 days after antiviral initiation	0.92 (19,909)	5.19 (2039)	0.29 (0.23-0.37)
Calvaruso[13]	2018	Prospective cohort	Italian multicenter cohort	HCV cirrhosis	Antiviral initiation	2.6% at 1 year (2140)	8.0% at 1 year (109)	0.35 (0.19-0.64)†
DAA treatment versus IFN treatment						**DAA**	**IFN**	
Ioannou[7]	2018	Retrospective cohort	VA	HCV	180 days after antiviral initiation	1.32 (21,948)	0.81 (35,871)	1.12 (0.95-1.32)
Singer[8]	2018	Retrospective cohort	US administrative claims database	HCV	Antiviral initiation	1.18 (30,183)	0.98 (12,948)	0.69 (0.59-0.81)
Li[9]	2018	Retrospective cohort	VA	HCV cirrhosis	Antiviral initiation excluding HCC diagnosed during first 3 months	2.52 (1,161)	3.47 (463)	1.07 (0.55-2.08)
						DAA + SVR	**IFN + SVR**	
Innes[10]	2018	Retrospective cohort	Scottish HCV database	HCV cirrhosis	Antiviral initiation	2.53 (272)	1.26 (585)	1.15 (0.49-2.71)
Nahon[11]	2018	Prospective cohort	French multicenter cohort	HCV cirrhosis	Antiviral initiation	3.5% at 3 years (274)	3.1% at 3 years (495)	0.70 (0.28-1.74)
DAA treatment versus no treatment						**DAA**	**Untreated**	
Singer[8]	2018	Retrospective cohort	US administrative claims database	HCV	Antiviral initiation, index date in untreated	1.18 (30,183)	0.64 (137,502)	0.84 (0.73-0.96)
Li[9]	2018	Retrospective cohort	VA	HCV cirrhosis	Antiviral initiation excluding HCC diagnosed during first 3 months, index date in untreated	2.52 (1161)	4.53 (1236)	Not calculated

*DAA therapy with or without SVR relative to control group.
†Inverse of reported aHR of 2.88.

The residual incidence rate of HCC after SVR ranges from 1.4% to 1.96% per year in the aforementioned studies, which is roughly the incidence rate at which HCC surveillance is considered cost-effective. As such, we agree with current guideline recommendations that post-SVR patients with advanced fibrosis receive routine HCC surveillance.[14] In contrast, patients with no or minimal fibrosis at the start of antiviral therapy have low residual HCC incidence after SVR and do not warrant surveillance.

IMPACT OF DAAs ON HCC RECURRENCE

Meta-analyses show that IFN-based antiviral therapy after curative HCC treatment reduces the likelihood of cancer recurrence and improves survival.[15] Whether the same is true of DAAs is an area of ongoing debate due to small, single-arm studies that suggested that DAAs might precipitate HCC recurrence. The first such study included 58 patients with previously treated HCC, of whom 16 (27.8%) experienced recurrent tumor after a median follow-up of 6 months from DAA initiation.[16] A simultaneous publication reported HCC recurrence in 17/59 patients (28.8%).[6] These recurrence rates were alarmingly high compared with historic controls, and some recurrences appeared to be temporally associated with DAA exposure.

Other studies have arrived at different conclusions (Table 2). An analysis of two French cohorts reported lower recurrence rates of 7.7% and 12.7% in patients treated with DAAs followed for a median of ~20 months after antiviral initiation.[17] Moreover, there was no difference in recurrence rates between DAA-treated and untreated patients in multivariate analysis (aHR, 1.09; 95% CI, 0.55-2.16 and aHR, 0.40; 95% CI, 0.05-3.03, respectively). A single-center study of patients awaiting liver transplant compared patients treated with DAA with those who remained untreated and found no difference in HCC recurrence rates after locoregional therapy (aHR, 0.91; 95% CI, 0.58-1.42).[18] Two Japanese cohort studies and a French single-center study suggested that DAA-treated patients may in fact have lower rates of HCC recurrence than patients who do not achieve SVR or remain untreated.[19-21]

Various methodological limitations hamper the interpretation of existing studies and prevent firm conclusions from being drawn. These limitations are detailed in a recent meta-analysis.[22] (Fig. 1) First, sample sizes of studies are typically small, and many do not include control arms. Second, studies are inconsistent in excluding HCC or suspicious nodules prior to DAA treatment. Consequently, some "recurrences" may actually represent prevalent tumors that were present at the start of antiviral therapy. Third, most studies do not specify a standard surveillance protocol after curative treatment, leading to heterogeneity in ascertainment of recurrence. Fourth, studies variably include patients with non–early-stage HCC, patients with past recurrences, and patients who received non-curative locoregional therapies, all of which would be expected to increase recurrence rates. Lastly, determining when to start the clock in terms of follow-up varies. Follow-up may be calculated from the time of HCC treatment, antiviral therapy initiation, or antiviral completion, each of which produces different estimates of recurrence rates. The delay between HCC treatment and antiviral initiation also varies widely. In a meta-regression analysis, the most common factor associated with recurrence is a short interval between HCC cure and DAA initiation, suggesting that many cases of "recurrence" are in fact patients who have not achieved a durable complete response.

Given the inconclusiveness of existing evidence, some clinicians are hesitant to initiate DAA therapy in patients with previously treated HCC. Yet withholding treatment risks further liver decompensation, and the possibility remains that treatment may actually lower the risk for recurrence. Hence we propose DAA therapy be considered in patients with prior HCC provided a durable complete response has been demonstrated. It seems reasonable to wait at least 6 months after the first demonstration of complete response and to obtain two multiphase computed tomography or magnetic resonance imaging studies to document absence of HCC before initiating antivirals.

CONCLUSION

DAAs dramatically enhanced our ability to cure chronic HCV and prevent its downstream complications. Several large cohort studies demonstrate that DAA-induced SVR reduces the risk for *de novo* HCC. However, the residual risk for HCC after SVR means that surveillance is still required for patients with advanced fibrosis and cirrhosis. Additional well-designed studies are needed to determine the consequences of DAA therapy in patients with

TABLE 2. STUDIES EVALUATING THE ASSOCIATION BETWEEN DAA THERAPY AND RECURRENT HCC

First Author	Year	Data Source	HCC Treatments	Median Time From HCC Treatment to DAA Initiation (Months)	Start of Follow-up	Median Duration of Follow-up in Patients Treated with DAA (Months)	Number of Patients Treated With DAA	Number of Controls	HCC Recurrence (Proportion)	Comparison of HCC Recurrence in Patients Treated With DAA Versus Controls
Reig[16]	2016	Spanish multicenter cohort	Resection Radiofrequency ablation Chemoembolization	11.2	Antiviral initiation	5.7	58	—	27.6%	—
Conti[6]	2016	Italian regional database	Resection Radiofrequency ablation Chemoembolization Percutaneous ethanol	12.4	Antiviral completion	6	59	—	28.8%	—
Bielen[23]	2017	Belgian multicenter cohort	Liver transplant Resection Radiofrequency ablation Chemoembolization	12	Antiviral completion	—	41	—	15%	—
Cabibbo[24]	2017	Italian regional database	Resection Radiofrequency ablation Chemoembolization	11	Antiviral initiation	8.7	143	—	20.3%	—
Ogawa[25]	2018	Japanese multicenter cohort	Resection Radiofrequency ablation Chemoembolization Radioembolization	14.4	Antiviral initiation	17	152	—	17.1%	—
ANRS[17]	2016	French multicenter cohort	—	21.6*	Antiviral initiation	20.2	189	78 (untreated)	12.7%	aHR, 1.09 (95% CI, 0.55-2.16)
ANRS[17]	2016	French multicenter cohort	Resection Radiofrequency ablation	__	Antiviral initiation	21.3	13	66 (untreated)	7.7%	HR, 0.40 (95% CI, 0.05-3.03)
Ikeda[26]	2017	Japanese single center	Resection Radiofrequency ablation Chemoembolization Particle radiation therapy	10.7	Antiviral initiation	21.5	89	89 (untreated)	19.3%	aHR, 0.35 (95% CI, 0.19-0.65)
Nagata[19]	2017	Japanese multicenter cohort	Resection Radiofrequency ablation	—	HCC curative treatment	27.6	83	60 (IFN treated)	22.9% DAA + SVR	$P = 0.022$

(Continued)

TABLE 2. (CONTINUED)

First Author	Year	Data Source	HCC Treatments	Median Time From HCC Treatment to DAA Initiation (Months)	Start of Follow-up	Median Duration of Follow-up in Patients Treated with DAA (Months)	Number of Patients Treated With DAA	Number of Controls	HCC Recurrence (Proportion)	Comparison of HCC Recurrence in Patients Treated With DAA Versus Controls
									40.0% DAA – SVR (3-year incidence) 45.1% DAA 54.2% IFN (5-year incidence)	$P = 0.54$
Virlogeux[21]	2017	French single center	Resection Radiofrequency ablation Chemoembolization	7.2	Antiviral initiation	—	23	45 (untreated)	47.8%	HR, 0.24 (95% CI, 0.10-0.55)
Huang[18]	2018	US single center	Resection Radiofrequency ablation Cryotherapy Percutaneous ethanol	11.9†	Complete response	—	61	51 (untreated)	47% DAA 49.8% no DAA (1-year incidence)	aHR, 0.91 (95% CI, 0.58-1.42)
Mashiba[20]	2018	Japanese multicenter cohort	—	10.9	Antiviral completion	7.7	368	148 (IFN treated)	—	HR, 0.95 (95% CI, 0.61-1.45)‡

*From HCC diagnosis to inclusion in cohort.
†From HCC diagnosis to DAA initiation.
‡IFN versus DAA therapy, restricted to SVR patients.

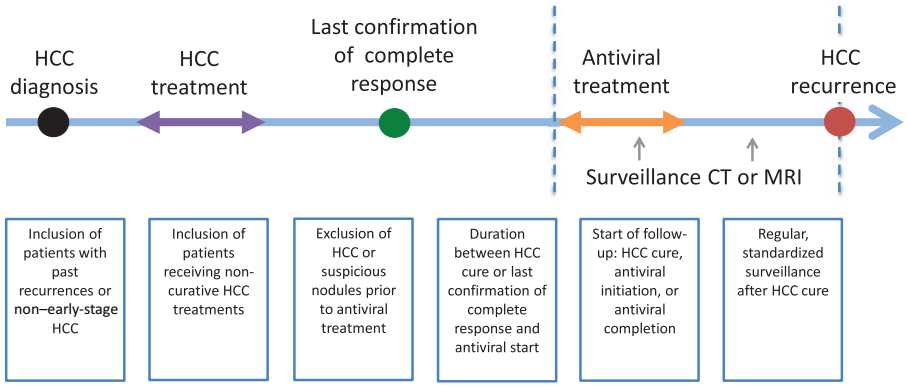

FIG 1 Sources of heterogeneity in studies examining the association between DAAs and HCC recurrence.

previously treated HCC, although the initial concern that DAAs increase recurrence risk has generally not been borne out in subsequent studies.

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REFERENCES

1) Goldberg D, Ditah IC, Saeian K, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology 2017;152:1090-1099.

2) Beste LA, Leipertz SL, Green PK, et al. Ioannou GN. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001-2013. Gastroenterology 2015;149:1471-1482.

3) Backus LI, Belperio PS, Shahoumian TA, et al. Impact of sustained virologic response with direct-acting antiviral treatment on mortality in patients with advanced liver disease. Hepatology. https://doi.org/10.1002/hep.29408

4) Morgan RL, Baack B, Smith BD, et al. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: A meta-analysis of observational studies. Ann Intern Med 2013;158:329-337.

5) Singal AK, Singh A, Jaganmohan S, et al. Antiviral therapy reduces risk of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. Clin Gastroenterol Hepatol 2010;8:192-199.

6) Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016;65:727-733.

7) Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2018;68:25-32.

8) Singer AW, Reddy KR, Telep LE, et al. Direct-acting antiviral treatment for hepatitis C virus infection and risk of incident liver cancer: A retrospective cohort study. Aliment Pharmacol Ther 2018;47:1278-1287.

9) Li DK, Ren Y, Fierer DS, et al. The short-term incidence of hepatocellular carcinoma is not increased after hepatitis C treatment with direct-acting antivirals: An ERCHIVES study. Hepatology 2018;67:2244-2253.

10) Innes H, Barclay ST, Hayes PC, et al. The risk of hepatocellular carcinoma in cirrhotic patients with hepatitis C and sustained viral response: Role of the treatment regimen. J Hepatol 2018;68:646-654.

11) Nahon P, Layese R, Bourcier V, et al. Incidence of hepatocellular carcinoma after direct antiviral therapy for HCV in patients with cirrhosis included in surveillance programs. Gastroenterology 2018;155:1436-1450.

12) Kanwal F, Kramer J, Asch SM, et al. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 2017;153:996-1005.

13) Calvaruso V, Cabibbo G, Cacciola I, et al. Incidence of hepatocellular carcinoma in patients with HCV-associated cirrhosis treated with direct-acting antiviral agents. Gastroenterology 2018;155:411-421.

14) American Association for the Study of Liver Diseases and Infectious Diseases Society of America. Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Accessed October 1, 2018.

15) Singal AK, Freeman DH, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. Aliment Pharmacol Ther 2010;32:851-858.

16) Reig M, Mariño Z, Perelló C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016;65:719-726.

17) ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of

hepatocellular carcinoma: Data from three ANRS cohorts. J Hepatol 2016;65:734-740.

18) Huang AC, Mehta N, Dodge JL, et al. Direct-acting antivirals do not increase the risk of hepatocellular carcinoma recurrence after local-regional therapy or liver transplant waitlist dropout. Hepatology 2018;68:449-461.

19) Nagata H, Nakagawa M, Asahina Y, et al. Effect of interferon-based and -free therapy on early occurrence and recurrence of hepatocellular carcinoma in chronic hepatitis C. J Hepatol 2017;67:933-939.

20) Mashiba T, Joko K, Kurosaki M, et al. Does interferon-free direct-acting antiviral therapy for hepatitis C after curative treatment for hepatocellular carcinoma lead to unexpected recurrences of HCC? A multicenter study by the Japanese Red Cross Hospital Liver Study Group. PLoS One 2018;13:e0194704.

21) Virlogeux V, Pradat P, Hartig-Lavie K, et al. Direct-acting antiviral therapy decreases hepatocellular carcinoma recurrence rate in cirrhotic patients with chronic hepatitis C. Liver Int 2017;37:1122-1127.

22) Saraiya N, Yopp AC, Rich NE, et al. Systematic review with meta-analysis: recurrence of hepatocellular carcinoma following direct-acting antiviral therapy. Aliment Pharmacol Ther 2018;48:127-137.

23) Bielen R, Moreno C, Van Vlierberghe H, et al. The risk of early occurrence and recurrence of hepatocellular carcinoma in hepatitis C-infected patients treated with direct-acting antivirals with and without pegylated interferon: A Belgian experience. J Viral Hepat 2017;24:976-981.

24) Cabibbo G, Petta S, Calvaruso V, et al. Is early recurrence of hepatocellular carcinoma in HCV cirrhotic patients affected by treatment with direct-acting antivirals? A prospective multicentre study. Aliment Pharmacol Ther 2017;46:688-695.

25) Ogawa E, Furusyo N, Nomura H, et al. Short-term risk of hepatocellular carcinoma after hepatitis C virus eradication following direct-acting anti-viral treatment. Aliment Pharmacol Ther 2018;47:104-113.

26) Ikeda K, Kawamura Y, Kobayashi M, et al. Direct-acting antivirals decreased tumor recurrence after initial treatment of hepatitis c virus-related hepatocellular carcinoma. Dig Dis Sci 2017;62:2932-2942.