

Liver Cancer Emergence Associated with Antiviral Treatment: An Immune Surveillance Failure?

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Abstract

The availability of new direct antiviral agents to safely and effectively treat the hepatitis C virus represents a major advancement in the field of liver disease. Most patients achieve complete viral eradication sustained over time. In addition, the administration of these new agents is safe and does not require limitations when liver function is impaired. Some now expect the hepatitis C virus to be completely eradicated in a few years. However, not all data are positive. In April 2016, we published a cohort study suggesting that viral eradication with the new agents could be associated in time with the emergence of recurrent cancer sites in patients previously treated for hepatocellular carcinoma. In this review, we update our report and summarize the data provided in recent publications. We also speculate about the mechanisms for cancer emergence and stress the need for further studies.

Keywords

- ▶ hepatitis C
- ▶ hepatocellular carcinoma
- ▶ direct antiviral agents
- ▶ incidence
- ▶ recurrence

The management of patients with hepatitis C virus (HCV) was revolutionized by interferon- (IFN-) free treatments with direct antiviral agents (DAAs) due to their efficacy in terms of sustained virological response and also their excellent safety profile during treatment.¹ This major advancement has been associated with an increase in the number of patients treated, some with more advanced liver dysfunction than patients treated with IFN-based regimens. Special populations such as patients with hepatocellular carcinoma (HCC) either successfully treated or still active, which may not have been included in the major studies assessing the antiviral effectiveness of DAAs^{2–13} (▶ **Table 1**), have since been treated with the new agents. The assumption was that HCV eradication would translate into a reduced incidence of de novo tumors in HCV patients and that the recurrence of HCC after initial success would also be reduced through HCV cure.¹⁴ This positive expectation was very appealing both for patients—who had been awaiting an effective and safe treatment option—and for physicians, who had seen their HCV

patients transition from chronic hepatitis to cirrhosis and ultimately to end-stage liver failure and/or cancer. The success of the new agents has been so striking that the current treatment guidelines of the European Association for the Study of the Liver (EASL)¹ recommend treating almost all HCV patients, including those with concomitant or prior HCC or any other cancer, with these new agents. This recommendation contrasts with the current controversy about a potential association between antiviral treatment and the emergence of HCC either de novo or as a recurrence: A higher incidence and more aggressive profile have been registered in some studies. In our April 2016¹⁵ report we described an increased incidence of HCC recurrence associated in time with antiviral treatment in patients who had been successfully treated for HCC and who had been free of disease for varied periods.

In this review, we summarize and update our data while simultaneously reviewing the results that have been reported by other groups reinforcing or denying the association

Table 1 Inclusion–exclusion criteria related to HCC and description of US screening evaluation in the pivotal studies showing the benefit of DAAs

Study	Clinical trial number	HCC inclusion criteria	HCC exclusion criteria	US screening of HCC
Poordad et al, 2013 ²	NCT01306617	–	–	No
Ferenci et al, 2014 ³	NCT01767116 NCT01833533	–	–	No
Feld et al, 2014 ⁴	NCT01716585	–	–	No
Kwo et al, 2014 ⁵	NCT01782495	HCC within MC before LT or without HCC post-LT for at least 1 y Out of MC on the explanted liver, but without recurrence for at least 2 y posttransplant.	–	No
Foster et al, 2015 ⁶	NCT02201953	–	Yes	No
Curry et al, 2015 ⁷	NCT02201901	–	Yes	No
Feld et al, 2015 ⁸	NCT02201940	–	Yes	No
Sulkowski et al, 2014 ⁹	NCT01359644	–	–	No
Poordad et al, 2014 ¹⁰	NCT01704755	–	Yes (within 3 mo) or AFP >100 ng/dL	US at screening/EOT ^a
Afdhal et al, 2014 ¹¹	NCT01768286	Liver imaging within 6 mo of baseline/day 1 to exclude HCC in patients with cirrhosis	Yes	No
Jacobson et al, 2013 ¹²	NCT01542788	–	Yes (within 3 mo)	US at screening/EOT/ premature DC
Lawitz et al, 2013 ¹³	NCT01497366 NCT01641640	Liver imaging within 6 mo of baseline/day 1 to exclude HCC in patients with cirrhosis	–	US at screening/EOT ^a

Abbreviations: AFP, alpha-fetoprotein; DC, DAA discontinuation; DDA, direct-acting antiviral agents; EOT, end of treatment; HCC, hepatocellular carcinoma; LT, liver transplantation; MC, Milan Criteria; US, ultrasound.

^aSubjects with a historical negative liver ultrasound, CT or MRI (within 3 months prior to screening) are not required to have a screening ultrasound performed.

between HCC emergence and DAA therapy. We also speculate about the mechanisms for such an event and raise the need for major clinical and laboratory research efforts.

The Cohort Study that Raised the Signal

The main clinical and tumor characteristics of the patients described in our 2016 report¹⁵ are provided in ► **Table 2**. The retrospective cohort included 124 patients from four Spanish hospitals; 105 presented HCC under complete response before starting DAAs. After excluding patients with potential confounding factors, we retained 77 of the cohort. Mean age was 66 years and 69% were male. The baseline Barcelona Liver Cancer Clinic (BCLC) stage at HCC treatment was BCLC-0/A ($n = 75$) and BCLC-B ($n = 2$), 89% received resection/ablation. Up to 94.7% achieved sustained virological response. After a median follow-up of 8.2 months since the start of DAA therapy, the rate of recurrence was 27.3% (21/77).

► **Fig. 1** illustrates the relevant time points of the cohort from HCC treatment (with achievement of complete response without any suspicion of additional tumor sites at imaging) to antiviral treatment initiation and the time to recurrence or last follow-up. The initial data raised the pharmacovigilance alarm; hence, we have now incorporated data on additional recurrences.

In addition to the recruitment of additional patients, we have also been able to characterize the evolution of the recurrences and their response to therapy. In ► **Table 2**, the tumor stage at first treatment, stage at recurrence, and the treatment applied and its success are given. As shown, although most recurrences were apparently able to be effectively treated, the evolution has been dismal in most instances. Six of the 19 patients who received HCC treatment at recurrence presented progression within the next 6 months; a large proportion transitioned into end stage. As a result, only 8 of 21 (38%) patients could effectively

Table 2 Characterization of the evolution of the recurrences and their response to HCC therapy in the 21 patients with recurrence in September 2016

Before DAA	HCC evolution post-DAA				
BCLC stage at first HCC treatment	BCLC stage at HCC recurrence post-DAA	Recurrence treatment	Time from recurrence to progression (months)	BCLC at HCC progression	Progression treatment
A	A	LT			
0	A	Percutaneous	6.6	B	TACE
A	A	Percutaneous			
A	A	Resection			
0	A	Resection	2.7	C	Sorafenib
0	C	Sorafenib			
A	A	Percutaneous	5.7	C	Sorafenib
A	A	TACE			
A	A	Percutaneous	6.6	A	LT
A	A	Percutaneous			
A	C	Sorafenib			
A	B	RE			
B	B	TACE	1	C	Sorafenib
A	A	Percutaneous			
A	C	Sorafenib	6.8	C2 ^a	Regorafenib
A	A	LT			
A	D	BSC			
A	A	LT			
0	D	BSC			
B	C	Sorafenib			
A	D	BSC			

Abbreviations: BCLC, Barcelona Liver Cancer Clinic staging; BSC, best supportive care; DAA, direct antiviral agents; HCC, hepatocellular carcinoma; LT, liver transplantation; percutaneous, percutaneous treatment; TACE, transarterial chemoembolization.

Note: Boldface values mean that only two patients were BCLC-B before starting DAA and patients with fastest and unexpected HCC evolution after starting DAA.

^aBCLC up on progression classification.⁴²

benefit from resection/ablation/liver transplantation, whereas almost half (10/21, 47.6%) received systemic/locoregional treatment and 3 of 21 (14%) patients received best supportive care.

Follow-up of the cohort further confirmed our initial data; furthermore, we found a recurrence pattern that is more aggressive than what is observed in conventional clinical practice and in clinical trials. Even if a direct comparison is not possible between the studies, the pattern of recurrence in the placebo arm of the STORM (Adjuvant Sorafenib for Hepatocellular Carcinoma after Resection or Ablation) trial¹⁶ (12% of patients developed extrahepatic recurrence at the end of follow-up) or the one-year HCC-stage-transition estimation from early to advanced stage according to the Ikeda–Markov model¹⁷ (1.7% of patients in the whole population and 1.35% in the group of patients with a similar age as our cohort) seems less aggressive than what we observed in our cohort.

The Emerging Data: Confirming or Refuting

The publication of our cohort coincided with the presentation of data from Buonfiglioli¹⁸ et al as a poster at the 2016 annual meeting of EASL. There they also reported an unexpected high recurrence rate in patients with successfully treated HCC. The rate of early HCC recurrence was similar to ours (28.8%), and both datasets primed the publication of the experiences of several groups around the world. Data about HCC appearance affect two different dimensions: the development of HCC after DAA treatment in patients without a prior history of HCC, and the development of tumor recurrence in patients with a prior history of HCC.¹⁹ As shown in ►Table 3, some of the information is reported in Letters,^{22–25,31–34} and in some instances the data are the results of post hoc analyses of studies in which HCC was not among the initial endpoints.^{26,30} Finally, in other reports, HCC development was an endpoint, but there was no formal

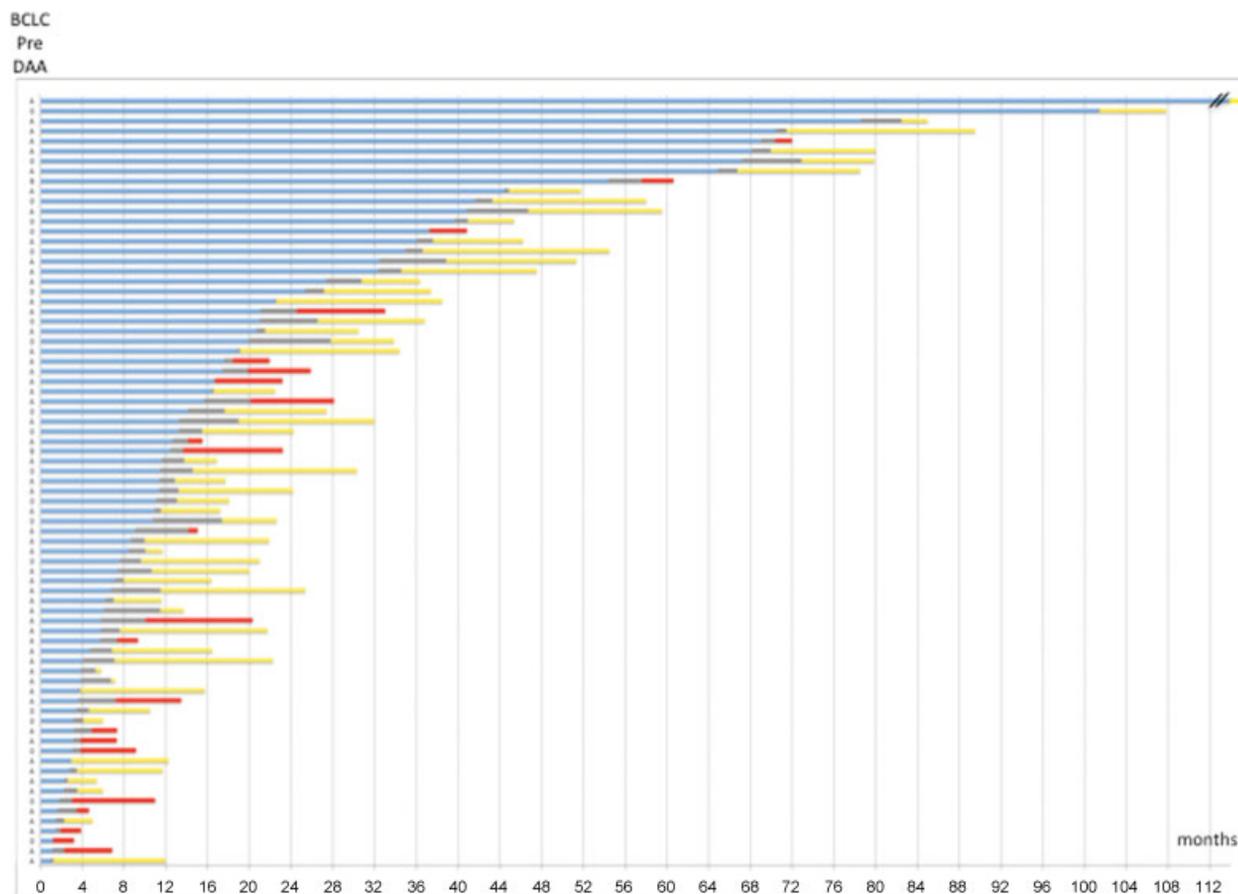


Fig. 1 Time points for radiology evaluation of tumor status. The evolution of each patient is described in three time periods: Blue boxes reflect the time between hepatocellular carcinoma (HCC) treatment and the last assessment of complete response (CR) by imaging. It shows the interval between HCC treatment and the date of the last radiologic evaluation (which confirmed the CR in each patient) prior to direct antiviral agent (DAA) therapy. Gray boxes represent the second time period—time window between last CR assessment and DAA initiation—reflecting the time between the date of the last radiologic confirmation of CR, and the start date of DAA. The last time period depicts HCC evolution after starting DAA, which depends on the outcome of the patients. Red boxes indicate the time between the date of the first dose of DAAs and the date of radiologic tumor progression. Yellow boxes denote the last radiologic evaluation during follow-up in patients without radiologic tumor progression.

adherence to the proper screening strategy every 6 months or the follow-up time may have been too short to reach robust conclusions about incidence.^{20,21}

Recurrence of HCC after DAA Treatment

As commented before, the majority of these publications are Letters without enough data to confirm or refute the alarm. However, the time association between DAA initiation and HCC recurrence was reported in many. As shown in ► **Table 3**, the Letters/articles include less patients than in the Spanish¹⁵ and Italian cohorts¹⁹ and/or do not report essential information such as a schedule of the HCC evaluation, the median follow-up time, and/or if HCC was evaluated regularly in their cohort.

An important dataset is available in the French cohort studies of HCV patients under the ANRS (French Agency of Research on AIDS) acronym.²⁶ Three cohorts of patients accounting for more than 500 cases have challenged the alarm signal and suggested that the risk did not exist.

Although the sample size is relevant, there are several issues that need clarification. Hepatocellular carcinoma was not an endpoint in two of the cohorts (ANRS CO22 HEPATHER-NCT01953458-³⁶ and ANRS CO23 CUPILT cohort-NCT01944527-). Thus, if the evaluation of HCC was not part of the prospective collection data at well-defined regular time intervals, underregistration is feasible and the study cannot properly inform about the rate of radiologic recurrence. Hepatocellular carcinoma was an endpoint in the ANRS CO12 CirVir,^{28,37,38} but at the time of the first report they had only 13 patients treated with DAA therapy.²⁶ A later update of the CIR-VIR study will be commented in the part devoted to patients without prior HCC.^{28,38}

Interestingly, the HCC recurrence in two of the cohorts was reported as HCC recurrence/person-months²⁶ to avoid the bias related to the analysis of evolutionary events in a cohort with widely different follow-up times. The time-dependent estimated hazard ratio in the ANRS CO22 HEPATHER cohort was 1.21 (95% confidence interval [CI], 0.62–2.34, $p = 0.5782$), and 0.41 (95% CI, 0.05–3.08, $p = 0.386$), in

Table 3 Publications of HCC incidence or recurrence after IFN-free based treatments (DAA) HCV treatment

Authors, Year	Journal	Type of publication	Type of study	n	Cirrhosis % whole cohort	Child-Pugh	%	HCV treatment	Period of analysis		Follow-up (median)	HCC (%)		Time association (median)	
									First time point	Last F-up/Death/LT		Incidence	Recurrence	DAA- HCC de novo	DAA- recurrence
Interferon-free (DAA)															
Reig, Marinho et al., 2016	Journal of Hepatology ¹⁵	Original	Retrospective	58 ^a	94.8	CPA	91	DAA	Start date of DAA	Last F-up/Death/LT	5.7 mo	NA	27.6	NA	3.5 mo
							5.4								
							3.6								
Conti et al., 2016	Journal of Hepatology ¹⁹	Original	Retrospective	344 (59 of them with HCC history)	100	CPA	88.7	DAA	Start date of DAA	Last F-up/Death/LT	6 mo	3.16	28.8	NR	
							11.3								
Cheung et al., 2016	Journal of Hepatology ²⁰	Original	Prospective	406	100	CPA	17.2	DAA	End of DAA	Mo-15 after starting DAA	15 mo	4.2% at 6 mo	NA	287 d	
							72.7								
							10.1								
Foster et al., 2016	Journal of Hepatology ²¹	Original	Retrospective	261	NR	CPA	NR	DAA	Start date of DAA	Mo-6 after starting DAA	6 mo	5.4% at 6 mo	NA	NR	
							68.3								
							9.2								
Zeng et al., 2016	Journal of Hepatology ²²	Letter	NA	31	100	NR	NR	DAA	Start date of DAA	NR	15 mo	0%	NA	NR	
Zavaglia et al., 2016	Journal of Hepatology ²³	Letter	NA	31	100	CPA	81	DAA	Start date of DAA	Last F-up	8	NA	3.2	19.3 mo	
							19								
Tsai et al., 2016	Journal of Hepatology ²⁴	Letter	NA	NR											
Kozbial et al., 2016	Journal of Hepatology ²⁵	Letter	NA	22	NR ^b	NR	NA	DAA	NR	NR	NR	6.6%	NR		
Interferon based-treatments or interferon-free based treatments (DAA)															
ANRS cohorts et al., 2016	Journal of Hepatology ²⁶	Original	Prospective/Retrospective ^c	HEPATHER (n = 267); DAA = 189 ^c	77.5	NR	NA	DAA +/- DAA	NR	Last F-up	DAA +/- 20.2 mo DAA -26.1 mo	NA	HR 1.21 (95% CI 0.62-2.34), p = 0.5782)	NA	NR
Sugimoto et al., 2015	Oncology ²⁷	Original	NR	DAA n = 17	38.8	NR	NA	DAA +/- DAA	LT	Last F-up	NR	NR	2.2% ^d	7 ± 3 mo	
Sugimoto et al., 2015	Oncology ²⁷	Original	NR	Peg-IFN-RBV/Telaprevir n = 25	NR	NR	NA	DAA	NA (Mixed HCC incidence and recurrence)	NR	NR	NR	NR	NR	
Sugimoto et al., 2015	Oncology ²⁷	Original	NR	Peg-IFN-RBV/Simeprevir n = 15	NR	NR	NA	DAA	NA (Mixed HCC incidence and recurrence)	NR	NR	NR	NR	NR	

(Continued)

Table 3 (Continued)

Authors, Year	Journal	Type of publication	Type of study	n	Cirrhosis % whole cohort	Child-Pugh	%	HCV treatment	Period of analysis		Follow-up (median)	HCC (%)		Time association (median)		
									First time point	Last F-up/Death/LT		Incidence	Recurrence	DAA-HCC de novo	DAA-recurrence	
Ganne-Carrie et al, 2016	Hepatology ²⁸	Original	Prospective	720 (Training cohort)	100	CPA	100	IFN	Start HCC screening	Last F-up/Death/LT	49 mo	0-20.3% at 5 y	NA	NR	NA	
				360 (Validation cohort)	NA	DAA (few patients)			54.4 mo							
Kobayashi et al, 2016	Journal of Medical Virology ²⁹	Original	Retrospective	77 (DAA)	NR	NA		DAA	SVR	NR	4 y ^e	2.6%	NA	NR	NA	
				528 (IFN)				IFN		7.3 y ^e	2.3%					
Petta et al, 2016	Alimentary Pharmacology and Therapeutics ³⁰	Post hoc analysis of information from other publications	Retrospective	58	100	CPA	91	DAA	HCC treatment	Last F-up	18 mo	NA	27.6%	NA	NR	
						CPB	5									
						CPC	4									
				57	100	CPA	90	IFN					34 mo		38.6%	NR
						CPB	10									
						CPC	(-)									
Torres et al, 2016	Journal of Hepatology ³¹	Letter	NA	8	87.5	CPA	42.9	DAA	DAA use	NR	12 mo	NA	0	NA		
Yang et al, 2016	Journal of Hepatology ³²	Letter	NA	63 (no-DAA)	NR	NR	NR	No-DAA	LT	NR	NR	NR	9.6	NA	NR	
				18 (DAA)				DAA		NT				4/5 patients within 6 mo of LT	27.8	
Toyoda et al, 2016	Journal of Medical Virology ³³	Letter	NA	413 (DAA)	NR	NR	NR	DAA	NR	NR	NR	0.62-0.85% ^f	NA	NR	NA	
				578 (IFN)				IFN						0.28-0.035% ^f		
Minami et al, 2016	Journal of Hepatology ³⁴	Letter	NA	27	100	CPA	100	DAA	NR	Last F-up	1.3 y	NA	29.6%	NA	5.8 mo	
				38	100	CPA	100	IFN				NR		68.4%	5.4 mo	
				861	100	CPA	74	No HCV treatment							64.2%	NR

Abbreviations: CI, confidence interval; CPA, Child-Pugh A score; CPB, Child-Pugh B score; CPC, Child-Pugh C score; DAA, direct-antiviral agents; F-up, follow-up; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; LT, liver transplantation; NA, not applicable; NR, not reported; Peg, pegylated; RBV, Ribavirin; SVR, sustained virological response.

^aThis cohort was updated by the International Liver Cancer Association in 2016: 77 patients; median follow-up 8.2 mo; 27.3% of HCC recurrence; 14.3% evolved to terminal HCC. 47.6% transarterial chemoembolization, radioembolization, or regorafenib treatment after the recurrence and regorafenib and 38.1% had the option of receiving resection, percutaneous treatment, or liver transplantation after HCC recurrence.

^bThe CP score was reported only in patients who developed HCC on or after treatment with DAA combinations, n = 19 (CPA n = 11, CPB n = 4, CPC n = 1).

^cThe HCC development data were not a primary end-point. These data were retrospectively analyzed.

^dA recurrence of HCC was observed in seven patients (2.2%; mean age 58.0 ± 8.4 y) within mean time after LT of 70 ± 64 mo, 7 ± 3 mo, 21 ± 14 wk following the introduction of DAAs and after obtaining viral clearance, respectively. Five of the seven patients (71%) died 58 ± 47 mo after LT.

^eThe median observation period was shorter for the DAA group (4.0 y) compared with the PEG-IFN/RBV group (7.3 y, p < 0.001).

^fAnnual incidence.

the ANRS CO12 CirVir cohort. Bearing in mind the risk of underregistration, the small number of patients who received DAAs, and the 2.34 and 3.08 upper 95% CI, these data are not robust enough to rule out an increased recurrence risk.

The Craxi group³⁵ in Italy raised a major criticism of the initial data. They extracted data from our study¹⁵ and used the time of HCC therapy as Time 0 to estimate the incidence of recurrence. This approach is flawed as is their use of a meta-analysis³⁹ assessment for any valid comparison. It neglects the evolution of those who died/recurred prior to the availability of DAAs and/or did not receive DAAs for any reason.

Comparing the recurrence rate by using the time from HCC treatment and the last time on complete response reflects a post hoc and data-driven strategy based on the observed data that is known to imply a high risk of bias as the analysis includes both the factor used for the comparison and the selection of the cutoff point.

Development of HCC in Patients without Prior HCC

The development of HCC was not evaluated in the initial studies that led to registration (►Table 1).^{2–13} Follow-up within the trials was usually 6 to 12 months, and registration of HCC during follow-up was not an endpoint. Thus, HCC surveillance was not part of the mandatory trial assessments. Hence, the current data about HCC incidence after DAA therapy come from cohort studies done after the commercialization of DAA treatment.^{20,21,40} In patients without cirrhosis, the risk of HCC is known to be low; thus, attention has to be given to the information about patients with cirrhosis. One important aspect when assessing the incidence of de novo HCC in patients treated with DAAs is to recall that the profiles of the patients who are treated with these agents are far more advanced than those treated with prior IFN-free regimens. Although most patients with portal hypertension would be excluded from prior options, the safety of DAAs allows their use in patients with portal hypertension and liver decompensation. Because the incidence of HCC is known to increase along the evolution of cirrhosis, any assessment not taking into account this concept would be misleading. The degree of portal hypertension measured as hepatic vein pressure gradient or elastography also stratifies HCC risk within compensated cirrhosis. In addition to this liver-function-related predictor, conventional clinical parameters such as male gender, age > 60 years old, alcohol intake, diabetes, and baseline alpha-fetoprotein serve to identify the population at higher risk. An important prospective cohort has been crafted in France under the name *CIR-VIR* (“Cirrhose Virale”).^{28,37,38} It has served to establish the benefits of screening intervals and HCC incidence along time, as well as to refine the HCC risk according to conventional and novel parameters. In a recent study, they have proposed an HCC risk stratification using simple clinical parameters, which should serve as a benchmark to compare data

arising in studies assessing the HCC incidence after DAA therapy.²⁸

The Italian multicenter cohort from Veneto presented the incidence of HCC in HCV patients treated with DAA therapy in the last *American Association for the Study of Liver Diseases* meeting.⁴¹ As described there, they ruled out the presence of HCC by ultrasound before starting DAAs and then performed ultrasound screening every 6 months in all patients. They analyzed 3,075 patients, who were followed for 300.8 days (mean) from the start day of DAA treatment. The majority presented compensated cirrhosis or F3 (only 7% Child-Pugh B) when starting DAA treatment. With half of the patients having less than 300 days of follow-up, they reported a 1.64% person/year incidence (95% CI, 1.18–2.21). The authors concluded that the results were no different from that to be expected in untreated patients, but the expansion of the follow-up may further increase this figure.

The French CIR-VIR cohort^{28,37,38} will be instrumental in providing relevant information about incidence rate, time association, HCC pattern at diagnosis in compensated HCV, and the impact of DAAs in liver cancer development. This is a prospective cohort study that follows up patients with cirrhosis who undergo regular screening according to guidelines. It has raised a proposal to stratify patients according to different magnitudes of risk based on easily available clinical parameters (age > 50 years, past excessive alcohol consumption, platelet count, gamma-glutamyl transferase, and nonsustained virological response during the study period). The group at higher risk is expected to have a one-year incidence of 3.15%. Abstracts presented by the ANRS/Association Française des Enseignants de Français (AFEF) Study Group at the 2016 EASL annual meeting⁴² have reported an incidence of 18/1,000 person/y during the first 6 months after DAA therapy; this is reduced by half after 12 months. With such a description, it is key to ascertain to what extent DAA therapy is associated with a peak in incidence in the following 12 months, or if the incidence has become very high at the time of DAA and the values after 12 months represent a real reduction. Because the cohort may have data about the tumor stage at detection over the last few years, the study will also inform about the potential aggressive profile of the DAA-associated cancers.

Interestingly, the Veneto cohort, which includes 27.7% noncirrhotic patients, describes a more aggressive HCC pattern at diagnosis after DAA treatment. A single nodule was registered in 48.8% and an infiltrative/more than three nodules in 39% (a quarter of these presenting vascular invasion or extrahepatic spread), while in the CIR-VIR cohort with 100% cirrhotics the pattern was a single nodule in 69.6%, up to two to three nodules in 19.8%, and an infiltrative/more than three nodules in 10.8%. This more aggressive profile coincides with our finding about HCC recurrence.

If the tumors are more aggressive, this should be due to faster tumor growth leading to a more advanced stage earlier in time. Hence, clinical and radiologic recognition should occur earlier than expected, more cases would be detected

during the follow-up period, and this would translate in increased incidence. It could be argued that in some centers the screening expertise was not optimal and detection was done late. If this were the case, the suboptimal expertise would impair the HCC detection and its incidence would be underestimated.

A striking finding in several reports is the clearcut time association between DAA treatment and HCC emergence.¹⁵ This time association is key in pharmacovigilance programs, and it should be carefully assessed in all studies.

Studies of other cohorts of HCV cirrhotic patients treated with DAAs have been published. As mentioned earlier, the endpoint of these studies was not HCC development or the methods in place did not secure HCC screening and diagnosis following an established protocol that adhered to current practice guidelines. In addition, some studies of the same cohort such as the UK one have presented data using different follow-up periods.^{20,21} Foster et al²¹ and Cheung et al²⁰ evaluated the same cohort of patients, but the initial time point in Foster et al²¹ was the day of DAA initiation, whereas in Cheung et al²⁰ it was at the end of DAA treatment. This explains the discrepancy in their 6-month incidence (5.4% and 4.2%, respectively) and exposes the importance of the time-point definition when comparing different studies. Furthermore, Cheung et al²⁰ compared DAA-treated patients with a cohort of untreated patients in which the information about baseline liver function was not reported. An Italian study in decompensated cirrhotics treated or not treated with IFN-based regimes describes a 3% incidence at 6 months.⁴³ Even if a direct comparison between these cohorts is not robust, it reinforces a concern.

Additional results from separate studies and information from follow-up investigations in industry trials as well as population registries will provide the necessary information to fully elucidate this controversial issue.

The need to collect more data triggered the November 2016 Press Release from the European Medicines Agency.⁴⁴ The Press Release outlines the Agency's need for more information from different sources to properly define the potential risk of cancer associated with the treatment of HCV using the new DAA agents. Interestingly, the acceptance of a potential risk of hepatitis B virus (HBV) reactivation associated with DAA therapy even in patients with positive core antibody only (in whom the risk is very low) and the instruction to carefully monitor HBV reactivation during treatment was based on less data as compared with HCC emergence and has not been as controversial.

The Immune Connection

The immune system has the intrinsic ability to recognize tumor cell antigens and control cancer growth.⁴⁵ Immune cells are continuously struggling with tumor cells, resulting in the establishment of a dynamic equilibrium in which tumor dormancy may be achieved.⁴⁶ The presence of T cells within tumors is associated with a better prognosis, confirming the role of the immune response in maintaining subclinical tumor in the equilibrium state.⁴⁷ Indeed, a fall of

antigenic load (as may happen upon HCV eradication) promotes a hyporesponsive state of memory-helper T cells.⁴⁸ The reports about HBV⁴⁹ and herpes virus reactivation⁵⁰ associated with DAA treatment strongly suggest a breakdown of immune surveillance as the main mechanism that might be involved in cancer emergence. Tumor immune-related dormancy has been shown in metastasized tumor cells from early primary tumors,⁵¹ and immune surveillance controlling tumor dormancy uses effector immune pathways similar to those active during tumor destruction. All these data suggest that immunological changes related with the acute HCV clearance have a role in the emergence of cancer events.

Furthermore, tissue-associated macrophages are a major field of research as they are shown to influence tumor evolution and could become a target for therapeutic infiltration. Sorafenib has a marked effect on macrophages and it has been suggested that the benefits in survival may be in part mediated by immunomodulation.⁵² Finally, major hope has been placed in immunotherapy and following its success in other tumors, active research is now underway in HCC.

Altogether, it is clear that immune phenomena might be involved in the evolution of HCC. If we accept that immune surveillance is affected by the successful eradication of HCV replication, it could be that the same phenomena should have been registered with prior treatments based on IFN. However, this is not the case as all registries indicate that viral eradication under IFN-based regimes translates into a reduction of HCC incidence. The reason for such a difference is probably related to the kinetics of viral eradication that is faster under DAAs. Thus, it is appealing to hypothesize that the abrupt resolution of infection within days or weeks affects immune cell populations, which will no longer guarantee tumor cell destruction and consequently allow the wake-up of dormant cancer clones. In addition, IFN might also play a role in controlling tumor growth due to its antiproliferative action and activation of innate immune responses.

Tumor dormancy results from several conditions: immune surveillance controlling tumor outgrowth, hostile tumor microenvironment, or tumor cells being quiescent.

If immune cancer surveillance is distorted, a major concern about extrahepatic cancer development would become apparent. Chronic inflammation such as long-lasting HCV infection increases the risk of extrahepatic cancer and transformed cells may stay subclinical or even remain indolent for a long period. However, information about this issue is very limited³⁸; we should await more results based on large datasets.

In summary, several sets of data suggest there is an increased cancer risk in HCV patients successfully treated with the new DAAs. Although this may be seen as counterintuitive and not aligned with the expectations of patients and physicians, we need major epidemiological and clinical research that avoids the previous research flaws that may have affected some of the prior investigations. This will allow us to accurately define the risk and identify the patient profile that may be associated with this dismal event.

Abbreviations

ANRS	French Agency of Research on AIDS
BCLC	Barcelona Liver Cancer Clinic
CirVir	Cirrhose Virale
DAAs	direct antiviral agents
EASL	European Association for the Study of the Liver
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
IFN	interferon.

Conflicts of Interest

María Reig has received support from Bayer, BTG, and Gilead, attended conferences sponsored by Bayer, and is an advisor for Bayer. Zoe Mariño has received speaker fees from Abbvie, Gilead, Janssen. Xavier Fornas has received unrestricted grant support from Abbvie and Gilead and is an advisor for Abbvie, Gilead, and Janssen. Jordi Bruix is a consultant for Gilead, Abbvie, Kowa, Bayer, BTG, Arqule, Terumo, BMS, Boehringer Ingelheim, Kowa, Novartis, OSI, Roche, and Onxeo.

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