Risks: HCV Clearance by DAA

Subjects: Oncology

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Direct-acting antivirals (DAAs) induce a rapid virologic response (SVR) in up to 99% of chronic hepatitis C patients. The role of SVR by DAAs on the incidence or recurrence of hepatocellular carcinoma (HCC) is still a matter of debate, although it is known that SVR does not eliminate the risk of HCC. In this review, we made an updated analysis of the literature data on the impact of SVR by DAAs on the risk of HCC as well as an assessment of risk factors and the role of epigenetics. Data showed that SVR has no impact on the occurrence of HCC in the short–medium term but reduces the risk of HCC in the medium–long term. A direct role of DAAs in the development of HCC has not been demonstrated, while the hypothesis of a reduction in immune surveillance in response to the rapid clearance of HCV and changes in the cytokine pattern influencing early carcinogenesis remains to be further elucidated. HCV induces epigenetic alterations such as modifications of the histone tail and DNA methylation, which are risk factors for HCC, and such changes are maintained after HCV clearance. Future epigenetic studies could lead to identify useful biomarkers and therapeutic targets. Cirrhosis has been identified as a risk factor for HCC, particularly if associated with high liver stiffness and α-fetoprotein values, diabetes and the male sex. Currently, considering the high number and health cost to follow subjects' post-HCV clearance by DAAs, it is mandatory to identify those at high risk of HCC to optimize management.

Keywords: hepatocellular carcinoma ; direct acting antivirals ; HCV ; cytokines ; sustained virological response ; epigenetic modulation

1. Introduction

Treatment based on direct-acting antivirals (DAAs) has radically changed the natural history of chronic hepatitis C virus (HCV) infection [1]. In fact, while the previous therapeutic regimens based on the use of Interferon (IFN) were characterized by a sustained virological response (SVR) of 40%–50%, DAAs allow an SVR almost in 100% of patients [2][3][4]. The result is of utmost clinical importance as HCV clearance is expected to prevent most of the serious complications due to progression of chronic hepatic C, as well as to the associated immune system dysregulation and chronic systemic inflammatory response [5][6][7][8][9][10][11]. However, DAAs are likely to affect the immune response, but the underlying biological mechanisms remain largely unexplored [12][13].

Hepatocellular carcinoma (HCC) is an important complication of HCV-related cirrhosis and it is reported with an average incidence of 1–4% per year [14]. The appearance of HCC is mainly related to two conditions: the first one is cirrhosis per se, with its necro-inflammatory activity, and the second one is the failure of immune surveillance with escape mechanisms [15][16][17][18].

In addition, HCV proteins exert a direct carcinogenic effect by deregulating the host cell cycle checkpoints and increasing the immune-mediated oxidative stress, which in turn leads to an increased DNA mutations frequency in the liver cells [19]. Thus, HCV clearance by DAAs and the consequent reduction in the hepatic necro-inflammation activity should reduce the risk of developing HCC.

Several long-term studies in HCV patients treated with IFN-based regimens have documented a reduction in the incidence of HCC by 75% in patients with SVR and a residual risk of the development of HCC mainly associated with some comorbidities such as metabolic syndrome and diabetes mellitus [20][21][22][23].

Some data obtained in HCV patients treated with DAAs have reported an unexpected increase in the incidence of early HCC in these patients [24][25], while other studies have not systematically confirmed these data. The controversial data have sparked heated debate about the risk of developing HCC after HCV clearance by DAAs and the potential involvement of DAA in liver carcinogenesis [26][27][28].

The purpose of this review is to analyze the published data on the incidence or recurrence of HCC and on the associated risk factors in patients with chronic HCV infection treated with DAAs and SVR, in order to gather an updated overview of the available scientific evidence on such a debated topic. We selected original published studies by searching PubMed,

Embase and the Cochrane Library database (through December 2019) using the following keywords: hepatocellular carcinoma, chronic hepatitis C, direct-acting antivirals, occurrence and recurrence. We evaluated the full-text and the references from relevant articles. Moreover, we included the relevant conference proceeding from the 2018 International Congress (AASLD and EASL).

2. Occurrence of HCC after Treatment with DAAs

2.1. Prospective Studies on the Occurrence of HCC after SVR by DAAs

Table 1 shows the main prospective published studies on the occurrence of HCC after treatment with DAAs. In 2016, our group was the first to report an unexpected occurrence rate of HCC [29] in a cohort of 280 HCV patients after SVR by DAAs. Unfortunately, the few reported cases did not allow a rigorous analysis of the potential risk factors. In two separate research letters, Cardoso et al. [24] and Kobzial et al. [30], two authors from Portugal and Austria, respectively, reported a significant and unexpected high incidence of HCC after clearance of HCV by DAAs. In a series of 54 HCV patients treated with sofosbuvir and ledipasvir for 24 weeks, Cardoso et al. [24] reported that 7.4% of patients were diagnosed with HCC after a median follow-up of 12.0 months (IQR 9.4–12.5 months) from viral clearance. No causative role in HCC development for any considered baseline factor was identified, nevertheless the authors speculated that immune system dysregulation may play a role. Kozbial et al. [30] reported an overall cumulative incidence of de novo HCC after SVR by DAAs in 5.2% of patients during a 48-week follow-up.

Table 1. Prospective study of hepatocellular carcinoma (HCC) occurrence after rapid virologic response (SVR) by direct-acting antivirals (DAAs).

Authors	Year	Country	Study Design	Sample Size	Control Group	Follow-up (Months, Median)	HCC Occurrence Rates (%)
Rinaldi [29]	2016	Italy	Prospective; cirrhosis	280	NA	3	3.2
Cheung [31]	2016	United Kingdom	Prospective; Decompensated cirrhosis	406	Untreated	18	5.4
Foster [32]	2016	United Kingdom	Prospective; cirrhosis and decompensated cirrhosis	467	Untreated	6	5.4
Romano [33]	2018	Italy	Prospective; cirrhosis	3917	NA	7.4	2.1 (year)
Mettke [34]	2017	Germany	Prospective; cirrhosis	158	Untreated	15	3.7
Calvaruso [35]	2018	Italy	Prospective; cirrhosis	2249	NA	14	3.5

Carrat [36]	2019	France	Prospective; Cirrhosis and non-cirrhosis	7344	Untreated	33.4	4.3
Pinero [37]	2019	Latin America	Prospective; Cirrhosis and non-cirrhosis	784	NA	16	3 (year)
Shina [38]	2020	Egypt	Prospective; cirrhosis	2372	NA	23.6	2.34 (year)
Tani [39]	2020	Japan	Prospective; Cirrhosis and non-cirrhosis	1084	NA	24	3.71

NA: not available.

In contrast to previous studies, Cheung et al. [31] observed a HCC occurrence rate after SVR by DAAs similar to that observed in untreated HCV patients. Similarly, Foster et al. [32] did not observe significant differences in HCC occurrence rates in the 6 months post SVR in a prospective study including 467 patients treated with DAAs compared with a similar group of untreated HCV cirrhotic patients. In a large Italian cohort of more than 3000 patients undergoing treatment with DAAs, during a median follow-up of 17 months [33], the rate of occurrence of HCC in the sub-cohort of cirrhotic patients was similar to that expected for untreated patients. There was a progressive reduction in the incidence of HCC after the first year in the cirrhotic patients. The authors hypothesized that the progressive decline over time of HCC could be related to the reduction in post-treatment intrahepatic inflammation. Mettke et al. [34] evaluated the incidence of HCC in a cohort of HCV cirrhotic patients after SVR by DAAs as compared with historical data of untreated patients, concluding that treatment with DAAs does not change the short-term risk of HCC. A multivariate analysis revealed that elevated MELD (Model of End-stage Liver Diseases) and alpha-fetoprotein values were independent factors associated with HCC development.

Calvaruso et al. [35] studied a cohort of 2249 consecutive HCV cirrhosis patients treated with DAAs. Seventy-eight patients (3.5%) developed HCC during a mean follow-up of 14 months. In this cohort, low levels of albumin (<3.5 g/dL), a low platelet count (<120 × 109/L) and the absence of SVR were associated with an increased risk of HCC. Recently, a cohort of 9895 HCV patients was evaluated in a French multicenter study by Carrat et al. [36]. The occurrence of HCC in patients treated (n = 7344) with DAAs and untreated (n = 2551) was 2.5% and 2.8%, respectively, during a median follow-up period of 33.4 months. The authors concluded that treatment with DAAs was associated with a reduced risk of HCC in patients with chronic HCV infection. Similarly, Pinero et al. [37], in a cohort of 784 HCV cirrhotic patients who underwent treatment with DAAs, observed that the cumulative incidence of HCC was 0.03 (CI 0.02–0.05) and 0.06 (CI 0.04–0.08) at 12 and 24 months of follow-up, respectively. SVR was associated with a 73% reduction in the overall relative risk for HCC recurrence. An Egyptian cohort of 2372 patients infected by genotype 4 HCV with advanced liver fibrosis and cirrhosis was prospectively followed for at least 12 months [38]. The overall HCC incidence was 2.3 per 100 patient-years. In patients with cirrhosis, the incidence of HCC was 2.9 per 100 patient-years, while in patients with advanced liver fibrosis, the incidence of HCC was 0.66 per 100 patient-years. Overall, the results showed a reduced incidence of HCC in both patients with cirrhosis or advanced liver fibrosis.

Recently, Tani et al. [39], who followed for 24 months 1084 HCV patients who achieved an SVR, showed that the incidence of HCC was 0.61%, 1.88%, 2.82% and 3.71% at 6, 12, 18 and 24 months after treatment with DAAs, respectively. Furthermore, they identified age and alfa-fetoprotein levels as the independent predictors of HCC occurrence.

2.2. Retrospective Studies on the Occurrence of HCC after Treatment with DAAs

Table 2 shows the retrospective studies on the occurrence of HCC after treatment with DAAs. The first retrospective observation was reported by an Italian study group that analyzed a cohort of cirrhotic patients treated with DAAs. The rate of occurrence of HCC during the first 6 months after treatment was 3.1%, which was higher than that previously observed

throughout the natural history of patients with untreated HCV cirrhosis [40]. Likewise, Nakao et al. [41] observed cumulative HCC incidences of 1.7% and 7% at 1 and 2 years after treatment with DAAs, respectively. In a large retrospective cohort study conducted in 22,500 patients with chronic hepatitis C infection treated with DAAs, Kanwal et al. [42] showed a significant 76% reduction in the HCC risk in cirrhotic patients with an SVR compared with non-SVR patients. Cirrhotic patients had a higher annual incidence of HCC after SVR than that observed in non-cirrhotic patients (1.82 vs. 0.34 per 100 person-years; adjusted hazard ratio, 4.73. 95% CI, 3.34–6.68). In a recent multicenter retrospective study, Marino et al. [43] reported an incidence rate of HCC of 3.7% during a median follow-up of 19.6 months post-treatment with DAAs. Basal liver function, the presence of uncharacterized liver nodules, alcohol intake and hepatic decompensation were associated with a higher risk of developing HCC.

Table 2. Retrospective study of HCC occurrence after SVR by DAAs.

Authors	Year	Country	Study Design	Sample Size	Control Group	Follow-Up (Months, Median)	HCC Occurrence Rates (%)
Cardoso [24]	2016	Portugal	Research letter; Cirrhosis	54	NA	12	7.4
Conti [25]	2016	Italy	Retrospective; Cirrhosis	344	NA	6	3.1
Kozbial [30]	2016	Austria	Research letter; cirrhosis	195	NA	12	6.6
Nakao [41]	2017	Japan	Retrospective; Cirrhosis and non-cirrhosis	242	NA	15	2.8
Kanwal [42]	2017	USA	Retrospective; Cirrhosis and non-cirrhosis	22500	NA	*	*
Marino [43]	2019	Spain	Retrospective; Cirrhosis and non-cirrhosis	1123	NA	19,6	3.7
Mecci [44]	2019	United Kingdom	Retrospective Cirrhosis	245	NA	32.4	*

Ioannou [45]	2019	USA	Retrospective; cirrhosis	48135	NA	64,8	3,66

* SVR vs. non-SVR: 0.90 vs. 3.45 HCC per 100 person-years; aHR, 0.28, 95% CI = 0.22–0.36). NA: not available.

Mecci et al. **[44]** focused on decompensated cirrhotic patients and compared 80 patients with HCC with 165 patients without HCC treated with DAAs and followed for a mean of 32.4 months. The authors concluded that the presence of baseline nonmalignant liver lesions, diabetes and thrombocytopenia increases the risk of HCC, and HCC is associated with a decreased SVR rate.

Recently, Ioannou et al. [45] retrospectively evaluated the incidence of HCC in 29,033 HCV patients treated with DAAs and followed between 2015 and 2019. The results showed that patients with cirrhosis continued to present a high risk of HCC (>2%/year), regardless of whether the FIB-4 score decreases over time, and therefore the authors recommend a long-time surveillance. Meanwhile, among patients without cirrhosis, those with FIB-4 scores ≥3.25 continue to present a relatively high risk of developing HCC, and are therefore deserving of surveillance.

In summary, considering prospective and retrospective studies, the data show that clearance of HCV by DAAs does not have a significant impact on the occurrence of short–medium term HCC, but reduces the risk of medium–long term HCC.

3. Comparative Studies between the Therapeutic Regimens Based on DAAs and IFN on the Occurrence of HCC

Several studies compared cohorts of patients treated with DAAs compared with IFN treatment (Table 3). Nagata et al. [46] retrospectively evaluated two cohorts of HCV patients treated with DAAs or IFN, using a propensity score analysis to reduce the bias of the different follow-up after achieving SVR (6.8 vs. 1.8 years). The results of this study showed that the cumulative occurrence rate of 3-year HCC was similar in the two groups (3.3% vs. 1.4%). The cumulative incidence of HCC was significantly lower for patients who achieved SVR in both groups. Similar results have also been reported in a cohort described by Affronti et al. [47], characterized by a high proportion of decompensated cirrhosis. Using a propensity score matching analysis, Nagaoki et al. [48] evaluated the cumulative incidence of HCC in 154 HCV patients with chronic hepatitis or cirrhosis treated with daclatasvir/asunaprevir compared with a historical cohort of 244 patients treated with IFN-based regimens. The data showed that in the two groups treated with DAAs and with IFN, the incidence of HCC at 1, 3 and 5 years of follow-up was 0.6%, 9% and 9% and 0.4%, 3% and 5% (p = 0.053), respectively. In a retrospective multicenter analysis involving 15 centers in Belgium, Bielen et al. [49] evaluated 567 HCV patients treated with an IFN-based regimen, 77 treated with PEG-IFN + DAAs between 2008 and 2013 and 490 who received DAAs between 2013 and 2015. The HCC occurrence rate was 1.7% and 1.1% in patients treated with DAAs with and without PEG-IFN, respectively (p = 0.540), so no significant difference in early post-treatment onset of HCC in patients treated with DAAs or IFN. Ioannou et al. [50] retrospectively evaluated 62,354 HCV patients who were started on antiviral treatments (DAAs, DAAs plus IFN and IFN). A total of 3271 incident HCC cases were diagnosed during a mean follow-up of 6.1 years. Regardless of the treatment used (IFN, DAAs or the combination of both), SVR was associated with a significant reduction in HCC in cirrhotic patients compared with those who did not achieve SVR. Treatment with DAAs or DAAs plus IFN was not associated with a different HCC risk compared with treatment with IFN. SVR by DAAs was associated with a 71% reduction in HCC risk. Innes et al. [51] evaluated a total of 857 patients, of whom 31.7% received an IFN-free regimen. In a univariate analysis, IFN-free therapy was associated with a significantly increased risk of HCC. However, after the multivariate adjustment for baseline factors (age, ethnicity, Child–Turcotte–Pugh; platelet count; genotype), no significant risk attributable to IFN-free therapy was confirmed.

Table 3. HCC occurrence compared to DAAs and IFN-based regimens.

Authors	**Year**	**Country**	**Study Design**	**Sample Size (DAAs/IFN)**	**DAAs: HCC Occurrence Rates (%)**	**IFN: HCC Occurrence Rates (%)**	***p***

Nagata [46]	2017	Japan	Retrospective	752/1145	3.3	1.4	0.49
Nagaoki [48]	2017	Japan	Retrospective	154/244	0.6 (1st year)	0.4 (1st year)	0.053
Bielen [49]	2017	Belgium	Retrospective	490/77	1.7	1.1	0.54
Ioannou [50]	2017	USA	Retrospective	21948/35871	No difference		
Innes [51]	2018	United Kingdom	Retrospective	272/585	No difference after multivariate adjustment		0.744
Li [52]	2018	USA	Retrospective	5834/3534	No difference		
Singer [53]	2018	USA	Retrospective	30183/12948	DAAs treatment was associated with a reduced risk		
Nahon [54]	2018	France	Retrospective	336/495	5.9	3.1	0.001
Waziry[55]	2017	Australia	Meta-analyses	13875	No difference		
Janjua [56]	2020	Canada	Retrospective	3905/8871	6.9/1000 PY	1.8/1000 PY	
Teng [57]	2019	Taiwan	Retrospective	79/102	0,38	0,56	0.186

Using the Electronically Retrieved Cohort of HCV-Infected Veterans database, Li et al. [52] evaluated a large group of 17,836 HCV patients treated with IFN or with DAAs. Among patients with cirrhosis who achieved SVR, neither the incidence rate of HCC-free survival nor HCC was significantly different between the DAAs and IFN groups (21.2 vs. 22.8 per 1000 person-years; $p = 0.78$ and log-rank $p = 0.17$, respectively). Furthermore, the results showed a significantly higher HCC incidence rate in patients with untreated cirrhosis (45.3 per 1000 person-years). In a retrospective study evaluating more than 30,000 patients undergoing treatment with DAAs, Singer et al. [53] showed a significantly lower risk of HCC compared with untreated patients (Odds ratio (HR) = 0.84, 95% CI: 0.73–0.96), or to IFN-treated patients after adjustment by gender, age and stage of the disease.

Nahon et al. [54] collected data from 35 centers in France on 1270 patients with HCV divided into subgroups: (1) treated with DAA ($n = 336$), (2) those who obtained an SVR following an IFN-based regimen ($n = 495$) and (3) those never treated or not compliant with the IFN ($n = 439$). Patients were followed up with ultrasound every six months to detect the onset of HCC. The three-year cumulative incidence of HCC was in groups 1, 2 and 3 of 5.9%, 3.1% and 12.7%, respectively. Compared with patients in the SVR-IFN group, patients in the DAA group were older, had higher diabetes, portal

hypertension and impaired liver function. The authors hypothesized that the high occurrence rate of HCC could be related to patient characteristics (age, diabetes, reduced liver function) and lower screening intensity. In a recent meta-analysis that includes 26 patient cohorts, Waziry et al. [55] did not identify a high risk of developing HCC after HCV treatment with DAAs in patients with cirrhosis, but an individual risk reduced by 63%.

In a recent study, Janjua et al. [56] evaluated a large Canadian cohort treated with DAAs compared with a retrospective cohort treated with IFN. Among patients who responded to DAAs treatment, the incidence rate of HCC was 6.9 per 1000 person-years. Among individuals successfully treated with interferon, the incidence rate of HCC was 1.8. The authors concluded that similar to the interferon era, DAA-related SVR is associated with a 70% reduction in HCC risk.

Teng et al. [58] compared the preventive tertiary effect between DAAs and peg-IFN-RBV in 301 patients with HCV-HCC by a propensity score corresponding to age, tumor staging, HCC treatment modality and cirrhotic status. The results showed that the tertiary prevention effect lasted in the Peg-IFN/RBV arm ($p < 0.001$), but decreased in the DAA arm ($p = 0.135$) compared with untreated patients.

4. DAAs Treatment and Recurrence of HCC in HCV Patients

Recently, some concerns have been raised regarding the possible increased risk of recurrence of HCC after treatment with DAAs (Table 4). In a multicenter retrospective study, Reig et al. [59] showed that 27.5% of the 58 patients treated with DAAs had a recurrence of HCC after a median follow-up of 5.7 months after treatment. In the same way, Conti et al. observed that 29% of 59 patients had a recurrence of HCC during the six months of follow-up after treatment with DAAs. Kozbial et al. and Yang et al. [60], in retrospective studies, confirmed a high relapse rate of HCC after treatment with DAAs. A hypothesis to explain the possible high recurrence rates of HCC observed in these cohorts of patients treated with DAAs is a dysregulation of the antitumor immune response after the sudden clearance of HCV that would promote tumor recurrence [61]. On the other hand, in a study from France [62] including HCV patients previously treated for HCC among whom 13 cirrhotic patients received treatment with DAAs and 66 received no treatment, 7.7% of patients treated with DAAs showed a recurrence of HCC, while in the untreated group, 47% showed a relapse of HCC. Therefore, the results of this study did not confirm that patients treated with DAAs had a high recurrence of HCC. Similar results have been reported in a study conducted in Italy [63], which included 31 consecutive HCV cirrhotic patients with HCC after being cured by locoregional or resection treatment and who received DAAs. The median time between treatment with HCC and the start of treatment with DAAs was 19.3 months and the median follow-up period after treatment with DAAs was eight months. The recurrence of HCC was 3.2% and the authors concluded that treatment with DAAs was not associated with an increased risk of recurrent HCC.

Table 4. Prospective and retrospective study of HCC recurrence after SVR by DAAs.

Authors	Year	Country	Study Design	Sample Size	Control Group	Follow-Up (Months, Median)	HCC Recurrence Rates (%)
Reig [58]	2016	Spain	Retrospective	58	NA	5,7	27.6
Conti [25]	2016	Italy	Retrospective	59	NA	6	28.8
Kozbial [30]	2016	Austria	Research letter	22	NA	7	86
Yang [59]	2016	USA	Prospective	18	NA	NA	27.8
Pol [61]	2016	France	Prospective	13	66	16,5	7.7

Zavaglia [62]	2017	Italy	Research letter	31	NA	8	3.2
Singal [63]	2019	USA	Retrospective	304	489	10,4	42,1
Virlogeux [64]	2017	France	Retrospective	23	45	13	47.8
Imai [65]	2020	Japan	Retrospective	13	64	36	23.8
Nakano [66]	2019	Japan	Prospective	459	NA	29.4	47.2

NA: not available.

In the multicenter North American cohort study [64], 793 patients with HCV-associated HCC were evaluated, of whom 38.3% received DAAs therapy and 61.7% were untreated. HCC recurred in 42.1% of treated and in 58.9% of untreated patients. The authors concluded that DAAs therapy was not associated with an increased overall or early HCC recurrence.

A French study [65] evaluated 68 consecutive HCV patients with apparently cured HCC, of which 34% were treated with DAAs. The recurrence rate among treated and untreated patients was 1.7/100 and 4.2/100 person-months, respectively ($p = 0.008$). The conclusion was that the HCC recurrence rate was significantly lower in patients treated with DAAs than in untreated patients. Similar results were achieved by Imai et al. [66], who identified the SVR by DAA as an independent factor for the prevention of HCC recurrence. Nakano et al. [67] evaluated 459 patients who had HCC for the recurrence rate and to identify the predictors of HCC recurrence after DAAs treatment. In a median time of 29.2 months, 47.2% of patients developed HCC recurrence. The factors associated were the AFP levels and the number of HCC occurrence before the DAAs treatment.

These conflicting results have generated a heated debate. Studies showing high HCC recurrence rates in patients treated with DAAs may suffer from a selection bias due to a failure to detect HCC in patients with impaired liver function who are eligible for anti-HCV treatment because of the safety of DAAs [68].

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