Review Article

Direct antiviral agents for HCV infection and hepatocellular carcinoma: facts and FADs

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Abstract: The advent of directly acting antivirals (DAA) has determined a showy change in the management of hepatitis C virus (HCV) infection, the most common cause of hepatocellular carcinoma (HCC) in many countries. It was demonstrated that the achievement of sustained virologic response (SVR) with interferon (IFN) reduces the incidence of HCC. Recently, published data in the literature suggested an increased risk of HCC after IFN free treatments. The mechanism evoked to explain this trend is the deregulation of antitumor response, following the sudden decrease of HCV viral load, due to immune subversion which could favour the progressive development of pre-existing neoplastic clones. The lack of randomised controlled trials (RCTs) with control groups of patients and the fact that majority of studies are limited by retrospective settings, recruitment bias and lack of clinical goals scheduled at the start of treatment make difficult an adequate analysis of data. Main evidence seems to confirm that DAA therapy has not a carcinogenic effect per se but can lead to the earlier manifestation of latent tumours still present but underestimated. At present patients with HCV infection should be encouraged initiating DAA therapy to prevent cirrhosis and HCC but intensive screening is necessary to exclude HCC before initiating DAA. Curing HCV infection does not eliminate the possibility of ongoing liver disease and HCC, as such an adequate monitoring should continue for an indefinite period after SVR.

Keywords: Recurrence; hepatocellular carcinoma (HCC); hepatitis C; occurrence; direct antiviral agent (DAA)

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Background

Hepatitis C virus (HCV) infection, affecting about 150,000,000 individuals, is the predominant cause of chronic hepatitis resulting in cirrhosis and hepatocellular carcinoma (HCC) (1). HCC is lethal cancer with overall 5-year survival of around 14%. HCC is considered the fifth most frequently diagnosed cancer and the second leading cause of cancer deaths among adult male (2). This high mortality is partly favoured by the co-existence of liver cirrhosis in most of the patients. Advent of direct antiviral agents (DAA) dramatically changed the therapy of hepatitis C (3) because of the high efficacy in all categories of HCV infected patients: sustained virological response (SVR), achieved in over 90% of treated patients whatever the stage of liver fibrosis, is associated with few side effects (4). In the past, therapeutic regimens based on interferon (IFN) resulted in a lower response rate (viral suppression in less than 50% of treated patients) with limited use by adverse effects and contraindications. The effects of IFN induced HCV clearance were three: decrease of cirrhosis-related complications, improvement in liver fibrosis and drop of overall mortality. In particular multiple studies have reported a decrement in "de novo HCC" among SVR patients compared to non-SVR ones (5-7). Antiviral and antiangiogenic properties of IFN seem to elide the pro-

inflammatory and carcinogenic effects of HCV. Multiple studies have confirmed that the risk of HCC following an IFN induced SVR is around 1% (8) while the annual incidence of HCC in untreated HCV cirrhosis is 3–7% (9).

Risk of HCC occurrence

An increased risk of "de novo HCC", after IFN free treatments, was first described by the Italian group of Conti *et al.* (10). They assessed, in a single centre retrospective study, the risk of HCC in 285 cirrhotic patients, without a previous diagnosis of HCC, treated with DAA. In this group, the SVR rate was 91%. De novo HCC was detected in nine patients (3.16%, 95% CI: 1.45–5.90%), during a six months post-treatment follow-up, suggesting that SVR, achieved after DAA, is not associated with a consistent reduction of HCC occurrence. The incidence of HCC in this population, after viral clearance, was similar to that of viremic cirrhotics. However, in this study, underlying HCC at time of DAAs was not excluded, and the follow-up was too short, limiting the reliability of the results. Additional limitations were: lack of a control group, old age of subjects, the more advanced fibrosis and the higher BMI respect to patients treated with IFN which were historical controls. All these elements favour higher incidence of HCC regardless of treatment chosen. A high rate of "de novo" HCC after DAAs was reported by others retrospectives studies: in the cohort of Ravi (11), 9.1% (6/66) cirrhotic patients with SVR, following DAA therapy, developed HCC within 24 weeks after the conclusion of treatment. In this case, the incidence of *de novo* HCC was higher than what previously reported in cirrhotic patients successfully treated with IFN. In the cohorts of Cardoso (12) after longer follow up (12 months), an incidence of 7.4% was reported. In the prospective study of Kozbial (13), 13 months after DAA cessation, 6.6% of 195 treated patients developed HCC, showing a higher incidence of HCC *de novo* respect to a historical cohort who achieved SVR with IFN/ribavirin (annual HCC rates of <1.5%). Even if there was a control group, the two populations were dissimilar, and the follow up had a different duration.

Toyoda *et al.* (14) evaluated peculiarities of 1,533 patients successfully treated with IFN and 1,086 patients who achieved SVR after DAA, from five Japanese institutions. The incidence of HCC was significantly higher in the DAA group (7.29%) than in the IFN group (3.09%). The median follow-up was not specified. The incidence of HCC after pre-treatment characteristics of patients influenced SVR (IFN-based and IFN-free groups), which correlated with a pre-existing unequal risk of HCC. This finding makes it very difficult to compare the hepatocarcinogenesis suppression correlated to IFN free or IFN based therapy.

In contrast with these observations, several other studies were published, suggesting a lower HCC incidence of than traditionally reported. Kanwal *et al.* (15) reported an annual HCC incidence of 1.18% among infected patients who obtained SVR after DAA therapy. It was a retrospective cohort study. The HCC risk was lower in patients who achieved SVR compared to unsuccessfully treated patients (0.90 *vs.* 3.45 HCC/100 person-years; HR 0.28, 95% CI: 0.22–0.36). Cirrhotic patients with SVR had a higher incidence of HCC (1.82/100 person-years) than those without (0.34/100 person-years; HR 4.73, 95% CI: 3.34–6.68). Ioannou *et al.* (16) analysed 62,354 patients who started antiviral treatment from 1/1/1999 to 12/31/2015, including IFN therapy, the association of DAA plus IFN and DAA only regimens. The highest incidence of HCC (follow-up of 6.1 years) was found in cirrhotic patients and case of treatment failure (3.25 per 100 patient-years). The risk of HCC was conditional on SVR, regardless of the antiviral treatment chosen (DAA-alone, DAA+IFN or IFN-alone). Regimes based on DAA (alone or combined with IFN) were not associated with an increased risk of HCC compared to IFN-alone therapies. On the contrary, SVR achieved using DAA was associated with a consistent (71%) reduction in HCC risk. Both these two studies were retrospective. The main limitation of the former was a lack of data relating to the surveillance strategy of HCC. It is possible that greater surveillance in "non-SVR population" was adopted compared with the groups which achieved SVR. In the latter, baseline differences in the groups mentioned above (SVR and not SVR), and the overall inadequate surveillance measures could have introduced bias.

Ogata *et al.* (17) described a lower incidence of HCC than traditionally reported: the occurrence of HCC among 1,170 patients treated with DAAs and with SVR was 1.4% and 1.8% at 1 and 2 years respectively. The inclusion of only Asians and the heterogeneity of population made up of cirrhotics, and noncirrhotic represented the main limitations of this retrospective single-centre study.

In the prospective study of Cheung (18), 377 cirrhotic patients (Child B in 72.7%, Child C in 10.1%) without a previous diagnosis of HCC were treated with DAA. HCC developed in 15 (3.9%) during the first six months after initiation of DAAs and 10 (2.6%) at longer follow-up

(6–15 months). Patients with SVR had rates of HCC incidence compared to those without and to untreated patients. A trend towards progressive reduction of the risk was observed over time in SVR patients.

In the prospective study of Foster *et al.* (19) the HCC incidence was of 5.4% six months after DAA initiation. Reduced risk of the novo HCC was also reported by Calleja (20) and Kobayashi (21), 0.9% and 2.6%, after 18 months and 4 years follow-up. In a study published by Calleja (20), development of *de novo* HCC, within 18 months of starting DAA therapy, was found in 30 of 3,233 patients without a prior neoplastic history (HCV genotype 1 patient recruited in Spain between April 2015 and February 2016. About 46.7% of theme had stage 4 of fibrosis. In the study of Kobayashi (21) in patients with severe fibrosis (Fib-4 score of >3.25), the 3- and 5- year HCC development rate were 4.35% and 9.66% in the group of patients treated with DAA, whereas in the IFN/ribavirin group the rates were of 3.95% and 8.37%, respectively. In patients with less fibrosis (Fib-4 score ≤3.25), the 3- and 5-year HCC development rates were 0% for patients treated with DAA, whereas 0.48% and 1.05% for patients treated with IFN with or without ribavirin. No significant difference in the development rate of HCC, between the two groups, emerged from the propensity score analysis using the inverse probability of treatment weight.

The sustained virological response achieved after a DAA treatment seems to reduce HCC incidence, as demonstrating by Calvaruso *et al.* (22), in a prospective study of patients with compensated or decompensated cirrhosis. They collected data from 2,249 patients, 3.5% of them (about 78) developed HCC. The follow-up time was, on average, 14 months. In this study, the lack of SVR was independently associated with a risk for HCC (HR, 3.40; 95% CI: 1.89–6.12; P<0.001).

In the prospective French series of 167 cirrhotic patients achieving SVR with DAAs, only 1 (0.6%) was found to develop HCC during follow-up (23). In line with these observations a prospective study, on 3,075 patients (24) with advanced liver disease, without a previous history of HCC, treated with DAAs was carried on in the Veneto region, in Italy, and monitored by the NAVIGATORE database. The rate of HCC occurrence was 0.23×100 patients/year with F3, 1.64×100 patients/year with Child A cirrhosis and 2.92×100 patients/year in Child B cirrhosis. HCC was more frequent in patients without SVR (8.38×100 patients/year), compared to patients with SVR (1.55×100 patients/year).

Data about HCC occurrence are summarised in *Table 1*.

Why is the incidence of new HCC very difficult to be determined?

A definitive position cannot be assumed on the IFN-free therapy role on the occurrence of HCC because of all the limitations of the above studies, in particular, the retrospective nature of them and the absence, in most of the cases, of a real match with a control group. In some cases, it was replaced by a historical cohort that means patients treated with IFN, with enormously different baseline characteristics, especially the less advanced fibrosis stage compared with patients treated with DAA. A further limitation of this study was the exiguous number of patients and limited duration of follow up. Lastly, unknown HCC, still present at the start of treatment, could negatively influence the response to antiviral therapy explaining the possible association between failure of SVR and higher HCC *de novo* rate.

Recurrence of HCC

First observations of a "surprisingly" high HCC recurrence after SVR came from Reig and co-workers (25). They described 58 cases of HCC, treated by ablation (PEI/RFA), resection, chemoembolization (TACE) with a complete radiological response, who were then treated with DAA in 4 hospitals in Spain. The vast majority (97.5%) of patients achieved SVR 12. During a follow-up period of 5.7 months after DAAs, 27.6% of them (16 patients) developed HCC recurrence, radiologically evident, with a median time frame, from the start of DAA therapy and tumour recurrence, of only 3.5 months (range, 1.1–8 months). HCC recurrence was seen in 7/20 (35%) patients in which HCC had been resected, in 9/32 (28.1%) who had undergone HCC ablation and in 0/6 (0%) treated by TACE (25). Reig *et al.* noted an increased risk of recurrence when DAA therapy was taken in the four months following HCC treatment (41.17%). This short interval (<4 months) between oncologic treatment and last check, by imaging of complete response became of most interest.

A similarly high rate of early tumour recurrence was reported by Cammà *et al.* (26) who extracted the Kaplan-Meier HCC recurrence estimation curves from Reig's paper. These authors showed that the chance of cancer recurrence during the first 24 weeks after starting DAAs was more than double (approaching 50%) in patients with a time interval between cancer treatment and last evaluation of its complete response <6 months, compared to the probability (<15%)

Table 1 Studies evaluating the risk of de novo HCC after DAA therapy

Authors (references)	HCC incidence within			Cirrhosis (%)
	6 months	12 months	24 months	
Conti (10)	3.16%	–	–	100
Ravi (11)	9.1%	–	–	100
Cardoso (12)	–	7.4%	–	100
Kozbial (13)	–	6.6%	–	NA
Toyoda (14)	HCC incidence of 6.23% but median follow-up was not specified			NA
Kenwal (15)	Overall annual HCC incidence of 1.18% during 22963 PY of follow-up			39
Ioannou (16)	1.32 per 100 patients years during a follow-up of 6.1 years			24
Ogata (17)	–	1.4%	1.8%	NA
Cheung (18)	3.9%	6.7%	–	100
Foster (19)	5.4%	–	–	77.5
Calleja (20)	–	–	0.9% (18 months)	52
Kobayashi (21)	2.6%, after a follow-up of 4 years			NA
Calvaruso (22)	–	3.5% (14 months)	–	74.9
Nahon (23)	31.9% after a median follow-up period of 58.2 months			100

HCC, hepatocellular carcinoma; DAA, directly acting antiviral; NA, not available.

estimated in patients with a longer time frame.

In the study of Conti and co-workers (10), 59 patients with a positive anamnesis for HCC, treated with surgical approach, ablation (RF/PEI), TACE and a combination of procedures had a complete tumour response and were treated with approved oral DAA combinations after a median interval of 376 days (range, 45–2,706 days). During a 24 week post-treatment follow-up, 17 (28.8%, 95% CI: 17.76–42.07%) showed HCC recurrence, that was associated with younger age and with more severe liver fibrosis.

In the Yang *et al.* (27) study the relapse rate, among HCC patients who received DAA before orthotopic liver transplantation, was higher (27.8%) respect to the control group (84 patients) not treated with antivirals (9.5 %) (P=0.06). The median follow-up after DAA therapy was not specified.

In the study of Calleja *et al.* (20), the rate of recurrence was 30% within one year of starting IFN free therapy. "Post hoc analyses" of HCC recurrence or incidence must be evaluated with adequate consideration because of the absence of surveillance plan. The study was an observational real world designed. The electronic data collection included potential bias, incomplete records and data input errors.

Other studies, did not confirm a supposed rise of HCC recurrence after IFN free regimes. The French report on the different ANRS collaborative prospective studies of HCV patients described recurrence of HCC in 3 cohorts: In the CO22 HEPATER Cohort, made up of 267 patients with a positive anamnesis of cured HCC, the HCC recurrence rate was 12.7% (8.76×100 patients/year) in 189 patients who had received DAAs treatment compared to 20.5% (7.92×100 patients/year) of the 78 untreated patients. In the CO12 CirVir cohort, incidences of HCC recurrence were 13.32×100 patients/year in 13 DAAs treated patients and 20.76×100 patients/year among 66 untreated patients. In the CO23 CUPILT cohort, including 314 patients undergoing liver transplant for HCV related HCC, HCC recurrence was seen in only 2.2% of the cases during a follow- up of 7±3 months after antiviral therapy. In conclusion, therapy with DAA was not associated with an additional risk of HCC recurrence (28). Similar results have been reported by Zavaglia *et al.* (29) and by Cheung *et al.* (18) with the incidence of 3.2% over a mean eight months of follow-up and 6.29% over a mean 15 months follow-up, in cirrhotic patients treated with DAA. The heterogeneity

of all these results most likely reflects the heterogeneity of the clinical setting they refer to, with many variables that could have profoundly affected HCC recurrence rates. The absence in many studies of matched untreated controls further complicates interpretation and do not allow to draw firm conclusions. Petta *et al.* (30) compared HCC recurrence rates retrospectively in untreated patients with persistently high viremia, and in healed patients, which achieved SVR after traditional IFN-based therapy or DAAs. The results were suggestive for a reduction of HCC recurrence in not viremic patients (after SVR), regardless of therapeutic strategy, IFN-based and IFN-free therapy. During follow-up, cancer recurrence developed in 43.3% viremic patients, in 27.6% and 38.6% SVR patients treated with IFN-free regimens and IFN-based therapies. The 24-week recurrence rates were 9.5%, 5.2% and 3.7%, and the 2-year recurrence rates were 40.6%, 26.3% and 15.2% in patients with active HCV infection, with SVR achieved following IFN-free treatment, and with SVR achieved following IFN-based therapies, respectively. The three groups, however, were derived from different published cohorts, with a high risk of selection bias.

A Japanese experience about HCC development after DAA came from Kobayashi *et al.* (31) who demonstrated that HCC risk rate was similar regardless of the treatment chosen (DAA of IFN based regimes). In this study, it was also confirmed that HCC development rates after DAA were lower than those reported previously in patients with active HCV infection (32). The retrospective evaluation of 77 patients with SVR after DAA and 528 after IFN plus ribavirin, during a median follow up of 4 years, showed that 2 of 77 patients treated with DAA (2.6%) developed HCC. The 3- and 5-year cumulative HCC development rates were 1.3% and 3.03% respectively, in the DAA group and 1.02% and 2.19% in the IFN/RBV group (P= not significant). A multicenter study by the Japanese Red Cross Hospital Liver study group (33) obtained the same results: no differences in the early recurrences of HCC (after curative HCC treatment) between patients treated with IFN or DAA.

Another perspective, coming from Japan, reported a lower relapse rate after DAA in a cohort of 1,191 HCC patients, mostly cirrhotic, treated with radiofrequency ablation. A subgroup of them (n=27, where then treated with DAA and 38 with IFN (median time frame between ablation and HCV treatment of 5.8/5.4 months) while a third group made up of 861 patients was not treated. The relapse rates after 1 or 2 years were 21.1% and 29.8% in DAA group, 26.3%/52.9% in the IFN group and 30.5%/61% in the control group (P=0.101; median follow up of 15.6 months) (34).

In the study of Cabibbo and co-workers (35), 143 HCC patients effectively treated with curative strategies, who subsequently started DAAs, were monitored by a web-based database. About 96% of them achieved SVR. In 24 cases a recurrence of cancer was observed, with a nodular pattern in 83% and infiltrative pattern in 17% of patients. At 6, 12 and 18 months, HCC recurrence rates were of 12%, 26.6% and 29.1%, respectively. Risk of HCC recurrence, in a short frame time, among HCC patients previously cured remained high, despite HCV clearance obtained by DAAs. The risk was not higher to that reported in the literature in DAA-untreated patients.

Recently Huang *et al.* (36) performed a retrospective study of 149 HCV positive liver transplant candidates with HCC, treated with local-regional therapy, in order to evaluate the impact of DAA therapy on cancer recurrence and eventual waitlist dropout. Cumulative incidence of HCC recurrence, within 1-year of complete response after curative loco-regional treatments, was 47.0% in the group of patients treated with DAA and 49.8% in the group without DAA (P=0.93). Risk of HCC recurrence appeared similar in DAA group compared to no DAA group without (HR 0.91, 95% CI: 0.58–1.42, P=0.67) but the risk of waitlist dropout due to cancer progression or death was lower in DAA treated patients.

Main data relative of HCC recurrence studies are summarised in *Table 2*.

What could explain the supposed increased risk of HCC?

To explain the supposed increased risk of tumour only speculative hypotheses were made. The first mechanism seems to be related to the fastest viral suppression achieved by IFN-free regimens. HCV eradication occurs immediately, in a few days after therapy with DAAs and it takes a long time after IFN. IFN plays an anti-proliferative role, regulates angiogenesis and moreover, the activity of immune cell types, which solicits a robust immune response against malignancy. Deregulation of immune-system, caused by a sudden drop of HCV viremia after DAAs, decreases immune-cells activation against malignant cells, already present before starting antiviral treatment. HCV promotes IFN production that directly eliminates malignant clones acting on inflammatory responses and natural killer cell/cytotoxic T lymphocytes mediated cytotoxicity (37).

Table 2 Studies evaluating the risk of HCC recurrence after DAA therapy

Authors (references)	HCC recurrence within		
	6 months	12 months	24 months
Patients not receiving any antiviral therapy	7.4%	20%	47%
Reig (25)	27.6% (median 5.7 months)	–	–
Conti (10)	28.8%	–	–
Calleja (20)	12.9%	30%	–
ANRS (28)			
Hepather	–	–	13% (20 months)
Cupilt	–	2.2% (7±3 months)	–
Zavaglia (29)	–	3.2% (8 months)	–
Cheung (18)	–	–	6.29% (15 months)
Petta (30)	5.2%	12.9%	–
Minani (34)	–	21.1%	29.8%
Cabibbo (35)	12%	26.6%	29.1% (18 months)

HCC, hepatocellular carcinoma; DAA, directly acting antiviral.

Neoplastic clones emerge, replicate undisturbed in a setting of reduced inflammation which usually exerts anti-neoplastic immune surveillance (25).

Some studies demonstrated that the abrupt drop of viral load by DAAs was linked with restoration of HCV specific memory T cell differentiation, lymphocyte disabling and normalisation of natural killer cell activity (38-40). IFN-free therapy also leads to the down-regulation of type II and III IFNs (41). Lastly, Mir-122, which plays a pivotal role in carcinogenesis was recently found to be decreased in serum samples after DAA therapy (40).

A study has investigated the role of natural killer group 2 member D (NKG2D). NKG2D is an immune-receptor able to activate the immune responses against infected and malignant cells. In this study, the fast decrease of NKG2D expression after DAA therapy significantly correlates with early HCC occurrence in treated patients (42).

In other words, the rapid drop of viral load favoured by DAAs, reducing inflammation, impairs hepatitis progression, which is a decisive goal but impacts negatively on controlling cancer.

It is also possible that as HCV infection is cleared and as the liver regenerates and repairs itself, small tumours that were present but were not clinically apparent might accelerate their growth. Liver regeneration has been seen, both anecdotally as well as in case series, to promote rapid tumour growth or carcinogenesis. The lack of immune surveillance and immune attack might allow tumours to grow more rapidly. So, liver regeneration or lack of immune surveillance, or both, might lead to the clinical appearance of tumours in an accelerated rate following sustained virological response.

Villani and co-workers showed that vascular endothelial growth factor (VEGF) levels were significantly higher during DAA therapy, confirming an increased creation of blood vessels to supply cancerous grow. Assuming that neoangiogenesis acts as a vehicle of cancer cells dissemination, it appears logical that immediately after DAA treatment, the probability of malignant cells dissemination is increased. Levels of circulating VEGF, which acts a significant role in liver cancer angiogenesis, correlate with more aggressive disease; high tissue and serum levels of VEGF may be responsible for the higher incidence of HCC recurrence during DAA treatment (43).

Discussion

During the IFN era, sustained virologic response (SVR) provided a reduction of HCC. The advent of DAAs seems to have increased the risk of HCC, triggering a heated discussion in the scientific world. Some authors reported higher rates of *de novo* and recurrent HCC, after DAAs

than after IFN regimes, whereas others did not find any significant risk.

The results obtained by published studies are not enough to confirm an augmented risk of HCC. Indeed most of the studies seem to demonstrate that IFN-free treatment had a good impact on carcinogenesis similar to that of IFN based regimes, reducing HCC risk, in SVR patient.

Further, numerous prospective studies are necessary to determinate the mechanism of the protective effects of DAA against HCC, in particular, well-designed studies with proper comparison arms. The majority of studies published until now were observational; they were not randomised trials comparing patients who were treated and cured to patients not treated. It is important to remember that in the DAA era, the vast majority of patients are suitable for a cure, so patients need to be compared with historical controls or patients who for one reason or another were not treated, which always instils bias in a study. Only a randomised trial can equalise confounders. In this connection, an attempt to define a benchmark on HCC recurrence in the natural course of HCV patients in the absence of HCV drugs, Cabibbo *et al.* (35) have recently conducted a meta-analysis of published studies of HCV patients with adequate follow-up after curative treatment of HCC, not receiving any antiviral therapy. The Authors analysed 11 such studies inclusive of 701 patients: the estimated probability of HCC recurrence was 7.4% at 6 months, of 20% at 12 months and of 47% after 24 months. Second, the HCC rates in some of the European DAA studies were higher than expected (certainly higher than those seen in other studies), which raises the question as to whether these findings were a chance occurrence. As with any preliminary, notably retrospective, research, the European findings need to be replicated in different populations, and researchers need to make sure that the results are not due to biases, confounders, or chance occurrence (44) In addition to controversies tied to study design (no randomised, retrospective or prospective, lacking adequate control group).

Another important key point is that, in some patients, *de novo* or relapsed HCC, mistakenly attributed to DAAs, were already present and not detected before starting therapy because of inappropriate screening and follow up, planned before DAA. Because of the perfect side effect profile of DAA, some patients, after HCC curative treatment, were treated with IFN free regimes too earlier after the procedure, without a real and adequate follow-up.

Another heart of the matter is the different approach to prescription, considering the poorness of DAA side effects which leads to broader inclusions criteria in DAA group: older age (median 10–15 years older), more advanced fibrosis and worse functional setting (Child-Pugh B and C), more severe comorbidity (45), fundamentally heterogeneous baseline patients and tumour characteristics.

Also, most publications lack information about SVR, the severity of fibrosis, the time frame of monitoring, cadences of follow-up before and after treatment. Some publications combined patients with and without previous cancer in the same group of analysis while others count, among curative therapies, TACE. There is not a clear strategy for the assessment of the complete radiological response neither a clear definition of HCC recurrence. Substantial differences were also observed in the time frame between cancer treatment and the start of antiviral IFN free therapies, DAA start and HCC recurrence. Finally, positive anamnesis for HCC recurrences and impact of competitive risk on survival are not analysed in most studies.

What is certain is that virus C eradication remains a mainstream for cancer prevention because of its capacity to reduce chronic inflammation and improve the histological background characterised by necrosis and fibrosis. Furthermore, the expression of HCV genes is implicated in hepatocarcinogenesis. Viral eradication attenuates the impact of the inflammatory environment on dysplastic hepatocytes, and similarly, SVR contributes to a reduction in portal pressure, improving survival among cirrhotic patients.

In light of the above, before starting DAA, a complete imaging evaluation should be made primarily in patients with previous HCC, in order to rule out pre-existing cancer foci and confirm a complete remission. The risk, greater immediately after HCV clearance and lower after fibrosis restore, mimics immune reconstitution inflammatory syndrome during human immunodeficiency virus infection (46). While it is not reasonable to delay HCV treatment, residual HCC should be ruled out planning an accurate surveillance program. It is important to underline that, after virus eradication, patients with severe fibrosis and alcohol drinkers are still at risk to develop HCC. Once HCV infection is eradicated, patients still carry a risk of cancer in the setting of cirrhosis, and they still may have risks for ongoing liver disease, related to fat storage and alcoholic damage. Patients with cirrhosis need biannual imaging surveillance for HCC and tend to remain in the practice of hepatologists and gastroenterologists, regardless of SVR. At present patients treated with resection or

ablation of HCC should not be discouraged from receiving DAA to delay the progression of liver disease. Accurate HCC screening and planned follow up are necessary to confirm cancer eradication before initiating DAA.

Indeed DAA therapy is more useful in patients without advanced fibrosis, leading to a significant reduction in HCC incidence and lowering the risk of evolution in cirrhosis.

Conclusions

DAA therapy has not a carcinogenic effect *per se* but can lead to the earlier manifestation of latent cancer foci still present but underestimated. The fast drop of virus load with reduction of inflammation triggered immune-surveillance could increase proliferative input in a setting of liver degeneration.

Before starting IFN free therapy, especially in a histological background of cirrhosis, HCC should be carefully checked, and adequate monitoring should be continued for an indefinite period with a minimum of biannual imaging. After curative approach to HCC (chirurgical strategy or local ablation), relapse should be attentively excluded. DAA therapy should be initiated 24/48 weeks after complete cancer response, carrying on a long term follow after DAA. At present, IFN free therapy is not recommended for patients receiving palliative therapy (TACE, sorafenib) but could also be investigated prospectively. A careful evaluation of real-life data could help to define a subgroup of patients who could not benefit from DAA, in terms of HCC recurrence/occurrence or who require closer monitoring (47).

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