Hepatoma Research

Review

HCV clearance by direct antiviral therapy and occurrence/recurrence of hepatocellular carcinoma: still an issue?

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Abstract

New regimens with direct-acting antivirals (DAAs) agents have changed both efficacy and safety of hepatitis C virus (HCV)-treatment, as almost all patients can be treated and cured at any stage of liver disease. The rates of sustained virological response to currently available combinations exceed 95% in real-life practice. However, conflicting results have been produced on the occurrence/recurrence of hepatocellular carcinoma (HCC) in patients with HCV-associated cirrhosis treated with DAAs. In this review we analyse the data available in the literature in order to elucidate the impact of DAAs on the risk of HCC occurrence in patients without previous history of tumor, and of recurrence after successful treatment of the tumor. Data on "*de novo*" HCC incidence were quite homogeneous, suggesting that the treatment with DAAs does not modify the risk of HCC developing during the first 6-12 months after HCV eradication. On the contrary, HCC recurrence rates after DAAs were extremely variable across different studies, reflecting a large heterogeneity in this clinical setting. The possibility that treatment with DAAs may favour tumour growth and spread in individual patients with active HCC foci is supported by some observations but remains unproven.

Keywords: Hepatitis C virus, direct-acting antivirals, eradication, hepatocellular carcinoma, occurrence, recurrence

INTRODUCTION

Patients with hepatitis C infection (HCV) and cirrhosis have an increased risk of developing liver decompensation (LD), hepatocellular carcinoma (HCC) and liver-related death (LRD). Cirrhosis is a major risk factor for the development of HCC in Western countries, where HCC occurs at an average annual rate of 3%-5% in cirrhotic patients[1,2]. Data on the long-term outcome of patients with HCV infections,

treated with Peg-interferon (Peg-IFN) and ribavirin, demonstrated a reduction in LRD and non-LRD, with patients achieving sustained virological response (SVR) showing nearly the same life expectancy as the general population[3,4]. Patients with compensated cirrhosis, and without the clinical manifestations of portal hypertension, are those who experience the greater clinical benefits of HCV eradication, as they do not develop LD and rarely HCC[5].

This was confirmed in a meta-analysis of 12 studies including 25,497 patients that demonstrated a relative risk reduction for HCC at all stages of liver disease [hazard ratio (HR): 0.24; 95%CI: 0.18-0.31; $P = 0.001$] and an absolute risk reduction of 4.6% (95%CI: 4.2%-5.0%) in patients who achieved SVR compared to those who did not respond[6].

DIRECT-ACTING ANTIVIRAL THERAPY: A NEW STORY HAS STARTED

The more widely extended indication criteria and the greater affordability of direct-acting antiviral (DAA) therapy is leading to higher rates of HCV eradication and is expected to reduce the risk of HCC by preventing, at least in part, liver cirrhosis. Nevertheless, in cirrhotic patients, particularly in those with concurrent pro-carcinogenic co-factors, such as diabetes and/or advanced age, the risk of HCC remains elevated for several years after SVR. This underlines the importance of HCC surveillance even after SVR in cirrhotic patients and highlights the need for early initiation of DAA therapy, before cirrhosis is established[7]. Cabibbo *et al.*[8] published a meta-analysis of the HCV-untreated arms of the studies evaluating the outcomes of patients with early HCC who, after a successful treatment of the tumour, did not receive any antiviral treatment. This study provides a benchmark for indirect future comparisons aimed to determine the actual benefit of HCV eradication by antiviral treatment. They found an extremely variable 2 and 3-year HCC recurrence rate, respectively at 47% and 79.8%, in patients HCV-infected who did not receive antiviral therapy, and this heterogeneity was not completely explained by any single patient or study characteristic.

DAA AND HCC: HIGHER OCCURRENCE/RECURRENCE

In 2014, the introduction of DAAs has revolutionized the standard of care of HCV infection, allowing to reach SVR rates of over 90% in patients with genotype 1. Multiple oral interferon-free HCV regimes are now available and, although there is some evidence of response variability, related to specific patient characteristics and HCV genotypes, the SVR rates are high for all approved DAAs. Due to their high efficacy, tolerability and the relatively short treatment duration, DAAs are now the standard care for patient populations that were historically considered difficult to cure[9], even though data on the long-term outcome of patients with advanced liver disease treated with DAAs are still lacking.

The assumption that HCV eradication would translate into a reduced incidence of newly developed tumours in HCV patients as well as into a reduced HCC recurrence rate, is to be considered in the context of the controversy about a potential association between DAA treatment and an increased HCC risk, overall [Table 1].

In fact, in 2016 a report[10] described a totally unexpected early tumor recurrence in patients with HCV-related HCC undergoing DAA treatment.

In a cohort of patients who achieved a complete HCC radiological response before starting antiviral treatment with DAAs, Reig *et al.*[10] described an HCC recurrence rate of 28% (16 of 58 patients), with a median follow-up of only 6 months, recurrence rate that was extremely higher than expected and previously observed. Furthermore, the pattern of relapse was described as infiltrative or multinodular in 25% cases, this also being an unexpected finding. Even though the authors concluded that their data should only be taken as a "note of caution", and that large-scale studies were necessary to confirm their results, this report raised a debate about the risk of DAA treatment and suggested that a stricter pharmacovigilance action

should be undertaken by all prescribers and regulators involved in this issue. The above-mentioned study also led to the hypothesis that HCV eradication mediated by DAAs may induce a sudden modification in HCV-dependent inflammatory status and immune surveillance, dysregulating the anti-tumor response and boosting the growth of still undetected HCC foci. Recurrence after initial complete response may be explained by the dissemination of cells prior to treatment, and by the development of new oncogenic clones within a cirrhotic liver that has already suffered genetic damage. Immune surveillance plays a major role in regulating survival and growth of metastatic cells; DAA-based antiviral treatment, as a consequence of the inhibition of HCV replication and the abrupt resolution of chronic inflammation, may disrupt cancer immunosurveillance. This may lead to tumor progression.

A similar report on the management of patients with HCC undergoing DAA treatment was elaborated by Conti *et al.*[11]. Their data suggested that DAA-induced resolution of HCV infection did not decrease the occurrence of HCC in the short term and that HCC curative treatments, in patients undergoing antiviral therapy, do not reduce the risk of recurrence. In their study the recurrence rate of patients with a history of previous liver cancer was around 30% (17 of 59 patients) within 24 weeks. In contrast with the study by Reig *et al.*[10], the patients who experienced HCC recurrence were younger and had a more severe liver stiffness. Another study, published by Kozbial *et al.*[12], reported an unexpected high incidence of HCC occurrence and recurrence in patients treated with DAAs. Even though the study included a small number of patients, the authors concluded that decreasing inflammation could have a role in modulating liver regeneration and that the change in the immunological environment could induce the progression of pre-existing pre-cancerous changes[12,13]. The authors also noticed the reduction of miR-22 levels in patients treated with DAAs, which could play a possible role in tumor development, since miR-22 is involved in suppressing the replication of virus-infected cells and controlling carcinogenesis[14].

As suggested by Reig *et al.*[15], tumor dormancy derives from a dynamic equilibrium between cancer cells growth and immune cells infiltration; several conditions and DAA treatment could disturb this equilibrium by causing immunological changes, connected to the fall of the antigenic load due to HCV eradication. This phenomenon was not observed in patients who underwent IFN-based therapy, probably because of the immune-modulatory and anti-proliferative properties of IFN[16]. Moreover, chronic HCV infection activates the most prevalent innate cells in the liver, the NK cells, as well as increases the expression of IFN-stimulated genes, suggesting that infection activates an intrahepatic immune response. In fact, DAA-mediated HCV eradication is characterized by decreased levels of CXCL10 and CXCL11 and normalization of NK-cell phenotype and function, a fact that could explain the association between HCV clearance and loss of intrahepatic immune reactivation[17,18].

Cardoso *et al.*[19] in a study of a cohort of 54 patients successfully treated with IFN-free antiviral therapy, reported an HCC incidence of 7.4% after a median time of 7.6 months (IQR 6.3-10.6 months), in a median follow-up of 12 months (IQR 9.4-12.5 months). The authors, in agreement with Reig *et al.*[15], speculated that an oncogenic effect of the antiviral therapy was highly unlikely, but at the same time, due to the coincidence with viral elimination, the mechanisms responsible could be those previously hypothesized.

A recent report by Abdelaziz *et al.*[20] distinguished *de novo vs.* recurrent HCC following DAA treatment and evaluated their behaviour. No difference was found regarding patient baseline and tumor characteristics (age, gender, hepatic function assessed by Child Pugh Score, performance status, number or size of lesions) or their response to DAAs. On the opposite, a significantly different time before detection of HCC emerged between the two groups. *De novo* lesions developed later than recurrent tumors (14 ± 16.02 *vs.* 6.7 ± 5.1 months, $P = 0.008$) and showed a better response to ablation ($P = 0.03$). The above-mentioned studies represent the current bulk regarding the evidence of DAAs promoting liver carcinogenesis.

DAA AND HCC: JUST FICTION?

On the other hand, other published articles did not confirm the higher occurrence or recurrence of HCC in patients treated with IFN-free, DAA-based therapy. Strong evidence against this assumption was given by three French prospective multicentre studies by the Agency for Research on AIDS and Viral Hepatitis (ANRS in the French acronym) cohorts of DAA-treated HCV-infected patients treated with curative HCC therapies[21]. In detail, the rates of recurrence in the ARNS CO22 HEPATHER cohort (including 189 DAA+ and 78 DAA- patients) were 0.73/100 and 0.66/100 person-months respectively in the DAA+ and the DAA- group. In the ARNS CO12 CirVir cohort, the rates were 1.11/100 in 13 DAA+ and 1.73/100 person-months in 66 DAA-. Finally, the ARNS CO23 CUPILT cohort of HCC liver transplant recipients, successively treated with IFN-free antiviral therapy, showed a recurrence rate of 2% (7/314 patients). Notwithstanding the large number of patients that were analysed in these studies, no increase in the risk of HCC recurrence after antiviral therapy was detected in any of the cohorts. The recurrence rates did not differ between treated and untreated patients. A sharp criticism towards the ANRS study design was made by Kolly and Dufour[22] stating that it artificially decreased the rate of HCC recurrence in untreated patients. The ARNS collaborative group argued, as a defence of the accuracy of the design of the study, that treatment was considered as time-dependent variable and that patients who underwent treatment were considered part of the untreated group until the therapy started[23]. A study in an English cohort, including more than 400 treated patients, supported the French findings. Also, Cheung *et al.*[24], after a follow-up of 12 months, revealed a reduction in HCC rates after HCV eradication in DAA-treated patients. The preliminary data of another prospective observational study of patients with liver cancer and HCV infection treated with DAAs, show no HCC recurrence after curative treatment in a median follow-up of 12 months[25]. Furthermore, the study by Zavaglia *et al.*[26] did not confirm the alarming findings of Reig and Conti: amongst the 31 patients they followed, they only observed 1 case of liver cancer, with a median follow-up of 8 months. The longer interval between complete HCC curative treatment and antiviral therapy (median 19 months in Zavaglia's experience *vs.* 11 months in Reig's study) could partly explain the contrasting results. It appears that, the longer the interval between tumor eradication and antiviral therapy initiation, the lower the risk that residual tumoral cells are still present at the beginning of DAA treatment[26], and this is highly conceivable.

Cabibbo *et al.*[27] in a prospective study of 143 patients with previously successfully treated HCC, then treated with DAAs, showed 6-, 12- and 18-month recurrence rates of 12%, 26% and 29.1% respectively; in this group of patients, the authors found comparable results to those observed in DAA-unexposed patients. Previous history of HCC recurrence (HR: 2.22; 95%CI: 1.02-4.83; P = 0.043) and tumor size (HR: 2.73; 95%CI: 1.23-6.06; P < 0.014) were the two independent risk factors for HCC early recurrence that could be used to stratify the risk of HCC recurrence. A large amount of data was analysed by Waziry *et al.*[28] in a meta-analysis and meta-regression analysis based on 41 studies: no evidence of increased HCC occurrence or recurrence risk after DAA therapy *vs.* INF-based therapy was found. HCV eradication was confirmed to decrease HCC risk in patients who achieved SVR, whereas older age, advanced cirrhosis and worse patient baseline characteristics in DAA-treated population were independent predictors of HCC development and provide an explanation of the apparently higher risk (3.1 *vs.* 1.1/100 per years). Another study was conducted by Ioannou *et al.*[29] on a large cohort of HCV infected cirrhotic patients from the Veterans Affairs national healthcare system, treated with IFN regimen alone, DAA regimen or INF+DAAs, during a 6.1 years mean follow-up. A 71% HCC occurrence risk reduction was associated with DAAs-induced SVR compared to treatment failure, but the reduction was similar, irrespective of how SVR was achieved (DAA-only AHR: 0.29; 95%CI: 0.23-0.37; DAA + INF AHR: 0.48; 95%CI: 0.32-0.73; IFN-only: 0.32; 95%CI: 0.28-0.37). Maan and Feld[30] are also amongst the authors supporting the association between SVR achievement and HCC risk reduction due to the analysis of a retrospective study on cohorts of veterans treated with DAAs. In a study by Kobayashi *et al.*[31], 77 patients treated with DAAs, who achieved SVR, were compared to 528 patients who underwent viral eradication with Peg-IFN/RBV during a median follow-up of 4 years. Amongst DAA-treated patients, 2.6% developed liver cancer, while the 3- and 5-year cumulative HCC development rates were 1.30%

and 3% in the IFN-free treatment group and 1% and 2.2% in the Peg-IFN/RBV group, with no statistically significant differences[31]. A European multicentre study by Kolly *et al.*[32] assessed the HCC recurrence rate after DAA treatment, reported as the cumulative disease-free survival during the follow-up. In 47 patients previously treated for HCC, the time between tumor treatment and the initiation of DAAs was a predictor of recurrence, but whether this effect was due to the anti-viral therapy, or due to foci of HCC which were undetectable before treatment was undefined. Petta *et al.*[33], using the ITA.LI.CA liver cancer collaborative database, demonstrated that the eradication achieved by both IFN-based therapy and DAAs resulted in an increased time before tumour recurrence in patients with HCC curatively treated by radical ablation. Data deriving from their observation showed 16 (28%) and 22 cases (39%) of HCC, after a median follow-up of 18 months in DAA, and 34 months in IFN-based SVR, respectively.

Also, the retrospective large cohort study performed by Kanwal *et al.*[34] on DAA-treated patients from 129 Veterans Health Administration centres confirmed the lack of evidence that DAAs promote HCC and the preventive effect of the HCV eradication on HCC occurrence, with a 76% risk reduction. On the other hand, their analysis confirmed that the HCC risk persists despite SVR in DAA-treated patients, with an annual HCC incidence after HCV eradication with DAAs of 0.90%, compared to 0.3% in IFN-treated patients (as reported by previous studies). It must be said that the treated population has changed since the advent of DAAs, thus giving patients with other independent HCC risk factors, such as advanced cirrhosis, a chance to be treated. The incidence rate was greater in cirrhotic patients, underlying the importance of HCC surveillance in this scenario, as well as the need of not delaying treatment in order to avoid liver deterioration.

A retrospective population-based cohort study using the Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES) investigated whether DAA use was associated with higher rates of incident HCC compared to treatment with IFN-based regimes, the primary outcome being the development of incident HCC cases. A series of 17,836 persons was included, and amongst cirrhotic patients DAA treatment was not associated with higher risk of HCC compared to the IFN-treatment group (HR: 1.07; 95%CI: 0.55-2.08). The risk of incident HCC was higher, among patients with known HCC risk factors including older age (HR, per 10 years increased: 1.76; 95%CI: 1.26-2.16) and AFP > 20 (HR: 4.1; 95%CI: 2.75-6.10), but when an analysis in cirrhotics was performed, there were no differences in HCC-free survival between the DAA-treated and IFN group. According to the authors, this suggests that pre-treatment HCC risk is the factor that determines post-treatment risk. In contrast, untreated cirrhotic patients had a significantly higher incidence rate of HCC compared to both DAA and IFN treated groups (45.31 per 1000 person-years; *P* = 0.03)[35].

Very recently large cohort studies using real-world data demonstrated that DAA-based HCV treatment is not associated with an increased risk of incident liver cancer and suggested that DAA-based HCV treatments are associated with a reduced risk of incident liver cancer, irrespective of co-medication with interferon. Male gender, older age and baseline cirrhosis were the strongest predictors independently associated with subsequent incident liver cancer[36]. It's been demonstrated that reaching SVR allows all-cause mortality reduction, including HCC-related mortality, for all stages of hepatic disease. In advanced liver disease, this was first proven when SVR was reached with IFN-based regimens[37]. In the above mentioned study by Cheung *et al.*[24] on DAA treatment in patients with decompensated hepatic disease, HCC incidence in patients with SVR24 was lower than in those who did not accomplish it (17/317, 5.4% *vs.* 10/89, 11.2%; *P* = 0.049; HR: 0.33; 95%CI: 0.13-0.87). The results were compared to HCC incidence in untreated patients (4.2%). There was no evidence of a significant increase in HCC occurrence in treated patients[24].

Another interesting scenario is liver transplantation, and the clinical impact of viral eradication in patients on waiting list is still poorly evaluated.

Table 1. Current literature about the possible association between antiviral therapy DAAs based and the risk of HCC development

Authors (country)	Study population	Mean FU after DAAs (months)	Occurrence (DAAs)	Occurrence (controls)	Recurrence (DAAs)	Recurrence (controls)	Pos-LT recurrence (DAAs)	Post-LT recurrence (controls)
Reig et al.[10] (Spain)	58 cirrhotic patients with previous HCC (complete radiological response)	5.7	NA	NA	16/58* (28%); 25% were multinodular /infiltrative *Median time interval between HCC complete eradication and the start of therapy was 11.2 months	NA	NA	NA
Conti et al.[11] (Italy)	344 cirrhotic patients: • 59 with history of HCC • 285 without previous history of HCC	6	9/285 (3.2%)	NA	17/59* (28.8%) *Younger age and severe fibrosis associated with recurrence	NA	NA	NA
Kozbial et al.[12] (Austria)	16 patients who developed HCC (3 of them with previous history of HCC but successfully treated and in complete remission for > 3 years; 3 patients were F3, 5 patients relapsed)	NA	NA	NA	NA	Historical group of 94 cirrhotic pts with SVR after with IFN/RBV 10 developed a HCC within a mean follow-up of 7.8 years	NA	NA
Cardoso et al.[19] (Portugal)	54 patients (patients with "non-characterized nodules" and/or a previous diagnosis of HCC were excluded)	12	4/54* (7.4%) *No significant differences in baseline variables that could be associated with an increased HCC risk were found	NA	NA	NA	NA	NA
Yang et al.[38] (USA)	81 patients who underwent LT for HCC: • 18 → pre-LT DAA (3 of them treated with IFN based therapy) • 63 → no pre-LT therapy	NA	NA	NA	NA	NA	5/18#* (27.8%) *Proportion of pta beyond Milan (explant pathology) higher in DAA than controls; no difference in terms of microvascular invasion and HCC differentiation	6/63#* (9.5%) #P = NS

Study	Patients	Follow-up						
Carrat *et al.*[23] (French)	(1) 267 patients with previous history of HCC (HEPATHER cohort): • 189 treated • 78 untreated (2) 79 patients with previous history of HCC (CirVr cohort) • 13 treated • 66 untreated (3) 214 patient who underwent LT for HCC treated (CUPILT cohort)	(1) 20 (2) 59 (3) 70	NA	NA	(1) 24/189 (0.73/100 person-month) (2) 1/13 (1.1/100 person-month)	(1) 16/78 untreated (0.66/100 person-month) (2) 31/66 untreated (1.73/100 person-month)	NA	NA
Cheung *et al.*[24] (UK)	406 cirrhotic patients [29 (7.1%) with baseline HCC] with decompensated cirrhosis (317 achieved SVR 24)	6-15 (range)	15/288 (5.2%)	11/261 (4.2%)	2/18 (11.1%)	0/11 (0%)	NA	NA
Torres *et al.*[25] (USA)	Prospective observational study of 8 patients with HCC (curative treatment#) treated (1 non cirrhotic) #DAA not offered to patients receiving palliative treatment (i.e., TACE)	12 months* *From DAA start	NA	NA	No recurrence	NA	NA	NA
Zavaglia *et al.*[26] (Italy)	31 patients (4 patients underwent LT during FU)	8 months* *From DAA start	NA	NA	1* (3.2%) *Median time interval between HCC complete eradication and the start of therapy was 19.3 months	NA	Not reported	NA
Kobayashi *et al.*[31] (Japan)	SVR + patients *#(retrospective evaluation): • 77 DAA • 528 Peg-IFN/RBV *No previous history of HCC #Fib-4 score > 3.25 in 29.9% and 14.8%, respectively (< 0.001)	48	2 (2.6%) in DAA group 5-year cumulative HCC development rate 3% In high Fib-4 score group 5-year cumulative rate was 9.7%	5-year cumulative HCC development rates 2.2% (*P* = NS) In high Fib-4 group 5-year cumulative rate was 8.4% (*P* = NS)	NA	NA	NA	NA
Petta *et al.*[33] (Italy)	SVR + patients: • 58 DAA • 57 Peg-IFN/RBV	18 (DAA) 34 (Peg-IFN/RBV)	16 (28%)	22 (39%)	NA	NA	NA	NA

Study (Country)	Study design / details	FU						
Li *et al.*[35] (USA)	Retrospective populaton-based cohort study 17,836 patients: IFN 3534 DAA 5834 Untreated 8468 #Fib-4 score > 3.5 in 13.1%, 19.1% and 14.6% respectively *Excluded if baseline or prior HCC		50 (0.86%) 22.8 per 1000 person year for cirrhotic patients (*P* = NS using IFN as control)	436 (5.04%) 45.3 per 1000 person year for cirrhotic patients (*P* = 0.03 using IFN as control)	NA	NA	NA	NA
Kanwal *et al.*[34] (USA)	Retrospective cohort study 22,500 patients DAA (39% diagnosis of cirrhosis, Fib-4 score > 3.25 in 29.7 %) *No previous history of HCC		271 (1.18 %) (3.45% among who did not achieve SVR *vs.* 0.90% who achieved SVR, *P* < 0.0001)	NA	NA	NA	NA	NA
Zanetto *et al.*[41] (Italy)	46 patients who underwent LT for HCC: (1) 23 pre-LT DA (2) 23 no pre-LT therapy	(1) 10 months (2) 7 months	NA	NA	NA	NA	1/8 (12.5%)#	1/12 (8.3%)# #(*P* = NS); no difference in terms of number, TTV of HCC nodules, microvascular invasion and HCC differentiation
Ioannou *et al.*[29] (USA)	62,354 treated from 1999 and 2015: 35,871 (58%) IFN 4535 (7.2%) DAA + IFN 21,948 (35%) DAA 16.8% cirrhotic patients, 4.7% decompensated cirrhosis, 1.1% had undergone LT	1.53 years (180 days - 6.1 years)	445 (2%) 1.32 per 100 patient-year (AHR 1.12) DAA SVR associated with a 71% reduction in HCC risk (AHR 0.29)	DAA + IFN 1.06 per 100 patient-years (AHR 1.04) IFN 0.81 per 100 patient-years (AHR 1)	NA	NA	NA	NA
Cabibbo *et al.*[27] (Italy)	Prospective multicentre study 143 patients with previous HCC (curative treatment) treated with DAA, 76% BCLC stage A when HCC treated 138 (96%) achieved SVR	8.7 (3-19)	NA	NA	29/143 (20.3%): 13 (9.1%) during DAA therapy, 16 (11.2%) after DAA therapy. 62% BCLC A (17% infiltrative pattern) 6-, 12-, 18-month recurrence: 12%, 26.6%, 29.1%	NA	NA	NA

DAAs: direct-acting antivirals; HCC: hepatocellular carcinoma; LT: liver transplantation; FU: follow-up; BCLC: Barcelona Clinic Liver Cancer; SVR: sustained virological response; AHR: adjusted hazard ratio; IFN: interferon; TACE: transarterial chemoembolization; RBV: ribavirin; NA: not available; NS: not significant

A study showed a high risk of HCC recurrence in patients treated with DAAs before liver transplantation (LT) (5 of 18 patients, 28%) compared to untreated (6 of 63 patients, 9.5%). However, the difference did not reach statistical significance because of the small number of patients enrolled[38], a series definitely too limited to provide any information.

Belli *et al.*[39] published data from a European study, investigating the probability of delisting after DAA treatment. In this study the cumulative incidences of inactivation and delisting at 60 weeks were 33% and 19.2% respectively. In another recent study published by Pascasio *et al.*[40], 238 patients treated with DAAs while awaiting LT were enrolled, and 24% of the patients with decompensated cirrhosis were delisted after a median follow-up period of 50 weeks, as a result of clinical improvement, which appeared to remain stable in most patients. Indeed, only 9% of the patients were delisted because of HCC progression and the rate of microvascular invasion was 11%, similar to what reported in previous studies. Although these data do not indicate an increase in HCC progression, the lack of untreated patients as a control group is a limitation. As a consequence, the use of DAA therapy in HCC patients awaiting LT cannot be strongly recommended. As far as SVR is concerned, in the above-mentioned study SVR rates were similar in patients with and without HCC (87% *vs.* 84%, $P = 0,560$), and amongst patients with HCC there were no significant differences regarding tumor characteristics or BCLC staging comparing those with or without SVR.

In a recent retrospective study, conducted at the Padua Liver Transplant Centre, we investigated whether patients, listed for HCC and treated with DAAs, have an increased rate of tumor progression and consequently drop out from waiting list. Two groups (including 23 patients each) were evaluated, who underwent DAA therapy while awaiting LT or not. The two groups did not show any significant difference in terms of dropout rate, during a median follow-up of 10 and 7 months. Interestingly, a significantly lower probability of being transplanted was detected in the group of treated patients in comparison with the untreated, suggesting an improvement of liver function. With regard to post-LT recurrence of HCC, similar rates were found in the two groups (12.5% in DAA-treated *vs.* 8.3% in untreated group), suggesting that the risk of tumor recurrence was not higher in patients treated with DAA pre-LT than in those treated post-LT. Furthermore, liver explant histopathological analysis revealed similar HCC patterns in the 2 groups[41].

DAA AND HCC: HISTOLOGICAL PATTERN

Reig *et al.*[10] in their pivotal study also expressed concern about the histological pattern of HCC recurrence in patients treated with DAA therapy. In agreement with Reig's study, Romano *et al.*[42] demonstrated that about 30% of HCC presented with an infiltrative and/or multifocal pattern in a multi-centre cohort of cirrhotic patients treated with DAAs, even though their data on HCC incidence were in contrast with Reig's results. The more aggressive pattern of HCC was seen somehow more frequently (54.6%) in patients without SVR compared to those with SVR (12.1%) in which the single nodule pattern prevailed (69.7%).

Nakao *et al.*[43] also investigated the pattern of HCC recurrence and *de novo* development, reporting six cases of *de novo* HCC out of 242 patients. All of the patients had been submitted to DAAs treatment, and all showed SVR. In all six cases HCC was pathologically diagnosed, allowing inferences about tumor characteristics and kinetics. All tumours were single nodules, moderately differentiated and rapidly growing, the authors were therefore led to hypothesize that HCC carcinogenesis after DAA therapy occurs in a non-conventional, multi-step manner.

DAA AND HCC: ONLY IMMUNOLOGICAL ISSUE?

It is recognized that the immune system plays a key role in modulating tumour development, but a report by Debes *et al.*[44] attempted to distinguish the immuno-related changes by measuring 22 different soluble immune mediators in patients who developed HCC (both *de novo* and recurrent) after HCV treatment

with DAAs, comparing them to matched controls without HCC. Each marker was measured before and after DAA treatment, and very interestingly 12 of them, including apoptosis markers, cytokines and growth factors, resulted significantly higher before treatment in patients who developed *de novo* HCC, compared to controls. The authors suggested that a different immunologic pattern could be already present in patients who eventually develop HCC, before the immune changes due to DAAs occur. The immune background could therefore be a decisive factor in HCC development. Individuals who develop HCC may express a different pattern of immune mediators, that induces ongoing carcinogenic or pre-carcinogenic activity, prior to the appearing of HCC. In addition, TNF alpha levels remained stable or trended up during the first month of DAA treatment (with viral load being undetectable in serum) in patients who developed HCC, while decreasing in controls. TNF alpha could therefore be directly involved in HCC development even if HCV is absent, or on the other hand its production could be stimulated by the presence of occult tumor foci in the liver. Finally, this study suggested that tumorigenesis occurred with different characteristics in HCC recurrence compared to *de novo* HCC after DAAs, as IL-6 levels, were shown to be increased at the end of therapy in patients with HCC recurrence, while the levels of the cytokine showed a trend toward reduction in patients with *de novo* tumor. Again, these results should be interpreted with caution and additional studies could help to clarify their interpretation.

HCC AND DAA: POSSIBLE ROLE IN RESPONSE TO ANTIVIRAL THERAPY AND NATURAL HISTORY OF DISEASE?

Another matter of debate is whether the presence of HCC can influence the response to HCV therapy with direct-acting antivirals, and what could be the mechanism behind it. According to Prenner *et al.*[45], the presence of active HCC (and not merely a history of tumor) when starting HCV therapy was the strongest predictor of treatment failure, with an eight-fold increased risk of failing treatment at multivariate analysis compared to patients without tumour (OR 8.49; 95%CI: 3.90-18.49; $P < 0.001$). Interestingly, none of the well-known factors correlated with a lower SVR, and not even inadequate treatment regimens could explain the difference between the two groups. A possible explanation could be that HCC may serve as a sanctuary for HCV, where virus particles can evade DAAs, as already known for HBV cccDNA; it is also possible that DAAs may be unequally distributed within fibrotic areas, generated for instance after some loco-regional treatment, radioembolization above all, due to the decreased blood flow.

Very recently, a review by Konjeti and John[46] on DAAs and HCC presence/occurrence suggested deferring IFN-free therapy until complete radiological response to HCC curative treatment. Therefore HCV eradication with DAAs is still recommended in patients with history of treated HCC, until proven otherwise by future studies.

Similar data (and similar explanations) to Prenner *et al.*[45] study was obtained through the analysis of a large cohort of HCC identified by Beste *et al.*[47] in the national Veterans Affairs health care system. This study also suggested that a greater likelihood of SVR after DAA treatment was reached in patients with HCC history undergoing LT. This evidence is not fully explained by clinical reasons.

What is the most effective timing to offer HCV treatment in patients listed for LT, whether it is better to do so before or after LT, still remain open questions. Finally, another matter has been investigated: does SVR really matter in in the progression of liver disease? Nahon *et al.*[48], in a multi-centre French cohort of 1323 Child A patients, mostly treated with IFN-based therapy, reported that viral eradication and achievement of SVR was associated with a significant reduction of HCC incidence (HR: 0.29; 95%CI: 0.19-0.43; $P < 0.001$). They also noticed that SVR was associated with a reduction in both liver- and non-liver-related mortality (HR: 0.27; 95%CI: 0.18-0.42; $P < 0.001$). Petta *et al.*[49] seem to have come to the same conclusions: in an Italian study of 535 HCV cirrhotic patients, there was a reduction in disease progression and liver related mortality with the achievement of SVR. More specifically, the data of this report demonstrated a reduced incidence of

hepatic decompensation and HCC development, with a lower likelihood of liver related death at 10 years, in association with achievement of SVR[49]. Similar findings were reported in the Hepatitis Testers cohort from North America[50]. In the multivariable model, SVR was associated with reduced liver cancer risk (HR: 0.20; 95%CI: 0.13-0.30) in a median follow-up of 5.6 years.

DISCUSSION

The main points of strength of the previously mentioned studies are their prospective design and the large number of patients enrolled and the long follow-up. The largest studies included patients treated with IFN-based regimes and therefore a confirmation with DAA-based treatment only is needed.

Camma *et al.*[51] considered Reig's observations as premature, affirmed that a comparison with untreated controls is mandatory to solve the issue without generating excessive alarm on DAAs; Nault and Colombo[16], at the same time, did not consider the data published solid enough to confirm the increased risk in treated patients, even though they could recommend HCC surveillance after viral eradication; Alberti and Piovesan[52] underlined the great variability in occurrence and in recurrence rates, reflecting the extreme heterogeneity of the different clinical settings and patient cohorts on which studies were based; finally, Blanco and Rivero-Juarez[53] specified that prospective studies targeted on this problem are necessary before even considering a different therapeutic approach to patients with HCV-related liver disease.

Furthermore, the development of an aggressive tumor has been reported in some of patients[42], although the authors cannot exclude that what they observed in these patients merely reflects the natural history of their liver disease. It is important to point out that the current clinical practice does not include IFN-based treatment any more, due to the important improvement in HCV-treatment made by DAAs. As a consequence, to compare DAA treatments with pre-DAA treatments or no treatment is meaningless. Nevertheless, the lack of randomized control trials is an important clinical and methodological issue. In conclusion, the risk reduction in hepatic decompensation as well as in HCC incidence in patients achieving SVR is the only proven evidence. The reports about the increased risk of HCC occurrence/recurrence in DAA treated patients are afflicted by selection and methodologic biases, that weaken the impact of these studies. We strongly believe that is mandatory to treat HCV-infected patients with DAAs but also to maintain an active surveillance for liver cancer as the guidelines suggest; the previously presented data must be considered with caution.

DECLARATIONS

Consent for publication

Not applicable.

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