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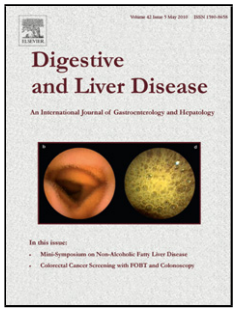

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PII: S1590-8658(17)30163-9
DOI: http://dx.doi.org/doi:10.1016/j.dld.2017.01.159
Reference: YDLD 3362

To appear in: *Digestive and Liver Disease*

Received date: 9-11-2016
Revised date: 11-1-2017
Accepted date: 13-1-2017

Please cite this article as: Russo Francesco Paolo, Bruno Savino, Farinati Fabio.HCV clearance by Direct Antiviral Therapy and occurrence/recurrence of hepatocellular carcinoma: a "true-or-false game".*Digestive and Liver Disease* http://dx.doi.org/10.1016/j.dld.2017.01.159

HCV clearance by Direct Antiviral Therapy and occurrence/recurrence of hepatocellular carcinoma: a "true-or-false game".

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Data on the long-term outcome after antiviral therapy with Peg-Interferon and Ribavirin in patients with hepatitis C infection (HCV) and cirrhosis, who are at increased risk of developing liver decompensation (LD), hepatocellular carcinoma (HCC) and liver related death, showed that HCV eradication reduces both liver-related and non–liver-related mortality (1), thus leading to a life-expectancy similar to that of the general population (2). The clinical benefit of HCV eradication is more significant in patients with compensated cirrhosis and without clinically significant portal hypertension (PH) who do not develop LD and rarely HCC (3).

What above was confirmed in a pooled analysis of 12 studies, reporting a total of 25497 patients, demonstrating that achieving SVR is associated with a reduction in the relative risk for HCC at all stages of liver disease (hazard ratio, 0.24 [95% CI, 0.18 to 0.31]; p=0.001), with approximately 1.5% of the 9185 patients responding to treatment developing HCC, compared with 6.2% of the 16 312 patients who did not respond. As a result, the absolute risk reduction was 4.6% (95% CI, 4.2% to 5.0%) in patients achieving SVR (4).

Nevertheless, the risk of HCC remains elevated for several years after SVR, especially in cirrhotics who present significant co-factors, such as diabetes and/or advanced age and this evidence supports early HCV treatment

before development of cirrhosis and continued HCC surveillance even after SVR in patients who already developed cirrhosis (5).

A useful benchmark for indirect comparisons of the benefit of HCV eradication by antiviral therapy has been recentely provided by Cabibbo et al. The authors just published a meta-analysis of single HCV-untreated arm studies of patients with early HCC who did not receive any adjuvant treatment after successful tumor treatment. The findings were an extremely variable 2-year recurrence rate (47%) and 3-year survival (79.8%), with no single patient or study characteristics fully explaining this heterogeneity. Study design (RCTs), low albumin levels, and follow-up duration showed association with higher likelihood of recurrence, whereas tumor size and AFP levels with a lower survival (6).

Three years ago, the new direct antiviral therapies (DAAs) were approved for HCV treatment and the scenario completely changed. The share of patients in whom eradication is obtained raised to over 90% (7), the limits in the stage of the disease that can be treated disappeared, but solid data on the long-term outcome of cirrhotics treated with these new are lacking.

A totally unexpected, intriguing and somehow hard-to-believe report of an increased incidence of HCC with rapid recurrence after HCV eradication

with DAAs was first presented at the 2016 EASL meeting and then published in the J Hepatol (8). In a cohort of patients who achieved a complete HCC radiological response before starting DAA, Reig et al described a HCC recurrence rate extremely higher than the incidence normally observed in patients with successfully treated liver cancer (16 of 58 patients, 28 %), with tumour recurrence after a median follow up of only 6 months, with an infiltrative or multinodular pattern in 25% of the cases. Dr. Reig and co-workers concluded that their data were to be taken as a “note of caution”, that large scale studies were needed to confirm these preliminary findings and that specific caution was required in advanced age patients. This deflagrating report led to the hypothesis that DAA-mediated HCV eradication could induce sudden changes in HCV-dependent inflammatory status and immune stimulation, with a dysregulation of the anti-tumor response, promoting tumor recurrence. This recurrence could be accelerated by DAA boosting the growth of invisible HCC as a consequence of a failure of immune surveillance, a phenomenon totally unlikely in patients exposed to IFN, probably owing to its discrete immune-modulatory and anti-proliferative properties (9). Indeed, it is well-known that chronic HCV infection activates an intrahepatic immune response, that implies an increased expression of

interferon-stimulated genes and an activation of NK cells, the most prevalent innate immune cells in the liver. Data in the literature indicate that DAA-mediated HCV clearance is associated with loss of intrahepatic immune reactivation, as indicated by decreased levels of CXCL10 and CXCL11 and normalization of NK-cell phenotype and function (10,11).

The paper by Reig was not the only one to suggest a particular attention in the management of patients with HCC undergoing DAA treatment for HCV infection. Conti et al confirmed that DAA-induced resolution of HCV infection does not reduce HCC occurrence in the short term, with a recurrence rate of 29%, despite DAA treatment (12), again within a very limited time span (24 weeks). In this study, in contrast with what reported by Reig et al, patients who experienced HCC recurrence were younger.

In a third series of patients, Kozbial et al confirmed these observations, reporting again an unexpectedly high incidence of both HCC occurrence and recurrence after DAAs. Also this study reported on a very small series of patients but the authors suggested that curing inflammation could have a role in an up-modulation of liver regeneration and that the changed immunologic environment could lead to a progression of precancerous lesions into malignant cell clones (13, 14). Finally, the authors pointed out a possible role of miR-122, that plays a central role in suppressing viral

replication and controlling hepatocarcinogenesis, whose levels decreased in patients on IFN-free DAA therapy (15).

Furthermore, in a cohort of patients treated with DAA for 24 weeks, after a median follow-up of 12 months (IQR 9.4– 12.5 months), 7.4% were diagnosed with HCC after a median time of 7.6 months (IQR 6.3–10.6 months). The authors agreed with Reig et al that a direct oncogenic effect of the antivirals was highly unlikely, but due to the coincidence with viral clearance the responsible mechanisms were probably those previously hypothesized (16).

Also, in the transplant setting, a small group of patients who received pre-Liver Transplant DAA treatment showed a trend towards a high risk of HCC recurrence (5/18, 28%) compared to the risk in untreated patients (6/63, 9.5%). However the figure did not reach statistical significance due to the small sample size (17).

This is, at present, the evidence suggesting an impact of DAA treatment in promoting liver carcinogenesis.

On the other hand, several papers were published that did not confirm this higher occurrence/recurrence of HCC in DDA treated patients. Probably the strongest evidence against this hypothesis derives from data of three French prospective multicentre ANRS cohorts of DAA-treated

patients who underwent curative HCC therapies (18). In none of the three cohorts was an increased risk of HCC recurrence after DAA treatment observed and the rates of recurrence were similar in treated and untreated patients or not different from what expected. The rates were:

- 0.73/100 in DAA+ and 0.66/100 person-months in DAA- in the ANRS CO22 HEPATHER cohort which included 189 DAA+ and 78 DAA- patients;
- 1.11/100 in 13 DAA+ and 1.73/100 person-months in 66 DAA- in the ANRS CO12 CirVir cohort;
- 7 among 314 (2%) HCC liver transplant recipients, subsequently treated with DAA in the ANRS CO23 CUPILT Cohort.

A debate raised with respect to the ANSR data. Kolly and Dufour (19) fiercely criticised the study design, stating that it artificially decrease the rate of HCC recurrence in patients not receiving DAA therapy.

The answer of the ANRS collaborative group (20) was that the design of the study was correct, with treatment as time-dependent variable, and patients receiving treatment considered in the untreated group until the start of treatment.

To support the French findings, data on a 12 months' follow-up after DAA treatment coming from a large English cohort (21) including more than 400 treated patients indicated a reduction in liver cancer rates from 4% in

261 untreated patients over 6 months to 1.9% over 9 months after achieving viral clearance in successfully treated patients.

The above findings reassured that HCC in treated patients did not occur and same feeling provided the preliminary results of a prospective observational study of HCV-infected patients with HCC given DAAs with no HCC recurrence following curative treatment, over a median follow-up period of 12 months (22).

Zavaglia et al., as well, did not confirm findings of Reig's and Conti's, since they observed only 1 case of HCC recurrence in their series of 31 consecutive patients who were followed up for a median of 8 months. The authors suggested that their longer interval between complete tumor eradication and antiviral therapy (median 19 months in their series versus 11 months in Reig's study) could explain, at least in part, the contrasting results. In fact, the longer the interval, the lower the risk that residual tumour tissue is present at the start of DAA therapy (23).

Kobayashi et al also retrospectively evaluated patients who achieved SVR by DAA interferon-free regimens (n = 77) and by Peg-IFN/RBV (n = 528). During a median follow-up period of 4 years, two (2.6%) of DAA-treated patients developed HCC. The 3- and 5-year cumulative HCC development

rates were 1.30% and 3 %, respectively, in the DAA group, and 1 % and 2.2 % in the Peg-IFN/RBV group (p not significant) (24).

Finally, the experience deriving from the ITA.LI.CA liver cancer collaborative group, recently summarized by Petta and co-workers (25) demonstrated that both IFN-based and IFN-free HCV eradication results in increased time to tumour recurrence in patients with HCC radically treated by either tumour resection or radical ablation, with no significant difference between the 2 regimens. After a median follow-up of 18 months in IFN-free and 34 in IFN-based eradication 16 (28%) and 22 cases (39%) of HCC were observed, respectively.

Another interesting issue was raised by Reig's report regarding the pattern of tumor recurrence in DAA treated patients. Romano et al. (26) in a large multi-centre cohort of cirrhotics in Northern Italy, treated with oral DAAs (patients with a past history of HCC were excluded), also showed that, even though the incidence of HCC was not higher than expected, the majority of liver cancer cases (54%) presented with an infiltrative and multifocal pattern. Again, caution is needed and additional information will be highly relevant to the interpretation of the above results.

Last but not least, does SVR really matter in the progression of liver disease? The answer seems to be affirmative, since Nahon et al. (27) in a

multi-centre French cohort of 1323 Child A patients with no previous history of LD, mainly treated with IFN-based regimens, reported that SVR achievement was associated with a significant reduction of HCC incidence (HR: 0.29; 95% CI: 0.19-0.43; p< .001) and of overall mortality (HR, 0.27; 95% CI, 0.18-0.42; P < .001) from both liver- and non-liver-related causes.

On the same line Petta et al. (28) recently published a study including an Italian cohort of 535 HCV cirrhotic patients with or without oesophageal varices (OVs) at the start of IFN-based antiviral treatment. Once again, the achievement of SVR was associated with reduced incidence of hepatic decompensation and HCC development with a lower likelihood of liver-related death at 10 years, clearly confirming a reduced disease progression and liver-related mortality.

Similar findings have been recently reported also in the Hepatitis Testers cohort from North America (29). Patients were followed for a median of 5.6 years and not surprisingly, in the multivariable model, SVR was associated with reduced HCC risk (HR=0.20, 95%CI: 0.13 - 0.30).

The prospective setting as well as the large number of patients and the long follow-up is the main points of strength of the studies above mentioned. Most of the patients included in the largest studies have been

treated with IFN-based regimens, and obviously this need confirmation in the DAA era.

Summarizing the available data with a rough and unrefined approach, far from being even similar to a metanalysis, and comparing the total number of the patients who were included in the papers reporting a high risk of early recurrence or occurrence of HCC versus the number of those included in the series in which such a risk was not confirmed, the number of the latter group clearly outweighed that of the former.

A number of Commentaries are also appeared on the point, among which those by:

- Cammà, whose conclusions were that it is premature to raise a red flag on DAAs based on Reig's observations and that a sound comparison with untreated controls will definitely solve the issue without generating undue alarms (30);
- Nault & Colombo, who did not consider the evidence published so far sound enough to confirm the increased risk of recurrence in treated patients, while they indicate the opportunity for surveillance for HCC even after HCV eradication (9);
- Blanco, whose indications were that prospective studies, aimed at specifically addressing this problem, are necessary before we could even

consider changes in our current therapeutic approach to patients with HCV-related chronic liver damage (31).

Remarkably, a very important clinical and methodological issue is the lack of randomized control trials in the setting of HCC recurrence after DAA therapy.

In essence, we agree with these commentaries and we confirm that also in our opinion the evidence of an increased risk of HCC recurrence/ occurrence following DAA treatment is still weak and that large prospective studies are mandatory to disentangle the biases, which afflict the quoted studies, and to lead to a full understanding of this phenomenon.

So far it has been clearly demonstrated that SVR in cirrhotic patients leads to a reduction in decompensation risk and reduces the risk of HCC occurrence. Few, sparse and conflicting data exist about the pattern of HCC recurrence/occurrence under DAA therapy. Thus, since with these data caution is desiderable, the importance of therapy must not be questioned.

Conflict of Interest:
Russo F.P.: Research grant from Abbvie and BMS, lecturing fess, advisory boards for Abbvie, Gilead Sciences, Biotest, BMS, Janssen Cilag;

Bruno S.: Advisory board MSD, AbbVie, speaker bureau MSD, speaker AbbVie, BMS, Gilead Sciences, Janssen, MSD.

Farnati F.: no conflict of interest

Financial disclosure:

All authors declare they have nothing to declare with respect to the Editorial.

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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 M and Marino Z (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 F (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 K (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 H (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 JD (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	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
Pol S, ANRS collaborative group (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 MC, HCV research UK (United Kingdom)	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 HA (USA)	Prospective observational study of 8 patients with HCC (curative treatment#) treated (1 non cirrhotic)	12 months * * from DAA start	NA	NA	No recurrence	NA	NA	NA

	# DAA not offered to patients receiving palliative treatment (i.e.: TACE)							
Zavaglia C (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 (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 S, I.T.A.L.I.C.A. working group (Italy)	SVR + patients: • 58 DAA • 57 Peg-IFN/RBV	18 (DAA) 34 (Peg-IFN/RBV)	16 (28%)	22 (39%)	NA	NA	NA	NA

Legend: HCC: hepatocellular carcinoma; DAAs: direct antiviral agents; FU: follow-up; Peg-IFN/RBB: Peg-Interferon/ribavirin; SVR: sustained virological response; NA: not available; LT: liver transplantation.