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Review

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Direct antiviral therapy for hepatitis C and hepatocellular carcinoma: facing the conundrum

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Abstract

Direct antiviral therapy has dramatically changed our possibility to eradicate hepatitis C virus (HCV) infection in all stages of chronic liver disease, with sustained virological response rates well above 90%. HCV eradication should lead to a better prognosis even after cirrhosis has established, including a reduced risk of developing hepatocellular carcinoma (HCC). Unfortunately, during the last two years different reports have raised the concern about a possible increased risk of developing HCC in cirrhotic patients treated with direct antivirals. In this review, we have evaluated the principal published data and have reached a few conclusions: (1) direct antiviral therapy does not seem to increase the cumulative annual rate of HCC *de novo* occurrence or recurrence; (2) direct antiviral therapy seems to accelerate the development of HCC, soon after the end of treatment, in those patients at higher risk of HCC occurrence or recurrence; and (3) preliminary reports seem to indicate that HCC developed after direct antiviral therapy has more aggressive features. These findings clearly indicate the need for aggressive and close monitoring of cirrhotic patients during and after antiviral treatment, to detect and treat HCC at their earliest occurrence.

Keywords: Direct-acting antivirals, hepatocellular carcinoma, liver cirrhosis, risk, hepatitis C

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most frequent form of cancer worldwide, and it holds the second place in malignancy-related mortality[1,2]. Incidence and death rates of HCC are steadily rising in most parts of the world (about 2%-3% per year).

Chronic hepatitis C is a necro-inflammatory process of the liver, due to hepatitis C virus (HCV) infection, that lasts lifelong and progresses to cirrhosis in about 20% of cases[3]. Even if liver cirrhosis *per se* is not a

premalignant lesion, it represents a premalignant condition since almost 90% of HCV-related HCC cases emerge after cirrhosis becomes established. The annual occurrence rate of HCC has been estimated to be around 3% in HCV-related cirrhosis[4,5]. Surgical resection, radiofrequency ablation and transarterial chemoembolization allow effective treatment of single and small HCC in a significant proportion of patients with compensated liver disease, but recurrence is common, affecting about 35% of treated patients after 2 years[6,7].

The aim of this review was to evaluate the effect of antiviral therapy on the *de novo* occurrence and recurrence of HCC in patients with chronic hepatitis C. We searched all available publications regarding "hepatitis C", "HCC", "antiviral therapy", "interferon-free", "DAA", "occurrence", "recurrence" and focused our review mainly on the data reported in high-quality full-text format.

EFFECT OF INTERFERON-BASED ANTIVIRAL THERAPY ON THE DEVELOPMENT OF HCC

Until 2011, peg-interferon alfa plus ribavirin combination was the only available therapy for chronic hepatitis C. This treatment had only 40%-50% probability of curing HCV infection, and the significant side effects contraindicated its use in a significant proportion of patients. Despite these limitations, many patients with compensated liver cirrhosis had been treated during the last decade, and the effect of treatment on the development of HCC has been evaluated. In summary, achieving sustained virological response (SVR) was associated with a reduced risk of developing HCC, in comparison with patients who did not obtain an SVR after antiviral therapy[8-10]. Despite these positive results, it remains not clear whether SVR was independently associated with the reduced risk of developing HCC. In fact, a different explanation could be that SVR occurred in those patients with a lower spontaneous probability of developing HCC, without altering the cumulative risk of HCC in the entire population of cirrhotic patients. Also, even in patients who obtain SVR, a residual annual rate of HCC is still present, as high as 2% in different groups of patients.

THE ADVENT OF DIRECT-ACTING ANTIVIRALS AGAINST HCV

Since 2013, the therapy of hepatitis C has dramatically changed. Direct-acting antivirals (DAA) are new oral drugs, with potent antiviral activity against HCV infection, highly efficacious, relatively safe and well tolerated, that can be used in all categories of patients with chronic HCV infection, including those with more advanced and even complicated liver disease[11]. This has allowed treatment of a huge cohort of patients with liver cirrhosis, obtaining the eradication of HCV infection in the vast majority of them. Resolution of HCV infection in these patients leads great expectations about the possibility of preventing the most serious complications of liver cirrhosis, including the development of HCC. In the following paragraphs, we try to summarize the best existing evidence regarding the effects of DAA-induced HCV eradication on the development of HCC in patients with compensated liver cirrhosis.

HCC DEVELOPMENT AFTER DAA THERAPY

The story learned from the interferon era teaches us that eradication of HCV infection is not sufficient *per se* to prevent HCC development after cirrhosis has been established. Due to the possibility of treating patients with more advanced liver disease, it is not surprising to expect that a few of them may develop HCC despite HCV eradication. This topic became immediately hot after the simultaneous publication of two papers from Spain and Italy suggesting a possible increased incidence of HCC after successful DAA treatment[12,13]. Since those publications, more than 100 papers, letters or communications have been published addressing the problem, without conclusive results. Most of the debate derives from the heterogeneity of the different studied population, the inclusion and exclusion criteria, the time points used to analyse the incidence rates, the length of follow-up, and finally the radiologic methods used for the diagnosis of HCC.

Regardless of these discrepancies, it is possible to review the published results to draw some conclusions, but a few statements need to be addressed at first: (1) the concept of incidence; (2) the characteristics of the study population; (3) the starting point and the ending point of the observation period; and (4) the distribution of events during the follow-up.

Incidence is a measure of the probability of occurrence of a given condition in a population within a specified period. The incidence rate is the number of new cases per population at risk in a given time period. From this concept derives that to analyse the incidence rate of HCC after DAA therapy it is fundamental to define both the exact starting point and the exact ending point of the observation period. Only if these time points are comparable, different study results can be compared.

The study population should be at risk of developing the medical condition. Therefore, the risk should be comparable among different study groups before performing any comparison. Since in HCV-related liver disease HCC occurs almost exclusively in patients with liver cirrhosis, the population at risk should include only patients with advanced liver fibrosis (F4 according to the METAVIR classification).

In analysing the incidence rate of HCC after DAA therapy, we must distinguish between analysing the new *de novo* occurrence of HCC and the recurrence of a new HCC in patients with prior history of successfully treated HCC. In the former situation, the starting point should be the end of DAA therapy, in the latter, we must distinguish between considering as a starting point the time of the previous HCC treatment or the end of DAA treatment. In all cases, the ending point should be defined after DAA therapy end, and the interval from the starting point must be clearly assessed.

Another important point is the distribution of events (HCC) during the follow-up. It is known that during the natural history of liver cirrhosis the development of *de novo* incident HCC is not clustered around any specific time point[12]. Similarly, HCC recurrence is generally not clustered around specific time points, even if recurrence rate is higher during the first two years after curative treatment of the neoplastic nodule[6]. For this reason, the median interval between DAA therapy and HCC diagnosis needs to be analysed to assess the latency period between exposure to DAA therapy and HCC development.

WHAT PUBLISHED STUDIES TELL US

In Table 1, we have summarized the results of the principal studies addressing the *de novo* occurrence and/or recurrence of HCC in HCV-infected patients, with compensated liver cirrhosis, who have been treated with DAA therapy. Due to the heterogeneity of the study populations and the different observation periods, any formal meta-analysis seems of limited utility to draw any sound conclusion. It seems more important to note some common and peculiar aspects of the results.

At first, we must differentiate between the *de novo* occurrence of new HCC in cirrhotic patients without prior history of HCC and recurrence of HCC in patients with previously treated HCC. In studies analysing the former group of patients, the observation period after DAA therapy ranged a median of 6 to 14 months, indicating a relatively short follow-up. Despite this short observation period, *de novo* HCC occurred in 1.5% to 3.9% of patients. If we consider an expected annual rate of 2% to 3% in these subjects, we can conclude that HCC occurrence is certainly not reduced after DAA treatment. On the other hand, we have not strong elements to assume that the occurrence rate is increased, without a control group. Therefore, the argument of the incidence rate of new HCC after DAA therapy remains unsettled without a definite conclusion. In any case, a real increased annual incidence rate of HCC does not seem to happen after DAA treatment.

More intriguing data come from the studies on the recurrence of HCC after DAA treatment. The analysis of the recurrence rate must take into account the interval since previous HCC treatment, due to the higher

Table 1. Principal studies reporting detailed data on the occurrence and/or recurrence of HCC after DAA therapy in patients with liver cirrhosis

References	Prior history of HCC	No. of patients	Months between HCC treatment and DAA start (median)	Months of follow-up since DAA therapy (median)	HCC cases, *n* (%)	Months between DAA therapy and HCC (median)
De novo HCC occurrence						
Conti *et al*.[14] (2016)	No	285	NA	6	9 (3.2)	NR
Renzulli *et al*.[15] (2017)	No	285	NA	14.1	11 (3.9)	2.7
Kanwal *et al*.[16] (2017)	No	6690	NA	9	172 (2.6)	5.6
Bielen *et al*.[17] (2017)	No	273	NA	6	4 (1.5)	NR
HCC recurrence						
Conti *et al*.[14] (2016)	Yes	59	12.5	6	17 (28.8)	NR
Kolly *et al*.[18] (2017)	Yes	47	21.5	9.6	19 (40.4)	NR
Reig *et al*.[13] (2016)	Yes	58	11.2	5.7	16 (27.6)	3.5
Renzulli *et al*.[15] (2017)	Yes	59	12.5	14.1	18 (30.5)	2.8
Bielen *et al*.[17] (2017)	Yes	29	12	6	5 (17.2)	NR
ANRS cohorts[19] (2016)	Yes	152	22.8	20.2	24 (15.8)	NR

HCC: hepatocellular carcinoma; DAA: direct-acting antiviral; NA: not applicable; NR: not reported

HCC recurrence rate during the first 2 years after HCC therapy. The interval since previous HCC treatment ranged from 11 to 22 months. On the other hand, the post-DAA follow up period ranged from 6 to 20 months. During this observation period, the recurrence rate was in the range from 16% to 40%. Due to the relatively short post-DAA follow-up and the relatively long pre-DAA interval since previous HCC treatment, the recurrence HCC rate does not seem negligible at all. Even in this setting, we can conclude that DAA treatment does not reduce HCC recurrence. Again, we have not strong elements to assume that the recurrence rate is increased, without a control group. Therefore, also the argument of HCC recurrence rate after DAA therapy remains unsettled without a definite conclusion.

A striking finding seems to emerge in both settings: the short median latency period between the exposure to DAA and the diagnosis of HCC. This latency period was very short both in the HCC occurrence and in the HCC recurrence cases: from a minimum of 2.7 months to a maximum of 5.6 months. As stated in the methodology of the studies, all patients had no evidence of HCC when starting DAA treatment. Why HCC developed after such a short latency period represents an important question. There is no reason to explain the clustering of HCC development soon after the end of DAA treatment in the natural history of the disease. Different hypotheses have been postulated to support rapid development of HCC after DAA therapy. They are mainly based on the possible dysregulation of the anti-tumor response, after the brutal decrease of HCV viral load induced by DAA, and/or the perturbation of the immune surveillance, caused by a swift clearance of HCV[20,21]. Despite the absence of conclusive biological explanations, these data clearly indicate the need for close imaging evaluations to detect early HCC development after DAA therapy in cirrhotic patients.

THE CHARACTERISTICS OF HCC DEVELOPED AFTER DAA THERAPY

In addition to the accelerated development of HCC after DAA therapy, additional alarming data have been published on the characteristics of the neoplastic nodules. Two preliminary reports suggested that after DAA therapy HCC may present aggressive macroscopic patterns[22,23]. This aspect has been recently addressed by a full paper published in *European Radiology*[15]. The authors compared the imaging features of HCC nodules developed after DAA therapy to those not occurred after DAA, in the same population. Surprisingly, despite being similar in number and size, neoplastic nodules developed after DAA treatment showed imaging features of microvascular invasion in the majority of cases. Microvascular invasion is a well-known predictor of recurrence and poor overall survival in HCC, and a major risk factor for early HCC recurrence after curative treatment. Additional recent data suggest that HCC occurring after interferon-free treatment show a rapidly growing pattern and moderately differentiated pathologic characteristics[24]. For these reasons, HCC developed after DAA treatment seems to have a more aggressive pattern, predictive of more severe clinical

outcomes. Even if the clinical significance of these findings needs to be confirmed in additional prospective studies, these data corroborate the hypothesis of a different biologic pathway in the neoplastic process leading to HCC after DAA treatment.

CONCLUSIONS

In this review, we have analysed the published data on the risk of developing HCC after DAA therapy. Even if definite conclusions cannot be probably drawn, there is sufficient evidence to summarize the most important findings: (1) direct antiviral therapy does not seem to increase the cumulative annual rate of HCC *de novo* occurrence or recurrence; (2) direct antiviral therapy seems to accelerate the development of HCC, soon after the end of treatment, in those patients at higher risk of HCC occurrence or recurrence; and (3) preliminary reports seem to indicate that HCC developed after direct antiviral therapy has more aggressive features. These findings clearly indicate the need for aggressive and close monitoring of cirrhotic patients during and after antiviral treatment, to detect and treat HCC at their earliest occurrence.

DECLARATIONS

Authors' contributions

Both authors equally contributed to ideation and conduction of the review.

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Conflicts of interest

There are no conflicts of interest.

Patient consent

Not applicable.

Ethics approval

Not applicable.

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