Editorial

The unexpected high risk of occurrence or recurrence of hepatocellular carcinoma after successful antiviral therapy with interferon-free direct-acting antivirals

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Chronic hepatitis C (CHC) infection is one of the major etiologies of hepatocellular carcinoma (HCC). In the previous era of interferon-based therapy, successful viral eradication has greatly reduced the risk of disease progression and HCC occurrence (1-3). Around three quarters of HCC events may be prevented at all stages of liver fibrosis (1,4,5), even among patients with compensated liver cirrhosis (6). On the hand, the effect of interferon-based antiviral therapy in tertiary prevention of HCC recurrence is much more controversial (7-11), which may attribute to heterogeneous patient characteristics and study designs.

The innovation of direct antiviral agents (DAAs) has drastically improved the treatment efficacy with a sustained virological response (SVR) rate >90% being achieved. Viral eradication by interferon-based therapy has proved to promote fibrosis regression. Recently, It has been suggested that the application of DAA may also improve liver stiffness after short term observation (12). From the pathophysiological viewpoint of liver fibrosis, HCV eradication by means of DAA has also shown to reduce hepatic venous pressure gradient in cirrhotic patients with portal hypertension (13). Before the long-term survival benefit of DAAs could be proved, the hot issue now is its impact on HCC occurrence among CHC patients or recurrence after curative HCC treatment.

HCC occurrence among patients without previous HCC

Given that the high potency and potential fibrosis regression that DAA treatment provides, one may take HCC risk reduction by DAA for granted. Unfortunately, several recent reports did not demonstrate the expected outcome of HCC risk reduction after successful DAA therapy. A study in Italy observed that HCC occurred in 9 of 285 (3.16%) cirrhotic patients (mainly compensated) without previous HCC after DAA, despite of high SVR rate of >90% (14). Another study in England also reported a cohort of 406 decompensated cirrhotic HCV patients with an SVR rate of 78% by DAA. Although there was a reduction in incidence of hepatic decompensation among DAA-treated compared to untreated historic controls, the incidence of HCC occurrence was similar between the two groups (2.5% in months 6–15 and 4% in months 0–6 for treated patients versus 4% in untreated patients) (15).

The discrepancy of risk reduction after successful antiviral therapy between interferon-based and interferon-free DAA therapies might result from the different characteristics between the antivirals themselves or diversity of the patients enrolled. Unlike interferon, lacking immune modulation and antineoplastic effect of DAA make the

issue to be elusive. Hepatic 186-gene signature has been associated with the development of HCC (16). Reversal of the signature genes after antiviral therapy might reduce the risk of HCC. Whether there exists difference in reversing the signature genes between interferon-containing and interferon free antiviral therapies needs to be explored. The most solid evidence may come from the comparison of the HCC incidence by using DAA with untreated cohort. Since it is unethical to create such a prospective study, most studies used historical untreated cohorts to answer the question. Attention should be paid due to unequal disease severities between groups. Alternatively, one may choose persistent HCV viremic patients who failed to prior interferon-based therapy as controls. It is noteworthy that it is unclear to what extend do transient application of interferon affects oncogenesis. For example, even among patients who failed interferon-based therapy, it has been suggested that the relapsers have lower risk of HCC development than non-responders (17). Similarly, the "interferon-difficult-to-treat" patients are prone to have more severe liver disease. Judging the HCC risk with DAA-treated patients should be weighed by adjusting potential confounders if the studies are to be conducted. Patients allocated to DAA may have more deteriorated liver function reserve with more advanced liver diseases that are contraindicated to interferon therapy. It may cause a higher potential of HCC occurrence in the DAA patient group. Disease severity has been always most important factors associated with HCC risk whatever among interferon-based therapy (18) or interferon-free DAA therapy (14). Taken collectively, it seems that direct comparison of HCC incidence of the SVR patients treated with DAA versus interferon will tell the truth. Until now, there is no data reported by such case-control studies. Noteworthy, it is not totally fair to compare the HCC risk between patients with interferon-based and interferon-free DAA therapy. Since all oral interferon-free DAA has only evolved for 3 years. Whether the incidence of HCC truly decreases and whether patients could benefit as much as interferon therapy do await further studies with well-controlled design and longer follow-up period.

HCC recurrence among patients with previous HCC post curative therapy (*Table 1*)

Compared with hepatitis B virus related HCC, HCV induced HCC may recur more frequently after surgical resection (21). It has been suggested that the recurrence rate was approximately 20% 1 year after surgical resection or radiofrequency ablation of HCC (22), and up to half of HCC may recur within 3 years of curative cancer treatment (21). The recurrence takes place by either intrahepatic micro-metastasis or subsequent *de novo* development. The discussion regarding the beneficial effect of antiviral treatment would be more complex in HCC recurrence than in HCC occurrence. Take interferon-based therapy for instance, not all studies were in agreement with the role of HCV eradication in tertiary prevention of HCC (9-11). A major issue recently is that will DAA not just have no beneficial effect, but instead do harm for HCC recurrence (14,19). The rationale may be based on the immune dysregulation during DAA therapy (23-25) that in turns promotes the reactivation of potential tumor clones.

It is imperative that mistaken definition of cured HCC due to incomplete treatment may mask the effect of antiviral treatment. HCC recurrence within 1–2 years primary cancer removal may be viewed as incomplete treatment. No matter interferon or DAA is applied, studies exploring this issue should clarify two points: how long the observation period before/after antiviral treatment is and how long the follow-up period is. Reig *et al*. (19) has reported a high percentage of 27.6% HCC recurrence rate 6 months after DAA. However, the median disease free time from initiating DAA treatment was 11.2 months. And 7 (43.8%) of the recurrent HCC happened <4 months between HCC treatment and last assessment of complete response. Similarly, Conti *et al*. (14) have noted an identical percentage of 28.8% recurrence rate sooner after DAA. The median observation period before DAA was 446 (range, 50–1,301) days in HCC patients. However, 35% and 73% of the recurrent HCC happened within 1 and 2 years after primitive HCC treatment, respectively. Both studies had short follow-up period after antiviral therapy. Given that we are talking about the risk of HCC, the comparison could only count on incidence rather than the percentage of HCC, which was lacking in both studies. Actually, another study (20) has recently shown that the incidence of HCC recurrence did not differ from that of untreated control after a median follow-up period of 20.2 months. The recurrent rate did not differ during the first 3 months of treatment or thereafter (P=0.18). The incidence rate was 0.73/100 person-months, which was not far from to the observation by Huang *et al*. (10) who used peginterferon/ribavirin combination therapy.

It takes more than one decade for the hepatologists to prove the benefits of interferon-based therapy toward HCV

Table 1 Summary of reports on HCC recurrence after antiviral therapy for HCV-related HCC post curative therapy

Treatment	Fibrotic stage	Disease free time to initiating treatment	Excluding HCC occurring time after treatment	Follow-up period after treatment	HCC (%)	HCC incidence	Note	References
IFN-based therapy	N/A	>3 months could be enrolled	No	2.01±1.67 years	69/282 (24.5)	Cumulative incidence: 16.2%, 41.8%, and 52.1% in 1, 3, and 5 years respectively	>16 weeks treatment course was viewed as benefit from antiviral treatment	Hsu *et al*. (7)
	F3–4: 37.5%	>3 months could be enrolled	Recurrence during treatment period was excluded	Median 52.7 (3.9–121.5) months	16/56 (28.6)	0.43/100 person-month	Among the SVR patients, 50% of the HCC patients had their recurrence within 6 months after completion of therapy	Huang *et al*. (10)
DAA	100% liver cirrhosis, child A–B	Median 446 (range, 50–1,301) days in HCC patients	No	24 weeks	17/59 (28.8)	N/A	35% and 73% of the recurrent HCC happened within 1 and 2 years after primitive HCC treatment, respectively	Conti *et al*. (14)
	91% child A cirrhosis	Median 11.2 (P25–75, 3.6–23.2) months	No	Median 5.6 (0.4–14.6) months	16/58 (27.6)	N/A	7 (43.8%) of the recurrent HCC happened <4 months between HCC treatment and last assessment of complete response	Reig *et al*. (19)
	80% liver cirrhosis	Median 1.9 (IQR, 0.6–4.5) years	No	Median 20.2 months	24/189 (12.7)	0.73/100 versus 0.66/100 person-month for DAA-treated and untreated patients, respectively	64% of the treated patients had > 1 year of disease free before inclusion. The recurrent rate did not differ during the first 3 months of treatment or thereafter (P=0.18). HCC incidence did not differ from that of untreated controls (P=0.8)	ANRS CO22 HEPATHER cohort (20)
	100% liver cirrhosis	N/A	The only one HCC recurrence after 37.1 months	90 treated person-month	1/13 (7.7)	1.11/100 versus 1.73/100 person-month for DAA-treated and untreated patients, respectively	HCC incidence did not differ from that of untreated controls (P=0.38)	ANRS CO12 CirVir cohort (20)

IQR, interquartile range; HCC, hepatocellular carcinoma; DAA, direct antiviral agent; SVR, sustained virological response; N/A, not available.

related liver and non-liver related long-term outcome. The innovation of DAA makes the elimination of HCV no longer a dream. We now have confidence of curing patients by using the very high potent weapon. The puzzle regarding liver fibrosis regression is on the way of completeness. Time is the best medicine and it would tell whether it decreases HCC occurrence, recurrence and patient survival in the near future.

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