

Impact of direct-acting antiviral agents on the risk for hepatocellular carcinoma

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Liver cancer stands now as the second leading cause of cancer-related death in men and the fifth in women. In 2015 there were 854,000 incident cases of liver cancer, primarily hepatocellular carcinoma (HCC) making it the 6th leading cause of cancer worldwide (1). Most HCC occur in chronic hepatitis or cirrhosis, and the major risk factors include hepatitis B virus and hepatitis C virus (HCV) infections. HCV is responsible for nearly 366,000 deaths annually and one-quarter of all cases of HCC and cirrhosis worldwide (2). The cumulative incidence of HCC in untreated cirrhotic patients with HCV infection has been estimated in 3–5% per year. Viral eradication is associated with a reduction in fibrosis progression and an improvement in clinical outcomes. It is well known that sustained virological response (SVR) following interferon (INF) therapy was associated with a significant reduction in *de novo* HCC occurrence. In a previous retrospective large cohort study including 33,005 HCV-infected patients (3), El-Serag *et al.* reported an overall incidence rate of 0.33% per year among 10,817 patients with SVR after INF regimen. However INF therapy was highly restricted to patients with compensated liver disease due to safety concerns, and HCC still occurred more often in patients with advanced fibrosis. The rapid development of the direct-acting antiviral (DAA) agents and their widespread use in the past four years have revolutionized HCV treatment with a cure rates beyond 90–95% and an excellent safety profile, even in patients with advanced liver disease (4,5). Whether DAAs combination

induce a decrease of HCC occurrence comparable to IFN-based therapies have been questionable during the last two years after the report of retrospective small cohort suggesting an increase occurrence of either *de novo* HCC or recurrence of HCC after cure, following successful DAAs treatment (6-10).

DAA have extensively been used in a broader spectrum of HCV-infected patients and the global characteristics of the DAA-treated population are significantly different from INF-patients, including a higher proportion of patients with more advanced liver disease or other HCC risk factors, as reported in Kanwal *et al.* study and in the French Hepather cohort (11,12). Several retrospective uncontrolled studies in 2016 reported an increased incidence of *de novo* HCC among patients treated with DAA (6-8). In contrast, some other retrospective and prospective cohort studies suggested no significant difference in liver cancer occurrence following DAA therapy. The results from the French prospective cohort (Hepather) demonstrated no increase in HCC occurrence among 2,156 patients treated with DAAs and followed up for mean time of 18 months (13). Multivariate analysis of risk factors for HCC showed that SVR significantly reduces this risk. Another prospective UK cohort study has failed to find any increase of *de novo* HCC risk after DAA treatment in patients with SVR [10/406 (2.5%) *vs.* 11/261 (4.2%) in untreated patients] (14). Similar results were observed in studies with retrospective design. The results from a

large American cohort (n=5,033) treated with the DAA sofosbuvir showed no significant difference regarding HCC incidence rates between patients who received DAA and an untreated control cohort of 69,374 HCV patients after adjustment [0.77% (0.40–1.35%) and 0.67% (0.60–0.75%) person-years, respectively among non-cirrhotics, and 3.24% (2.15–4.68%) and 3.67% (3.21–4.17%) person-years, respectively among cirrhotics] (15). Moreover HCC incidence was reduced in Taiwanese HCV patients with SVR whether they have been treated with DAA (N=150) or interferon regimen (N=201) after a median observation period of 46 [12–160] months (16). The authors concluded that the impact of DAA-based treatment was similar to that of INF-based regimen in term of HCC risk reduction. More recently data from 2,466 cirrhotic patients treated with DAA in real life practice in Italy and followed for a median time of 14 months (range, 2–22 months) were reported (17). In this cohort, an overall 3.1% incidence of *de novo* HCC was observed, suggesting no increase in HCC appearance. HCC development was associated with a more advanced liver disease and DAA failure. In the Veterans real-life clinical study, 22,500 HCV patients treated with DAAs combination, 87% achieved an SVR among a population with either advanced liver disease or comorbidities (cirrhosis 39%, medical comorbidity with history of alcohol use 61%, history of drug use 54%, type II diabetes 43% and/or previous HCV treatment 22.5%) (11). An annual HCC incidence rate of 0.90% per year (0.77–1.03%) for HCV patients with SVR was observed *vs.* 3.45% per year (2.73–4.18%) for those without SVR. Annual risk of HCC was increased among patients with cirrhosis (1.82%). Reduction in risk of HCC was 76% for patients with SVR, and there was no significant difference regarding tumor characteristics between early and delayed HCC that developed under DAA treatment. As HCC after SVR may still occur in patients with advanced liver disease, continued ultrasound surveillance is mandatory life-long. More recently results from the French Hepather cohort showed that among 9,238 HCV patients (DAAs n=7,036, untreated n=2,202), after a median follow up time of 24 months, DAAs treatment was associated with a decrease risk of death [HR =0.61 (95% CI: 0.41, 0.91)] by the use of a weighted Cox model (12). HCC [HR =1.00 (95% CI: 0.71, 1.40)] and decompensated cirrhosis [HR =0.84 (95% CI: 0.53, 1.35)] were no more increased in DAA treated patients.

Regarding HCC recurrence risk after DAAs treatment, controversial data has been published. Several retrospective uncontrolled studies have suggested an increased rate

of HCC recurrence and a higher tumor burden at recurrence (6,7,9,10), probably due to disruption of immune surveillance induced by DAAs treatment. On the contrary, prospective French studies (CirVir and Hepather cohorts) (18) and some large retrospective cohorts reported no additional risk of HCC recurrence after DAAs treatment in patients with previous history of HCC cured (19,20). In a retrospective case-control study assessing the impact of DAAs on tumor recurrence, we do not observe significant difference regarding rate of recurrence, time to progression and HCC pattern between HCV patients who received DAA agents and an untreated HCV cohort (21). Liver cancer recurrence after a curative-intent therapy is influenced by many factors related to tumor characteristics, presence of cirrhosis and treatment strategy. HCC recurrence is probably not related to the use of DAAs, but may due to the interval between HCC treatment and initiation of DAAs, with a higher risk of recurrence during the period of first months after HCC treatment (22). Thus, as suggested by several authors (23,24), the longer the interval between HCC treatment and start of DAAs therapy is, the lower the risk that any residual tumor is present at the start of DAAs therapy. Finally, Waziry *et al.* performed a systematic review and meta-analyses assessing the risk of HCC occurrence and recurrence in HCV-patients following DAA agents *vs.* IFN-based cure (25). A total of 13,845 patients were enrolled from 41 studies, and the authors reported no significant difference in risk of HCC occurrence or recurrence between patients who received DAA or IFN therapy.

In summary, HCV eradication by interferon-based therapy or by DAAs combination significantly reduce HCC occurrence. However residual HCC risk depends on the severity of underlying liver disease and comorbidities (alcohol and/or metabolic syndrome). SVR by interferon-based therapy or more frequently by DAA combinations reduces HCC recurrence. However long term benefit of DAA combinations need to be evaluated on long-term follow-up.

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Footnote

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References

1. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. *JAMA Oncol* 2017. [Epub ahead of print].
2. Perz JF, Armstrong GL, Farrington LA, et al. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 2006;45:529-38.
3. El-Serag HB, Kanwal F, Richardson P, et al. Risk of hepatocellular carcinoma after sustained virological response in Veterans with hepatitis C virus infection. *Hepatology* 2016;64:130-7.
4. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014;370:1889-98.
5. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;370:1973-82.
6. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *J Hepatol* 2016;65:727-33.
7. Kozbial K, Moser S, Schwarzer R, et al. Unexpected high incidence of hepatocellular carcinoma in cirrhotic patients with sustained virologic response following interferon-free direct-acting antiviral treatment. *J Hepatol* 2016;65:856-8.
8. Cardoso H, Vale AM, Rodrigues S, et al. High incidence of hepatocellular carcinoma following successful interferon-free antiviral therapy for hepatitis C associated cirrhosis. *J Hepatol* 2016;65:1070-1.
9. Reig M, Marino Z, Perello C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol* 2016;65:719-26.
10. Yang JD, Aqel BA, Pungpapong S, et al. Direct acting antiviral therapy and tumor recurrence after liver transplantation for hepatitis C-associated hepatocellular carcinoma. *J Hepatol* 2016;65:859-60.
11. Kanwal F, Kramer J, Asch SM, et al. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. *Gastroenterology*. 2017;153:996-1005.e1.
12. Carrat F. First prospective evidence of decreased mortality after Direct acting antivirals in the French ANRS CO22 HEPATHER cohort. *Hepatology* 2017;66:abstract LB-28.
13. Carrat F. Clinical outcomes in HCV-infected patients treated with direct acting antivirals 18 month post-treatment follow-up in the French ANRS CO22 HEPATHER cohort study. *J Hepatol* 2016;64:S215.
14. Cheung MC, Walker AJ, Hudson BE, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016;65:741-7.
15. Chokkalingam AP, Singer AW, Osinusi A. Risk of incident liver cancer following HCV treatment with sofosbuvir-containing regimen. *Hepatology* 2016;64:365A-366A.
16. Nagaoki Y, Aikata H, Kobayashi T. Hepatocellular carcinoma development in hepatitis C virus patients who achieved sustained viral response by interferon therapy and direct anti-viral agents therapy. *Hepatology* 2016;64:424A.
17. Calvaruso V, Cabibbo G, Cacciola I, et al. Occurrence of hepatocellular carcinoma in patients with hepatitis C virus related liver disease treated with direct-acting antivirals. *J Hepatol* 2017;66:S23-4.
18. ANRS collaborative study group on hepatocellular carcinoma (ANRS CO22 HEPATHER, CO12 CirVir and CO23 CUPILT cohorts). Lack of evidence of an effect of direct-acting antivirals on the recurrence of hepatocellular carcinoma: Data from three ANRS cohorts. *J Hepatol* 2016;65:734-40.
19. Minami T, Tateishi R, Nakagomi R, et al. The impact of direct-acting antivirals on early tumor recurrence after radiofrequency ablation in hepatitis C-related hepatocellular carcinoma. *J Hepatol* 2016;65:1272-3.
20. Petta S, Cabibbo G, Barbara M, et al. Hepatocellular carcinoma recurrence in patients with curative resection or ablation: impact of HCV eradication does not depend on the use of interferon. *Aliment Pharmacol Ther* 2017;45:160-8.
21. Adhoute X, Penaranda G, Raoul JL, et al. Hepatocellular carcinoma recurrence in HCV-related cirrhosis treated with direct-acting antivirals: a case control study. *Eur J Gastroenterol Hepatol* 2017. [Epub ahead of print].
22. Imamura H, Matsuyama Y, Tanaka E, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol*

- 2003;38:200-7.
23. Zavaglia C, Okolicsanyi S, Cesarini L, et al. Is the risk of neoplastic recurrence increased after prescribing direct-acting antivirals for HCV patients whose HCC was previously cured? *J Hepatol* 2017;66:236-7.
 24. Tsai PC, Huang CF, Yu ML. Unexpected early tumor recurrence in patients with hepatitis C virus-related hepatocellular carcinoma undergoing interferon-free therapy: Issue of the interval between HCC treatment and antiviral therapy. *J Hepatol* 2017;66:464.
 25. Waziry R, Hajarizadeh B, Grebely J, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. *J Hepatol* 2017;67:1204-12.

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