[Editorial] Direct-Acting Antivirals and the Risk of Hepatocellular Carcinoma: The End of a Polemic?

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Direct acting antivirals and the risk of hepatocellular carcinoma: the end of a polemic?

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The overall benefit associated with the sustained virologic response (SVR) has been extensively acknowledged over the past 2 decades with Interferon (IFN)-based regimens and seemed not debatable in the Hepatology community. It includes not only a reduction in the rate of occurrence of hepatocellular carcinoma (HCC), in retrospective (1-2) as well as prospective studies (3), but also of extra-hepatic manifestations (4).

This evidence has been markedly challenged in 2016 by the Barcelona group at the International Liver Congress (5) supported by other groups (6) suggesting that the oral direct-acting antivirals (DAA) which were massively given to “priority” HCV-infected patients, namely those with significant fibrosis, was associated with an unexpected high rate and aggressiveness of tumor recurrence in patients with apparent complete response after local treatment of HCC: among 58 patients with history of HCC treated by DAA, 3 patients died and 16 (27.6 %) had a radiological tumor recurrence after a short median follow-up of 5.7 months (5). This unexpectedly high rate and pattern of HCC coinciding with HCV clearance could be explained by a rapid retablishment of normal immunologic homeostasis which may facilitate the emergence of loco-regional or metastatic clones. The quantitative and qualitative alterations of the immune repertoire which are associated with chronic HCV infection are only slowly reversible (7) and the restoration of the cytokines profile is only partial; the imbalance of liver immunity with over- and under-expression of some cytokines (8) could also participate in the risk of HCC.

An original Japanese study published in this issue of Liver International adds a path to the large body of evidence (see below) that DAA do not promote or enhance the HCC risk. Authors nicely investigated the influence of HCV eradication by DAA therapy on HCC development (9). They prospectively evaluated in 401 DAA-treated patients who did not have a history of HCC, the prevalence and the changes of non-hypervascular hypointense nodules (NHHNs) by gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) prior to the start of DAA therapy and during a periodic follow up after therapy. After DAA therapy patients underwent routine ultrasound surveillance for HCC every 3 to 6 months and EOB-MRI examination was repeated every 6 to 9 months when NHHNs were detected at baseline and every 6 to 12 months in addition to ultrasound in those without NHHNs at baseline. The progression of NHHNs detected at baseline to typical HCC, as indicated by hypervascularization, and the incidence of newly emergent NHHNs was analyzed. NHHNs were detected in 35 patients

(8.7%) with a median size of 8.5 mm and SVR was achieved in 383 patients (95.5%). By comparing SVR patients after a median follow-up of 12.7 months post-SVR with propensity score-matched patients with persistent HCV infection, there was no difference in : 1. the incidence of hypervascularization of NHHNs to typical HCC among patients who had NHHNs at baseline (5 SVR patients and one non SVR patient); and 2. new emergence of NHHNs, 8 of the 350 patients without NHHs at baseline (2.3%) developped such nodules and no hypervascular typical HCC were detected after SVR. This well-done study, which strengths included the prospective analysis and the biopsy-proven diagnosis of HCC since all patients underwent hepatic resection, does not support the hypothesis that, even in high-risk patients with NHHNs during a 2-year observation period after SVR, the eradication of HCV achieved by IFN-free DAA therapy could enhance (or suppress!) HCC development.

In addition to these important results, mMethodological limitations have been pointed out (10) for some studies suggesting a higher risk of de novo HCC or HCC recurrence as well as a higher aggressiveness. Moreover, several retrospective or prospective studies (11-14) did not confirm such a risk. A systematic review, meta-analysis and meta-regression of 26 studies (IFN-based regimen = 17, oral DAAs = 9) did not confirm a significant risk of both HCC occurrence and recurrence associated with DAA (15).

Similar results have been reported from the very large US veterans cohort retrospectively analyzed from 1999 to 2015: among the 62,354 HCV patients without detectable HCC, 35,871 (58%) were treated by INF-only (11,988 -33.4%- achieved SVR), 4, 535 (7.2%) were treated by DAAs + INF (2,763 -60.9%- achieved SVR) and 21,948 (35%) were given DAAs only (19,909 -90.7%- achieved SVR)(16)**;** 3,271 incident HCC were diagnosed more than 6 months after initiation of antiviral treatment (mean follow-up: 6.1 yrs). Survival free of HCC by cirrhosis and SVR status was not different according to therapy with the following adjusted hazard ratio (aHR) for HCC: 0.29 (95% CI: 0.23-0.37) in DAA-only, 0.48 (95% CI: 0.32-0.73) in DAA+interferon and 0.32 (95% CI: 0.28-0.37) in interferon-only.

An Italian prospective study including 3 917 patients with a F3-F4 fibrosis score treated by DAA between January 2015 and June 2016 (SVR12 in 97.2 % of F3, in 92.7 % of F4 Child-Pugh A and 80% of F4 Child-Pugh B) also denied an increased HCC risk associated with DAAs : the HCC incidence of 1.18 % person/year (CI95% : 0.92-1.49) in the whole cohort of cirrhotic patients was not different than that of an historical control group (17). Incidence of HCC was related to the severity of the underlying liver disease (0.46% (95% CI 0.12-0.17) in F3, 1.49% (95% CI 1.03-2.08) in CTP-A and 3.61% (95% CI 1.86-6.31) in CTP-B during the first year and 0%, 0.2% and 0.69%, respectively in the second year.

By using weighting methodologies (IPTW, Cox models) given the hererogeneities of treated and untreated patients, at least in countries where treatment priorization was implemented, we established in the ANRS/AFEF Hepather cohort CO-22 first a decreased risk of de novo HCC and second a significant decrease in global, hepatic and extra-hepatic mortality in the former as compared to the latter (18), results which are clearly reassuring: they underline the need of weighting methodologies to avoid misinterpretations.

Thus, if we consider that the DAA-associated risk of HCC is not an issue anymore, the issue of an impact of DAA on the tumor growth and aggressiveness previously suggested (5-6, 17) is still a matter of debate. The influence of DAA therapy on the timing (early or late), frequency and aggressiveness of HCC recurrence after a so-called “curative” treatment clearly needs further investigation.

Very few studies have evaluated the kinetics of tumor growth. We have performed a blinded re-evaluation of the tumor kinetics of the 40 patients of the Hepather cohort who had recurrence of HCC after a so-called “curative” treatment (11): it is noteworthy that 7 patients (17.5%) were not cured and we did not observe any difference regarding the tumor kinetics between those who were given DAA and those who did not (unpublished data).

A residual unmet need is to define in HCV-infected patients undergoing a curative or a palliative treatment of HCC what is the better timing of the antiviral treatment.

References

1. Mallet V, Gilgenkrantz H, Serpaggi J, Verkarre V, Vallet-Pichard A, Fontaine H, Pol S. Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. Ann Intern Med 2008; 149: 399-403
2. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012; 308 : 2584-93.
3. Trinchet JC, Bourcier V, Chaffaut C, Ait Ahmed M, Allam S, Marcellin P, et al. ANRS CO12 CirVir Group. Complications and competing risks of death in compensated viral cirrhosis (ANRS CO12 CirVir prospective cohort). Hepatology 2015 ; 62 (3):737-50.
4. Nahon P, Bourcier V, Layese R, et al. Eradication of Hepatitis C Virus Infection in Patients With Cirrhosis Reduces Risk of Liver and Non-Liver Complications. Gastroenterology 2017; 152 (1): 142-56
5. Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S, et al. Unexpected early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016; 65: 719-726.
6. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolonfi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016; 65: 727-733.
7. Alanio C, Nicoli F, Sultanik P, Flecken T, Perot B, Duffy D, et al. Bystander hyperactivation of preimmune CD8+ T cells in chronic HCV patients. Elife 2015; 4. pii: e07916. doi: 10.7554/eLife.07916.
8. Meissner EG; Wu D, Osinusi A, Bon D, Virta,eva K, Sturdevant D. Endogenous intrahepatic IFNs and association with IFN-free HCV treatment outcome.J Clin Invest 2014; 124: 3352-63.
9. Hidenori T, Takashi K, Toshifumi T, et al. The Impact of HCV Eradication by Direct-acting Antivirals on the Transition of Precancerous Hepatic Nodules to HCC: a Prospective Observational Study. Liver Intern 2018 (In the press).

10. Cammà C, Cabibbo G, Craxì. A Direct antiviral agents and risk for HCC early recurrence: Much ado about nothing. J Hepatol 2016; 65:861-862
11. 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: 734-740.
12. Nahon P, Layese R, Bourcier J, Cagnot C, Marcellin P, Guyader D, et al. ANRS CO12 CirVir group. Incidence of Hepatocellular Carcinoma After Direct Antiviral Therapy for HCV in Patients With Cirrhosis Included in Surveillance Programs. Gastroenterology 2018. pii: S0016-5085(18)34781-4. doi: 10.1053/j.gastro.2018.07.015.
13. Finkelmeyer F, Dultz G, Peiffer KH, Kronenberger B, Krauss F, Zeuzem S, et al. Risk of de novo Hepatocellular Carcinoma after HCV Treatment with Direct-Acting Antivirals. Liver Cancer 2018; 7: 190-204.
14. Calvaruso V, Cabibbo G, Cacciola I, Petta S, Madonia S, Bellia A, et al ; Rete Sicilia Selezione Terapia–HCV (RESIST-HCV). Incidence of Hepatocellular Carcinoma in Patients With HCV-Associated Cirrhosis Treated With Direct-Acting Antiviral Agents. Gastroenterology 2018; 155:411-421.
15. Waziry R, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy. A systematic review, meta-analyses, and meta-regression. J Hepatol 2017; 67 (6): 1204-1212.
16. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2018: 68: 25-32.
17. Romano A, Angeli P, Piovesan S, Noventa F, Anastassopoulos G, Chemello L, et al. Newly diagnosed hepatocellular carcinoma in patients with advanced hepatitis C treated with DAAs: A prospective population study. J Hepatol 2018; 69:345-352.
18. Carrat F, Fontaine H, Dorival C, Simony M, Diallo A, Hezode Ch et al. Clinical outcomes in patients with chronic hepatitis C following direct-acting antiviral therapy: a prospective cohort study. Lancet 2018 (In the press)