Editorial

Direct acting antiviral agents and hepatocellular carcinoma development: don't take it for granted

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Hepatitis C virus (HCV) infection treatment has met a revolution since the introduction in clinical practice of direct acting antiviral agents (DAA). These drugs, even the ones belonging to the so-called first generation, were able to achieve high rates of sustained virologic response (SVR). Moreover, they allowed clinicians to treat also patients with decompensated liver disease for whom former HCV treatment (IFN-based ones) were contraindicated (1,2).

In these patients, DAA showed lower rate of SVR compared to those with compensated liver disease. However, they led to an improvement in liver function in patients reaching SVR and a reduction in decompensation episodes (3). Such exciting results were firstly showed by Foster *et al*. In their study, the authors showed SVR rates higher than 80% in decompensated cirrhosis, using data from the early access program (EAP) for treatment in the HCV Research UK registry. Lower rates of SVR were found among patients with HCV genotype 3 infection, who standed at 64% (4). Further studies showed comparable SVR rates among patients with advanced liver disease, as well as improvement in disease severity (namely improvement in MELD and CHILD scores). Such results were found early after the end of the treatment (5,6).

Despite the high efficacy in advanced liver disease, an association between DAA treatment and hepatocellular carcinoma (HCC) development was postulated and a large debate took hold in literature to such an extent to bother also Shakespeare when Cammà *et al*. with a soothing editorial stated "*Direct antiviral agents and risk for HCC early recurrence: much ado about nothing*" (7). Everything started from a study by Reig *et al*. that showed an "unexpected" high rate of HCC recurrence after DAA treatment in patients with a history of successfully treated HCC. In fact, they showed that 16 out of 58 patients (27.6%), with complete radiological response to HCC treatment, underwent DAA therapy and developed tumor recurrence (8). There were many pitfalls in considering as "high" this rate of recurrence, first of all the absence of a control group and the small sample size. Moreover, it is difficult to estimate the likelihood of HCC recurrence due to the high biological and clinical heterogeneity of early HCC and the consequent high variability of recurrence rates in historical controls. For instance, in the STORM trial, the early recurrence rate ranged from 2.45% in the ablation cohort to 3.8% or 13.5% (in low or high risk group, respectively) in the resection cohort and up to 21% in the entire cohort of the latter arm (9). Furthermore, in Reig *et al*. study new HCC diagnosis were considered as early recurrences even if the median time between HCC treatment and the start of DAA was 11 months.

Fortunately, during last year this doubtful association has lost its importance due to many studies assessing the safety and efficacy of DAA treatments also in advanced liver disease. It is noteworthy, since PEG-IFN era, that the achievement of SVR in patients with cirrhosis strongly reduces their risk of liver decompensation but not the risk

of HCC development (10,11). These data were confirmed in a recent study involving patients treated with DAA. Results from this study showed that risk for HCC was similarly and significantly reduced in patients who achieved SVR after IFN monotherapy (HR 0.32; 95% CI, 0.28–0.37), DAA + IFN (HR 0.48; 95% CI, 0.32–0.73) or DAA-ONLY (HR 0.29; 95% CI, 0.23–0.37) (12).

Finally, thanks to the large cohort of US Veterans, we can affirm with statistical solidity that both HCC occurrence and recurrence were not associated with DAA treatment. In fact, in a recent paper published in Gastroenterology, the authors enrolled 22,500 patients (19,518 achieved SVR) in which 271 cases of HCC after DAA treatment completion developed. HCC occurred in 183 patients with SVR during 20,415 person per year (PPY) follow-up, with an annual incidence of 0.9%. This rate was considerably lower than the 3.45% incidence rate showed in patients without SVR (88 HCC cases during 2,547 PPY follow-up). The SVR protective effect on HCC development was also similar in patients with (adjusted HR=0.32; 95% CI, 0.23–0.44) and without (adjusted HR=0.18; 95% CI, 0.11–0.30) diagnosis of cirrhosis (13). Moreover, another study from the same cohort analyzed the SVR sates among patients with and without HCC. The rate of SVR was higher in patients with HCC (74.4%) compared with those without HCC (94%) (14).

In these latter large real-life cohorts, it was clearly demonstrated the efficacy of new antiviral therapy among difficult-to-manage patients, such those with prior HCC. Moreover, Kanwal *et al.* demonstrated a 76% reduction in HCC risk in patients achieving SVR after DAA treatment and they confirmed that this risk persisted despite the achievement of virological eradication. These findings confirmed that the main risk factor for HCC development in patients with HCV infection is the presence of cirrhosis. In conclusion, we can state that delaying treatment of HCV infected patients may lead to increasing costs for future management of HCC once patients has progressed to liver cirrhosis.

One of the key points of the future management of DAA induced SVR is continuing HCC surveillance even in patients with advanced fibrosis and cirrhosis. It should also be attempted to design studies aimed to produce data that could help clinicians in stopping the HCC screening at the obtainment of fibrosis regression.

In the end, clinicians should support treatment of all patients before they progress to advanced stage of fibrosis or cirrhosis, thus preventing costs related to HCC surveillance and management.

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Footnote

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