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Is the risk of neoplastic recurrence increased after prescribing direct-acting antivirals for HCV patients whose HCC was previously cured?

To the Editor:

Direct-acting antivirals (DAA) have recently revolutionized the treatment of patients with HCV-related cirrhosis, due to their extraordinary potency, which allows very high rates of viral eradication. Recently, some concerns have been raised about the possible increased risk of neoplastic recurrence after DAA therapy particularly in cirrhotic patients with previously cured HCC. Indeed, in a multicentre retrospective study, Reig *et al.* [1] observed that 16 of 58 patients treated with DAAs had HCC recurrence after a median follow-up of 5.7 months. Similarly, Conti *et al.* found that 17 of 59 patients (29%) had HCC recurrence during the 24 weeks of follow-up after completing DAA treatment [2]. Two other retrospective studies have confirmed the high rate of HCC recurrence after treatment with DAA both in cirrhotic patients and in patients with a liver transplant [3,4].

In contrast, the large ANRS study from France did not confirm any aggressive accelerated pattern of HCC recurrence [5]. In fact, among 79 cirrhotic patients previously treated for HCC, neoplastic recurrence was found in 1 of 13 patients with cirrhosis (7.7%) who received DAAs as compared with 31 recurrences (47%) in the 66 who did not receive DAAs [5]. In a second cohort in the same study, HCC recurrence was found in 24 (12.7%) of 189 patients treated with DAAs as compared to 16 of 78 (20.5%) untreated patients [5]. The conflicting results of all the aforementioned studies have raised commentaries and criticism [6–8].

To fuel the debate on this crucial topic, we here present the outcome of 31 consecutive patients with HCV-related cirrhosis and HCC cured after locoregional treatment or resection, who received DAAs at two referral centers in Northern Italy. We used the same inclusion criteria adopted by Reig *et al.*: (i) HCC diagnosed by pathology or by non-invasive criteria according to American Association for the Study of Liver Diseases (AASLD) guidelines; (ii) Complete response following locoregional or surgical treatment; (iii) Absence of non-characterized nodules at imaging; (iv) Treatment with all-oral DAA combination and at least one tumour status assessment after starting antiviral therapy. All patients were HIV negative and had no history of alcohol intake. Twenty patients were males and 11 females. The mean age was 65 years (± 8). Twenty-five patients (81%) were Child-Pugh A and six (19%) were Child-Pugh B. Four patients were infected by HCV genotype 1a, 23 by genotype 1b, 2 by genotype 2a/2b, and 2 by genotype 4. The main characteristics of treated patients are given in Table 1. HCV-RNA levels were assessed by real-time PCR (limit of detection = 12 IU/ml). All patients achieved end of treatment virological response. Sustained virological response at 12 weeks (SVR12) was achieved in 26 patients and there was only one case of virologic relapse.

The median time between the last HCC treatment and start of DAA was 19.3 months (percentile [P]25–75: 12.6–36.9). The median time from the last radiological confirmation of complete response before starting antiviral therapy and the DAA start day was 1.7 months (P25-75: 1.05–2.4). The overall median follow-up

Table 1. Main characteristics of patients with HCV-induced cirrhosis and history of treated HCC who received DAA therapy.

Variable	Total cohort (n = 31) (%)
Antitumoral treatment	
Resection	13 (42%)
Resection and percutaneous ablation	1 (3%)
Resection and TACE and percutaneous ablation	1 (3%)
Resection and TACE	3 (10%)
Percutaneous ablation and TACE	3 (10%)
Percutaneous ablation	6 (19%)
TACE	4 (13%)
Worst BCLC stage prior to DAA therapy	
BCLC-0	8 (26%)
BCLC-A1	4 (13%)
BCLC-A2	9 (29%)
BCLC-A3	2 (6%)
BCLC-A4	3 (10%)
BCLC-B	4 (13%)
BCLC-C	1 (3%)
Bilirubin (mean ± SD)	1.1 ± 0.7
Albumin (mean ± SD)	3.7 ± 0.5
Prothrombin time (INR) (mean ± SD)	1.1 ± 0.1
Alanine aminotransferase (mean ± SD)	71 ± 30
Pre-DAA HCV RNA levels (Log_{10}), (median, range) (IU/ml)	5.6 (3.8-7.5)
Pre-DAA serum AFP levels (median, range) (ng/ml)	10 (2-278)
Treatment regimens	
SOF/LDV ± RBV for 12 or 24 weeks	15 (48%)
SIM/SOF for 12 weeks	6 (19%)
SOF/DCV ± RBV for 24 weeks	2 (6%)
PrOD or the 3D regimen ± RBV for 12 or 24 weeks	3 (9.6%)
SOF/RBV for 24 weeks	3 (9.6%)
End of treatment response	31 (100%)
Post-DAA serum AFP levels (median, range) (ng/ml)	6 (1-44)
Interval between start of DAA therapy and last radiological assessment (months) (median, percentile 25-75)	8 (5-10.9)
Recurrence	1 (3.2%)

HCC, hepatocellular carcinoma; DAA, direct-acting antivirals; BCLC, Barcelona Clinic Liver Cancer; TACE, transcatheter arterial chemoembolization; SOF/LDV, sofosbuvir/ledispasvir; RBV, ribavirin; SIM/SOF, simeprevir plus sofosbuvir; SOF/DCV, sofosbuvir plus daclatasvir; PrOD or the three-drug [3D] regimen, paritaprevir/ritonavir-ombitasvir and dasabuvir; SOF/RBV, sofosbuvir plus ribavirin; AFP, alpha-fetoprotein.

time after the start of DAA therapy was 8 months (P25-75: 5–10.9).

The post-DAAs radiological assessment was performed by CT scan or MRI scan in all cases but 3, who were assessed by contrast-ultrasound. Four patients underwent liver transplantation during the follow-up period. Overall, 1 case of HCC recurrence (3.2%) was observed after a median follow-up of 8 months.

In summary our findings do not confirm the findings of Reig *et al.* or of Conti *et al.* as we observed only 1 case of HCC recurrence in our series of 31 consecutive patients who were followed up for a median of 8 months. We suggest that our longer interval between complete eradication of the tumour and start of antiviral therapy (median 19.3 months in our series and 11.2 months in that of Reig and colleagues) explains at least in part the difference in results. In fact, the longer this interval, the lower the risk that any residual tumour is present at the start of DAA therapy. We did not even observe HCC recurrence in a patient who had undergone a left hepatectomy 3 years before for a tumour invading the left portal branch.

We conclude that DAA treatment is not associated with HCC recurrence after viral clearance in patients with HCV-related cirrhosis and previous history of HCC. Properly designed studies are urgently needed to address this relevant issue.

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Hepatitis C testing in U.S. veterans born 1945–1965: An update

To the Editor:

Sarkar *et al.* report that 51% of 1945–1965 birth cohort veterans in the Department of Veterans Affairs (VA) care had hepatitis C virus (HCV) testing between 2000 and 2013 and conclude that disparities exist in the testing of this cohort [1]. Their study's faulty methodology yields misleading conclusions. We comment here on the misrepresentation of VA birth cohort testing rates and disparities by Sarkar *et al.*, and present relevant updated information on VA HCV birth cohort testing rates.

The stated aim of Sarkar *et al.* was to study HCV birth cohort testing in VA from 2000–2013. The authors' state that "our analysis is restricted to the period 2000–2013, and therefore does not fully reflect the effect of CDC and USPSTF screening recommendations ..." fails to note that the US Centers for Disease Control and Prevention (CDC) did not recommend birth cohort testing until August 2012, while the United States Public Services Task Force (USPSTF) did not do so until June 2013. The VA adopted these recommendations in January 2014. Before August 2012, no major national guideline recommended anything other than risk-based testing for HCV [2–4]. The authors do not provide a rationale for studying birth cohort testing rates in VA during the 11 and a half years prior to the CDC's recommendations, the 12 and a half years prior to the USPSTF's recommendations, or the 13 years prior to the VA's adoption of birth cohort testing.

High birth cohort testing rates in the VA during the timeframe chosen by the authors would not be expected in the absence of other risk factors indicating the need for risk-based HCV testing. This is substantiated by the authors' findings that historical risk factors reflective of national recommendations during the period of study were predictive of testing, namely unexplained liver disease (high FIB-4/APRI or ALT), and co-infection with HIV or hepatitis B virus.

We do not question the accuracy of the authors' calculations yielding a national VA birth cohort testing rate of 51% from