Editorial

Hepatocellular carcinoma recurrence after interferon-free direct acting antiviral treatment for chronic hepatitis C virus infection: fact or fiction?

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Hepatitis C virus (HCV) infection is the leading cause of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC) and liver transplantation worldwide (1-3). Compared to HCV-infected patients who fail to achieve sustained virologic response (SVR) following interferon (IFN)-based antiviral therapies, those who achieve SVR have decreased long-term morbidity and mortality (4,5). In recent years, treating HCV with IFN-free direct acting antiviral agents (DAAs) has shown superb efficacy and safety and thus become the current standard of care for HCV infection.

Although treatment with IFN-free DAAs is generally potent and tolerable, Reig and co-workers published a report in *Journal of Hepatology*, claiming an alarmingly high rate of HCC recurrence after IFN-free DAA therapies among HCV-infected subjects who had received curative HCC treatment (6). In this retrospective study, 58 HCV-viremic subjects with no radiological evidence of HCC recurrence after curative therapy by surgical resection, local ablation or chemoembolization received 12–24 weeks of IFN-free DAAs and post-treatment imaging surveillance for HCC. After a median follow-up of 5.7 months after the starting of DAAs, they found an unexpected high rate (27.6%) of early tumor recurrence in these patients. Based on these observational data, Reig *et al*. raised a serious concern about the benefits of IFN-free DAA therapy in such patients.

The unusual high rate of early tumor recurrence among HCV-infected subjects after receiving IFN-free DAAs is intriguing. The reported 5- and 10-year accumulated incidence in HCV-infected subjects with or without advanced hepatic fibrosis/cirrhosis ranged from 1.5% to 5.1% post-SVR by IFN or pegylated IFN with/without ribavirin therapies (5,7,8). Although cirrhotic patients who achieved SVR by IFN-based therapies had an annual risk of 1.39% of HCC which was still higher than non-cirrhotic patients from a large U.S. Veterans Affairs database, the incidence rates of HCC were far lower than the rate reported in Reig *et al*.'s cohort (6,7). Several possible mechanisms have been proposed to explain the discrepant rates of HCC emergence. First, the use of potent IFN-free DAA therapies may cause rapid viral suppression and thus mitigate inflammatory cytokine responses (9). This immune "break" after IFN-free DAA therapies may potentially favor tumor progression. Because IFN can trigger anti-proliferative cytokines, patients receiving IFN-based therapies for HCV might have a reduced risk of HCC development, compared to those receiving IFN-free DAA therapies (10). Second, microRNA-122 (mir-122) is the most abundant microRNA in the liver, acting as an important host factor for enhancing HCV infection. Reduced mir-122 level has been shown to be associated with poor prognosis or metastasis of HCC (11). Furthermore, a number of mir-122 targets, including cyclin

G1, GSK-3 β/EBP-α, Wnt/β-catenin, IGF1R, SFR and ADAM10, were involved in the HCC tumorigenesis (12-17). A recent report indicated that the serum mir-122 levels declined rapidly after the initiation of IFN-free DAA (18). Based on the mechanistic evidence that mir-122 serves as a tumor suppressor for HCC, it is speculated that IFN-free DAAs might increase the risk of tumor recurrence after the curative therapy for HCC.

It is prudent to compare the prevalence rates of new HCC development between HCV-infected patients who have advanced hepatic fibrosis/cirrhosis and those who have no prior history of HCC following SVR to IFN-free DAAs. Four independent studies indicated that the prevalence rates of HCC for these patients following SVR to IFN-free DAAs were 1.2%, 6.4%, 6.8% and 3.2% after 3 years, 15, 12 and 3–6 months of post-treatment follow-up, respectively (19-22). In contrast, Buonfiglioli *et al*. found 17 of the 59 (28%) patients who had a previous history of HCC developed recurrent HCC after 3–6 months of post-treatment follow-up (22). Based on the assumption that patients without a prior history of HCC may also have the immune "break" and the decline of mir-122 following IFN-free DAA treatment for HCV, it is still unclear why great differences of the prevalence rates exist for HCC among the treated patients with or without a prior HCC history.

Is it possible that the highly observed HCC recurrence rate in IFN-free DAA-treated patients following curative therapy for HCC relevant to the pathophysiological mechanisms or just methodological misinterpretation? Reig *et al*. reported the crude rate rather than the cumulative incidence with a median follow-up of 5.7 months (range, 0.4–14.6 months) after the initiation of DAA therapies. Due to the relatively small sample size (16 of the 58 patients with HCC recurrence), we expected there would be wide range of 95% confidence interval (CI) (crude rate: 27.6%, 95% CI: 16.1–39.1%), making the point of estimation to be relatively inaccurate. In addition, large database analyses for the actual HCC recurrence rates following the pre-defined curative therapies for HCC, including surgical resection, local ablation, trans-hepatic arterial chemoembolization, or combined therapies are still limited, making direct comparison of these heterogeneous patients receiving or not receiving IFN-free DAA treatment difficult.

In addition to the potential overestimation of the HCC recurrence rate and the lack of robust data for the controls, there are wide ranges of time elapse from the curative HCC treatment to the start of DAA therapies (median 11.2 months, range, 3.6–23.2 months), and from start of DAA therapies to the last visit (median: 5.7 months, range, 0.4–14.6 months). Therefore, the effects of the DAA treatment on the HCC recurrence should be evaluated as a time-dependent manner rather than point estimation. Furthermore, the cumulative incidence rates of the effects should be evaluated from the start of the HCC treatment, rather than the start of DAA therapies. Cammà *et al*. re-evaluated the data by using the Kaplan-Meier analyses and showed that the accumulated HCC recurrence rates were 7% and 13% at 6 and 12 month-interval at variance of the reported crude rate of 27.6% (23). The time interval between HCC treatment and the imaging follow-up to confirm complete response (CR) were less than 4 months in seven of the 16 patients (44%) with HCC recurrence. By subgrouping patients with a cut-off time interval of 6 months between the start of HCC treatment and the imaging assessment for CR, the cumulative HCC recurrence rate was higher in patients with an interval of ≤6 months than those with an interval of >6 months (23). It is thus dubious to claim a given patient achieving CR of HCC in such a short time interval, although the authors excluded patients presenting "non-characterized nodules" by radiological assessment (24).

Taking these lines of evidence together, the link between HCC recurrence and IFN-free DAA therapy remains debatable. Although Reig *et al*. casted doubt on the benefits of IFN-free DAA therapies in this special clinical setting, more robust data are required to confirm the causal-relationship of their findings. As Reig *et al*.'s comments on their own study, large-scale well-designed observational studies or randomized controlled trials are urgently awaited to examine this interesting and important issue.

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Footnote

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References

1. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med 2001;345:41-52.
2. Liu CH, Kao JH. Nanomedicines in the treatment of hepatitis C virus infection in Asian patients: optimizing use of peginterferon alfa. Int J Nanomedicine 2014;9:2051-67.
3. Kao JH. Hepatitis C virus infection in Taiwan: Past, present, and future. J Formos Med Assoc 2016;115:65-6.
4. Singal AG, Volk ML, Jensen D, et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280-8, 288.e1.
5. van der Meer AJ, Veldt BJ, Feld JJ, 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.
6. Reig M, Mariño Z, Perelló C, et al. Unexpected early tumor recurrence in patients with hepatitis C virus -related hepatocellular carcinoma undergoing interferon-free therapy: a note of caution. J Hepatol 2016. [Epub ahead of print].
7. 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.
8. Ikeda M, Fujiyama S, Tanaka M, et al. Risk factors for development of hepatocellular carcinoma in patients with chronic hepatitis C after sustained response to interferon. J Gastroenterol 2005;40:148-56.
9. Meissner EG, Wu D, Osinusi A, et al. Endogenous intrahepatic IFNs and association with IFN-free HCV treatment outcome. J Clin Invest 2014;124:3352-63.
10. Toyoda H, Kumada T, Tada T. Changes in patient backgrounds may increase the incidence of HCC after SVR in the era of IFN-free therapy for HCV. Hepatology 2016. [Epub ahead of print].
11. Hsu SH, Wang B, Kota J, et al. Essential metabolic, anti-inflammatory, and anti-tumorigenic functions of miR-122 in liver. J Clin Invest 2012;122:2871-83.
12. Nakao K, Miyaaki H, Ichikawa T. Antitumor function of microRNA-122 against hepatocellular carcinoma. J Gastroenterol 2014;49:589-93.
13. Bai S, Nasser MW, Wang B, et al. MicroRNA-122 inhibits tumorigenic properties of hepatocellular carcinoma cells and sensitizes these cells to sorafenib. J Biol Chem 2009;284:32015-27.
14. Fornari F, Gramantieri L, Giovannini C, et al. MiR-122/cyclin G1 interaction modulates p53 activity and affects doxorubicin sensitivity of human hepatocarcinoma cells. Cancer Res 2009;69:5761-7.
15. Zeng C, Wang R, Li D, et al. A novel GSK-3 beta-C/EBP alpha-miR-122-insulin-like growth factor 1 receptor regulatory circuitry in human hepatocellular carcinoma. Hepatology 2010;52:1702-12.
16. Xu J, Zhu X, Wu L, et al. MicroRNA-122 suppresses cell proliferation and induces cell apoptosis in hepatocellular carcinoma by directly targeting Wnt/β-catenin pathway. Liver Int 2012;32:752-60.
17. Nassirpour R, Mehta PP, Yin MJ. miR-122 regulates tumorigenesis in hepatocellular carcinoma by targeting AKT3. PLoS One 2013;8:e79655.
18. Waring JF, Dumas EO, Abel S, et al. Serum miR-122 may serve as a biomarker for response to direct acting antivirals: effect of paritaprevir/R with dasabuvir or ombitasvir on miR-122 in HCV-infected subjects. J Viral Hepat 2016;23:96-104.
19. Lawitz E, Ruane P, Stedman C, et al. Long-term follow-up of patients with chronic HCV infection following treatment with direct-acting antiviral regimens: maintenance of SVR, persistence or resistance mutation, and clinical outcomes. J Hepatol 2016;64:S612.
20. Cheung MC, Foster GR, Irving WL, et al. Antiviral

treatment in patients with advanced HCV cirrhosis using sofosbuvir and ledipasvir/daclatasvir with or without ribavirin – 6 and 12 month outcomes compared to untreated patients. J Hepatol 2016;64:S185.
21. Kozbial K, Stern R, Freissmuth C, et al. High risk for hepatocellular carcinoma in cirrhotic patients with SVR following IFN-free DAA treatment within 1 year follow-up. J Hepatol 2016;64:S618.
22. Buonfiglioli F, Conti F, Andreone P, et al. Development of hepatocellular carcinoma in HCV cirrhotic patients treated with direct acting antivirals. J Hepatol 2016;64:S215.
23. Cammà C, Cabibbo G, Craxì A. Direct antiviral agents and risk for HCC early recurrence: much ado about nothing. J Hepatol 2016. [Epub ahead of print].
24. Torres HA, Vauthey JN, Economides MP, et al. Hepatocellular carcinoma recurrence after treatment with direct-acting antivirals: First, do no harm by withdrawing treatment. J Hepatol 2016. [Epub ahead of print].

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