

Risk of hepatocellular carcinoma for patients treated with direct-acting antivirals: steps after hepatitis C virus eradication to achieve elimination

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More than 180 million people have the hepatitis C virus (HCV) worldwide. Patients with chronic hepatitis C are asymptomatic and unaware of their illness until the onset of severe end-stage liver disease (1). Liver cirrhosis occurs in 20–30% patients with chronic hepatitis C 2–3 decades after infection. Every year, hepatocellular carcinoma (HCC) develops in 1–4% patients with HCV-induced cirrhosis. Historically, HCV-infected patients have been treated with interferon-based regimens. Interferon-based regimens require a therapy course of 24 or 48 weeks and induce non-negligible side effects including flu-like symptoms, nausea, anaemia, and depression. The treatment of hepatitis C has improved considerably as a result of direct-acting antivirals (DAAs). These effective drugs have drastically improved HCV treatment efficacy, and it is hoped that superior treatment options can be provided for patients with chronic hepatitis C. These novel antiviral drugs exhibit a high efficacy, short treatment course, can be administered orally, and are well-tolerated. The beneficial effects associated with viral clearance through DAAs should be further evaluated.

Kanwal *et al.* conducted a retrospective cohort study that included 22,500 patients with chronic hepatitis C treated with DAAs in the United States Veterans Affairs (VA) system (2). In total, 19,518 (86.7%) patients experienced a sustained virological response (SVR), indicating a satisfactory viral clearance rate. Patients were followed from the date of DAA treatment completion to the development

of HCC, the date of death, or September 30, 2016, whichever occurred first. There were 183 newly developed HCC occurrences after 20,415 person-years of follow-up among patients with SVR, indicating a HCC incidence rate of 0.90 (0.77–1.03) per 100 person-years. However, 88 patients developed HCC among 2,982 patients without an SVR after 2,547 person-years of follow-up, demonstrating an incidence rate of 3.45 (2.73–4.18) per 100 person-years. Compared with patients without an SVR, those with DAA-induced viral clearance had a decreased risk of HCC, with an adjusted hazard ratio of 0.28 (0.22–0.36). The study supported that an SVR was associated with a considerable reduction in the risk of HCC. The findings were in line with other studies that evaluated the HCC risk of patients with an interferon-based regimen (3–5). Several prospective studies have evaluated the subsequent risk of HCC among patients who underwent DAA treatment (6–8). However, DAAs are recently developed regimens; therefore, the period of follow-up in studies of DAA-treated patients were relatively short compared with studies that analysed patients treated with interferon-based regimens. Unless a prospective study enrolls a large number of patients or recruits high-risk patients treated in tertiary care centres to assure sufficient instances of HCC for subsequent estimations, evaluating HCC risk or exploring the predictors associated with HCC among patients treated with DAAs is challenging. Although the study conducted

by Kanwal *et al.* followed patients for less than 2 years, it is currently the largest known cohort study of DAA-treated patients in the world. The cohort study enrolled army veterans in a single-payer national healthcare system that had almost complete laboratory and pharmacy information for the participants. The large study population and the existence of comprehensive electronic medical records were suitable for the study of HCV treatment outcomes in a real-world setting. Although 40% of patients already had liver cirrhosis, compared with other prospective studies aimed to estimate HCC risks among patients treated in tertiary centres (6–8), the veterans included in this study were relatively healthy. However, at least 96% of participants were male, which limited the study's generalizability. But the direction or magnitude of the protective effect of an SVR would not be markedly different from those of other study populations.

In a separate study, El-Serag used the available VA data to evaluate how patients benefited from interferon-based treatment and the predictors associated with HCC risk after viral eradication (9). They revealed that the HCC incidence rate was approximately 0.35% per year for those treated by interferon. In the study of Kanwal *et al.* that included veterans treated with DAAs (2), the incidence of HCC was 0.9% per year. Compared with veterans that were administered interferon-based regimens, those treated with DAAs seemed to exhibit a higher risk of developing HCC. The cost of treating veterans with DAAs comprises the cost of the DAAs, additional medication, clinic visits, and laboratory tests. Therefore, the considerable expense involved may result in VA medical practitioners prioritising patients to be treated with DAAs. Veterans that are prioritised for DAA-treatment may either have advanced liver diseases or no have no treatment response to interferon regimens. This may explain why the new cohort of patients treated by DAAs had a higher HCC risk than the patients treated with interferon-based regimens. Both studies revealed that either cirrhosis or fibrosis were crucial risk factors for HCC (2,9). Among patients without cirrhosis at treatment, fibrosis stage was still relevant for HCC development. Compared with those with a FIB-4 score of <1.45, the adjusted hazard ratios for FIB-4 scores of 1.45–3.25 and >3.25 were 1.44 (0.57–3.66) and 4.58 (1.81–11.60), respectively. The data emphasised that treatment before the progression to advanced liver disease had a beneficial effect on patients (3). Interestingly, in both the DAA- and interferon-treated cohorts, diabetes and alcohol abuse were revealed as predictors for HCC after an SVR. Individuals with either of these risk factors had a 2- fold

risk of HCC occurrence. The data implied that patients still need to be consulted for behaviour modifications even after treatment-induced viral clearance to maximise the health benefits of SVR.

In the future, it is hoped that with more accessible and affordable drugs, more and more patients with chronic hepatitis C can receive effective treatment. However, the patients that experienced treatment-induced viral clearance still conferred risk for HCC. Compared with patients with HCV that experience spontaneous clearance, the incidence of HCC among patients with SVR was still high (0.11 *vs.* 0.90 per person-year) (10). Therefore, investigating the risk factors to identify high-risk patients for the surveillance of HCC is essential. In this VA cohort treated by DAAs, particularly for patients who already had cirrhosis at treatment, there was no relevant predictor for HCC risk except ethnicity. Conventional or novel biomarkers may provide insights into risk stratification for successfully treated patients. A recent prospective study in Japan revealed that a unique fibrosis-related glycomarker, *Wisteria floribunda* agglutinin positive Mac-2 binding protein (WFA⁺M2BP), may predict the development of HCC with a diagnostic accuracy higher than alpha-fetoprotein (11). Elevated serum WFA⁺M2BP levels in patients had a high correlation with the severity of fibrosis. The elevated serum levels of WFA⁺M2BP were associated with HCC risks independently of liver fibrosis. Serum levels of WFA⁺M2BP can be quantitated using an automatic machine, and it is less intrusive than a liver biopsy. Another prospective cohort, which included patients with chronic hepatitis C patients treatment experiences, revealed that post-treatment WFA⁺M2BP levels were significantly associated with HCC (12), suggesting that patients with high WFA⁺M2BP levels should be followed carefully for HCC development. In addition to the glycomarker, host genetic variants would be useful for implementing a personalised surveillance of HCC in patients with HCV infection (13). A recent study revealed that a variant of the Toll-like 1 gene was a predictor for HCC development after the eradication of HCV (14). Although the effect of this variant must be further validated in other ethnic groups, it provided insights for future studies on the mechanisms of hepatocarcinogenesis after HCV eradication.

Apart from liver-related outcomes, successful treatment was associated with favourable outcomes in extrahepatic diseases and prolonged overall survival (15). In addition, patients with treatment-induced viral clearance may have improved health-related quality of life and patient-

reported outcomes, and increased working productivity (16). It is obvious that treating hepatitis C successfully may result in direct cost savings (e.g., hospitalisations, medications, emergency services, and laboratory tests) and produce indirect savings (e.g., reducing family or social assistance spending) (17). Therefore, it is widely accepted that all patients with chronic hepatitis C should be treated regardless of their symptoms or disease stage. Identifying HCV-infected persons and referring them for clinical consultations should be a major priority in the elimination of HCV. Although large-scale screening is essential to identify individuals with HCV infection for clinical care, individuals with HCV infection are asymptomatic and therefore difficult to identify. Misinformation, lack of awareness, and refusal of blood testing are the main barriers for HCV screening. As a result, discovering the “hidden population” with HCV is challenging. New strategies to maximise screening uptake and increase the diagnostic rate of anti-HCV seropositivity are critical. In the VA healthcare system, at least 2.9 million (53% of total VA patients) veterans received screening for HCV, including 63.5% of those born during 1945–1965 (“baby boomers” recommended for one-time screening by the Centers for Disease Control and Prevention) (18). The healthcare system also made efforts to establish a hepatitis C screening day, during which all veterans underwent a routine phlebotomy in addition to screening based on traditional HCV risk factors. They also made efforts through telemedicine programmes to support primary care providers in delivering HCV treatment care for VA patients residing outside the catchment of tertiary centres. These efforts resulted in at least 39,388 (23% with HCV viremia) veterans undergoing antiviral treatment (18). Although HCV-infected veterans may be more likely to have additional risk factors that predispose them to liver diseases, their achievement is made more remarkable by the current high rates of medical or psychiatric comorbidities typically act as obstacles for treatment initiation or continuation. From the results provided, these efforts resulted in more patients being treated successfully, and reduced their risk of liver diseases. The VA healthcare system has been successful in treating patients with HCV, and has provided insights for other healthcare systems.

In 2016, the World Health Organization (WHO) drafted a strategy for combating viral hepatitis, and set a goal for the elimination of viral hepatitis by 2030. More specifically, the goals were to reduce the incidence of chronic hepatitis B and C infection by 90%, and to reduce

the mortality due to chronic hepatitis virus infections by 65%. To achieve this goal, the identification of individuals with HCV infection, laboratory testing and evaluation for appropriate treatment and clinical monitoring, and risk stratification for prioritising intensive care are crucial. The strategies should be tailored to meet the needs of different regions or nations to achieve a cost-effective treatment method with high efficacy (19). For the goal set by WHO, national and international efforts and collaborations are urgently required. Increased social awareness and political attention may facilitate the elimination of this virus. In the future, further novel research in the development of a HCV vaccine, social studies to characterise high-risk populations, improved screening uptake, increased public awareness in public populations, and the removal of the societal stigma surrounding HCV are crucial. In terms of public health strategy, diagnostic testing and antiviral treatment should be increased considerably to eliminate HCC.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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