



Risk management of hepatocellular carcinoma occurrence after hepatitis C virus eradication – from IFN based era to IFN-free DAA era

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Chronic hepatitis C virus (HCV) infection is a public health issue which affects people throughout the world, with more than 71 million people affected, and 400,000 deaths annually (1). HCV, which is when active carriage of HCV RNA is in the blood, is the leading cause of cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (2). Among HCV infected cirrhotic patients, the incidence rate of HCC steadily increases with increased degree of fibrosis, with annual reported incidence of 1.4% to 7% respectively (3). The eradication of the virus and therefore prevention of HCC development and liver related death is the ultimate treatment objective for chronic HCV. In 1991, the first treatment approved by the Food & Drug Administration (FDA) to treat chronic hepatitis C (CHC) was IFN α -2b monotherapy (4), which allowed 15–20% of sustained virological response (SVR) and also induced major side effects such as asthenia, neutropenia, myalgia and influenza-like syndromes (5). In 1998, SVR rates increased to 38% in IFN α -2b and daily oral administration of ribavirin (RBV) combination treated patients (6). In 2001 and 2002, the FDA approved pegylated-IFN (PEG-IFN) α -2b and PEG-IFN α -2a respectively, which allowed IFN-based treatment to be administered weekly. The combination of PEG-IFN α -2a or PEG-IFN α -2b and ribavirin allowed SVR in 56% and 54% of treated patients (7). This regimen given for 6 to 12 months depending on the HCV genotype became the new standard of care (4). After 10 years of stagnation with PEG-IFN/RBV combination, a desirable change spread over several stages. The first stage in 2011 was observed

with the launch of the first direct-acting antiviral agents (DAAs). More than 75% of patients infected with HCV genotype 1 who were treated with NS3/4A protease inhibitors in combination with PEG-IFN α achieved SVR, however both had clinically significant side effects, increasing the daily pill burden (8). This treatment was approved since patients treated with IFN-based therapy achieving SVR have been shown to have a significantly lower risk of developing HCC than those who did not (9).

Therefore, treatment of HCV infection has been through a recent revolution since the advent of the latest second-generation, DAA agents of all oral IFN-free regimens based on anti-NS5A and NS5B polymerase inhibitors and 2nd generation protease inhibitors increased SVR rates to 90–98% in naïve and PEG-IFN/RBV-experienced patients from 2014 (10). DAAs allow a virological cure in almost all of the treated patients, but this high efficiency is still uncertain regarding the association with perfect elimination of HCC occurrence.

Nagaoki *et al.* found that the risk for developing HCC after viral eradication by IFN-free DAA therapy may be similar to that in IFN-based therapy (11).

Further, Calvaruso *et al.* also reported that HCV viral clearance with DAA treatment lowers the risk of HCC occurrence, even in those patients with more advanced cirrhosis (12). However, the risk of HCC development remains even after SVR, and therefore the need for long-term follow-up in cirrhotic patients is still high (13).

It is unclear if HCC risk declines over time after the

eradication of HCV. Progressive fibrosis, assessed by sequential biopsies, was significantly correlated with development of HCC in patients achieving SVR for HCV.

After SVR was achieved, fibrosis regression was significantly associated with patient's platelet count and age. The index calculated from age, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count (PLT), Fibrosis score 4 (FIB-4), has been identified with high accuracy as a biochemical marker to predict hepatic fibrosis and cirrhosis (14).

In contrast to this, patients of advanced fibrosis or cirrhosis have the a very low risk of developing HCC in patients with no or only mild fibrosis who achieved SVR. Therefore, most HCV guidelines have almost no mention of HCC surveillance for this patient population.

As analyzed by Ioannou *et al.*, HCC annual incidence over time following the eradication of HCV and identified dynamic markers of HCC risk, they concluded that patients of cirrhosis before an SVR to treatment for HCV infection continued to have high risk for HCC, even if the patient's FIB-4 index score decreases, and should continue for surveillance (15).

Patients with FIB-4 scores ≥ 3.25 but without cirrhosis have a high enough risk to warrant HCC surveillance, especially if the patient's FIB-4 remains ≥ 3.25 post-SVR (15).

This tells us that continued follow-up will be necessary in order to determine potential benefits related to the HCC development and mortality with and without cirrhosis, and Fib-4 score.

Further studies are required to assess patients in different geographical regions and ethnicity, in order to prove utility as a predictive tool.

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Footnote

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