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Hepatitis C related hepatocellular carcinoma in the era of direct-acting antivirals

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Abstract

Globally, hepatocellular carcinoma (HCC) is the second leading cause of cancer related death. Hepatitis C virus infected patients with cirrhosis or bridging fibrosis are particularly at risk. The risk is reduced among patients who achieve viral clearance with interferon-based regimens. Direct-acting antivirals (DAA) have revolutionized the management of HCV as the treatment is well tolerated, convenient to administer and is highly effective. Earlier studies showed conflicting results in the effect of DAA induced sustained virologic response (SVR) on the subsequent development or recurrence of HCC, with some studies showing an increased risk. More recently, two large retrospective studies provided convincing evidence that DAA induced SVR reduces the risk of HCC development. Irrespective of viral clearance, patients with cirrhosis and advanced fibrosis and those with treated HCC continue to be at increased risk requiring long-term surveillance studies.

Keywords: Antiviral agents, viral clearance, hepatoma, hepatitis C virus, cancer surveillance

HCC INCIDENCE - USA AND GLOBAL

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, accounting for nearly three fourths of all liver cancers[1]. In the last decade, it has been the seventh most common cancer in the United States[2]. Yet, with its high lethality and limited effective therapeutic options, it has risen to be the second-leading cause of cancer-associated mortality world-wide[3]. In the United States, the incidence of HCC has quadrupled in the last four decades, from 1.5 cases per 100,000 in 1973 to 6.2 cases per 100,000

in 2011[4]. However, a recent epidemiological study observed that the rate of increase in HCC incidence has slowed down in recent years[5]. The study included data acquired from the surveillance, epidemiology, and end results (SEER) program and noted that although HCC incidence increased by 4.5% per year from 2000 to 2009, it only increased by 0.7% annually from 2010 to 2012[5]. Variations in HCC incidence by gender, age, ethnicity, race and geographical location were also noted. Men had a higher average annual percentage increase of 3.7% compared to the 2.7% increase in women. In spite of the overall plateauing of HCC incidence, the incidence in some sub-groups such as men aged 55-64 years continued to rise, corresponding to the baby boomer population with peak rates of hepatitis C virus (HCV) infection. By 2012, the rate of incidence in Hispanics was higher than that among Asians within the United States. Amongst the states included in the SEER database, Texas had the highest age-adjusted HCC incidence[5]. An earlier study based on SEER data showed similar results[6]. Thus, for the first time in four decades, there was no significant increase in the incidence or incidence-based overall mortality of HCC. The studies indicated a deceleration of HCC incidence around the year 2006[4].

Worldwide, HCC is still amongst the top three leading causes of cancer-related deaths. In the Asia-Pacific region, HCC incidence remains high because of the high prevalence of hepatitis B virus (HBV) infection[7]. Except for Japan, Australia, Singapore and New Zealand, where HCV is more prevalent, HBV accounts for almost 80% of HCC in this region[7]. HBV and HCV are also the most common risk factors for HCC in China that leads the world by accounting for more than half of the HCC cases world-wide[7].

ETIOLOGY: ROLE OF HCV IN THE DISEASE BURDEN OF HCC

Hepatitis C virus is a single-stranded RNA virus from the family *Flaviviridae*[8]. Along with HBV, it accounts for more than 70% of the HCC cases worldwide[9]. However, it is quite distinct from HBV with regards to its mechanisms of hepatocarcinogenesis[9,10]. Being a DNA virus, HBV has the ability to incorporate into the host genome and to intrinsically affect DNA replication and induce carcinogenesis. In contrast, HCV cannot integrate within the host genome and uses other mechanisms to promote carcinogenesis. Those mechanistic pathways invariably stem from chronic inflammation, which is the hallmark of HCV infection. HCV proteins have been implicated to play a role in hepatocarcinogenesis and some of the proposed mechanisms include induction of oxidative stress, modulation of cell regulation pathways and interaction with tumor suppressor proteins. In addition to the HCV core protein, other proteins such as E2, NS3 and NS5A have also been studied for their potential role in carcinogenesis[11]. The high rate of replication errors in the HCV RNA leads to the formation of quasispecies which are adept at evading the immune system and in establishing chronic infection[10]. Hepatitis C viral infection thus results in chronic hepatitis in nearly 80% of cases in comparison to 5% of HBV-infected patients who develop chronic disease[10]. Chronic hepatitis C progresses to liver fibrosis in 60%-70% of patients, cirrhosis in 10%-20% and eventually HCC in 1%-5% within two decades of harboring the virus. The ability of HCV to promote cirrhosis is 10- to 20-fold higher than HBV[10]. Therefore, unlike HBV, almost all HCV-infected persons who develop HCC have underlying cirrhosis[12,13]. An additional important factor for the high burden of HCV-induced HCC is the lack of a preventative vaccine like the HBV vaccine which has been instrumental in reducing the global incidence of HBV[9].

HCV PREVALENCE - USA AND GLOBAL

The World Health Organization (WHO) estimated the global prevalence of HCV to be around 3%, amounting to more than 170 million people worldwide[14-16]. There is a lot of geographic variation in the prevalence of HCV, with African and the Middle Eastern countries such as Egypt, Cameroon, Saudi Arabia, Iraq and Syria topping the list[15]. Egypt has the highest prevalence of HCV in the world with endemic levels of infection, and that is reflected in the high incidence of HCC[17]. Along with Egypt, the Asian countries of China, India, Pakistan and Indonesia also carry a heavy burden of HCV and together make up half of the global HCV population[14,15].

Table 1. Timeline of drug approvals for hepatitis C (USA)

Approval date	Anti-viral agent	Trade name
Feb 26, 1991	Interferon alfa-2b	Intron-A
1996	Interferon alfa-2a	Roferon
Sep 10, 1997	Interferon alfacon-1	Infergen
Aug 7, 2001	Peginterferon alfa-2b	Peg-Intron
Oct 16, 2002	Peginterferon alfa-2a	Pegasys
May 13, 2011	Boceprevir	Victrelis
May 23, 2011	Telaprevir	Incivek
Nov 24, 2013	Simeprevir	Olysio
Dec 6, 2013	Sofosbuvir	Sovaldi
Oct 10, 2014	Sofosbuvir/ledipasvir	Harvoni
Dec 19, 2014	Ombitasvir/paritaprevir/ritonavir/dasabuvir	Viekira Pak
Jul 24, 2015	Daclatasvir	Daklinza
Jul 24, 2015	Ombitasvir/paritaprevir/ritonavir	Technivie
Jan 28, 2016	Elbasvir/grazoprevir	Zepatier
Jun 28, 2016	Sofosbuvir/velpatasvir	Epclusa
Jul 18, 2017	Sofosbuvir/velpatasvir/voxilaprevir	Vosevi
Aug 3, 2017	Glecaprevir/pibrentasvir	Mavyret

Developed countries have typically demonstrated lower prevalence of HCV infection compared to developing countries. In the United States, HCV seroprevalence is 1.6% to 1.8%, amounting to 5-7 million individuals[15,18]. The populations at risk are intravenous drug users, incarcerated and homeless persons, and those born in the "baby boomer" years between 1945 and 1965. During those years, extensive illicit intravenous drug use in social settings and the use of contaminated blood products led to the spread of HCV. Since the establishment of standard screening practices for blood products and organs, a noticeable decline of incident HCV cases has been noted[18-20]. This is also true for other developed countries including Australia, Japan and parts of Europe[15]. Currently, the major risk factor for transmission in those countries is the sharing of infected needles by intravenous drug users[15].

As HCV and HIV have similar routes of transmission, co-infection is common especially in countries such as Thailand, Malaysia and China, where intravenous drug abuse and addiction are major problems[21]. Of the 40 million known HIV infected persons in the world, approximately 4.5 million are co-infected with HCV[22]. Unfortunately, HIV-induced immunosuppression leads to accelerated progression of HCV disease, resulting in cirrhosis within 5-10 years of infection rather than the usual 10-20 years[21]. Alcohol abuse also accelerates HCV disease progression.

HCV TREATMENT - EVOLUTION FROM INTERFERONS TO DIRECT-ACTING ANTIVIRALS

Before the turn of the century, standard treatment for chronic hepatitis C consisted of the combination of interferon-alfa administered three times a week with ribavirin daily for 24 or 48 weeks[23,24]. Subsequent introduction of pegylated interferons allowed for once a week injections and improved response rates. Still, treatment was associated with considerable side-effects limiting its applicability particularly among patients with comorbidities and organ transplant status other than liver transplantation.

The introduction of direct-acting antivirals (DAA), telaprevir and boceprevir, in 2011 dawned a new era in the management of HCV infection[25] [Table 1]. Both drugs were NS3/4A protease inhibitors, and were used in combination with peg-interferons and ribavirin to avoid the emergence of resistant variants[26]. Those agents improved SVR rates but did not improve the side-effect profile. Thus, the use of triple therapy came with its own challenges particularly with regard to compliance and monitoring[15]. Simeprevir was another protease inhibitor that was approved to be used in combination with peginterferon and ribavirin with similar effects. Those three drugs constituted the first generation of DAAs.

It was the approval of sofosbuvir (nucleotide analog NS5B polymerase inhibitor) in 2013 that heralded the advent of all-oral regimens and a change in treatment landscape once again[25] [Table 1]. The next two years saw the introduction of several other DAA - sofosbuvir in combination with ledipasvir (NS5A inhibitor), and combination of ombitasvir (NS5A inhibitor), paritaprevir (NS3/4A protease inhibitor), ritonavir (CYP3A inhibitor) and dasabuvir (non-nucleoside NS5B palm polymerase inhibitor), and daclatasvir (NS5A inhibitor)[25]. The latter was approved for treatment of HCV genotype 3 infection in combination with sofosbuvir. The regimens could be used in both non-cirrhotic and well compensated cirrhotic patients who were either treatment naïve or treatment experienced, and they achieved high SVR rates with reduced duration of treatment and better tolerability[25]. Elbasvir (NS5A inhibitor) and grazoprevir (NS3/4A protease inhibitor) fixed dose combination was approved for treatment naïve or treatment experienced patients infected with genotype 1 or 4, with or without cirrhosis. The regimen was contraindicated in patients with Child's B or C cirrhosis; however, it could be used in patients with advanced renal failure without dose adjustment. All regimens had overall SVR rates of greater than 95%. That was the second generation of DAAs.

The approval of sofosbuvir and velpatasvir (NS5A inhibitor) as a fixed dose combination initiated the third generation of DAAs [Table 1]. Whereas the response rate to previous regimens was HCV genotype dependent, this combination was pan-genotypic and could be used in patients with or without cirrhosis. It also had approval to be used in decompensated cirrhosis in combination with ribavirin; however, it was not recommended to be used in patients with severe renal impairment as defined by an eGFR of < 30 mL/min. Two other fixed dose combinations were more recently introduced to this pan-genotypic armamentarium of antivirals. Sofosbuvir, velpatasvir, and voxilaprevir (NS3/4A protease inhibitor) fixed dose combination was approved for patients without cirrhosis or those with compensated cirrhosis, and without severe renal impairment. The combination was indicated for patients previously treated with an HCV regimen containing an NS5A inhibitor, or those with genotype 1a or 3 who were previously treated with a regimen containing sofosbuvir without an NS5A inhibitor. Glecaprevir and pibrentasvir (NS5A inhibitor) fixed dose combination was approved for patients without cirrhosis or those with compensated cirrhosis. The combination could also be used in adult patients with genotype 1 infection, who were previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both. Hepatitis B reactivation during HCV treatment has been reported among coinfected patients resulting in fulminant hepatic failure and death. It is therefore recommended to test all patients for current or prior HBV infection before initiation of HCV treatment, and to monitor all coinfected patients for HBV reactivation during therapy and during post-treatment follow up.

IMPACT OF HCV TREATMENT ON DISEASE BURDEN OF CIRRHOSIS/BRIDGING FIBROSIS

In view of the etiologic role of HCV in the progression of hepatic fibrosis and hepatocarcinogenesis, viral clearance would be expected to cause cessation of fibrosis progression or potentially regression of fibrosis. Similarly, it may also reduce the risk of HCC development. This issue was evaluated among patients treated with interferon and ribavirin. A meta-analysis of four key randomized trials assessed the effects of HCV treatment on histologic features[27]. The pooled studies included 3010 treatment naïve patients who underwent liver biopsies before and after treatment. Treatment regimens involved unmodified interferon or pegylated interferon, in combination with ribavirin. To be deemed as an improvement in fibrosis, at least one-point reduction in METAVIR fibrosis stage from baseline was required. Conversely, an increase by one or more points was considered fibrosis progression. In addition to improvement in necrosis and inflammation, the analysis showed a significant improvement in fibrosis progression with all treatment regimens. In 49% (75/153) there was reversal of cirrhosis; however, fibrosis worsened in 8% to 23%. Factors independently associated with lack of fibrosis progression included low HCV RNA level (< 3.5 million copies/mL), minimal to no baseline inflammatory activity, healthier body mass index (< 27 kg/m^2), younger age (< 40 years), achievement of SVR and a lower pre-treatment fibrosis stage[27]. In another study, the effect of combination

therapy with thrice weekly interferon alfa-2b and daily ribavirin for 24-48 weeks was assessed[28]. Among 90 treatment naïve patients enrolled, 34 patients underwent a liver biopsy following completion of 48 weeks of therapy. Compared to the pre-treatment biopsy, fibrosis stage improved in 32% (11/34), and all three patients with cirrhosis had regression of fibrosis. Improvement in fibrosis progression was independently associated with younger age and low pre-treatment HCV RNA level. In another study of 933 patients with HCV who achieved SVR with interferon-based therapies, non-invasive markers (Fibrotest, Fibroscan) or liver biopsy were used to assess severity of fibrosis. Among the patients who achieved SVR (29%), 56% (24/53) of the patients with cirrhosis had regression of cirrhosis noted at a median follow-up of 6.3 years. However, during that period 12% of the patients with SVR developed new cirrhosis suggesting that the net reduction in cirrhosis was a meager 5%[29]. Those findings led to the suggestion that HCV therapy should ideally be initiated in earlier stages of fibrosis to achieve the benefit of cirrhosis prevention[30].

With the dawn of DAA era, the assessment of hepatic fibrosis incidentally shifted from liver biopsy to non-invasive modalities principally transient elastography (TE). One limitation of TE is that a change in liver stiffness (LS) following SVR may not entirely reflect a reduction in fibrosis as inflammatory component contributes to stiffness and it resolves quickly with SVR[30]. This limitation needs to be considered while inferring from studies that examined the effect of DAA on hepatic fibrosis by using LS as a surrogate marker. In a study of 392 patients treated with DAA, an average reduction in LS from 12.65 kPa pre-therapy to 8.55 kPa 40 weeks after achieving SVR was noted, suggesting a 32% reduction in LS. That correlated with a significant reduction in the FIB-4 and APRI fibrosis scores[31]. Another study demonstrated a progressive reduction in LS among 255 patients who achieved SVR with DAA - from average score of 26.4 kPa prior to therapy to 23.5 kPa at the end of therapy and subsequently to 21.3 kPa at 12 weeks following completion of treatment, indicating a 20% reduction in fibrosis[32]. In a Japanese study of 210 patients who achieved SVR with daclatasvir and asunaprevir (NS3/4A protease inhibitor) combination, there was significant reduction in LS values, progressively from baseline to end-of-treatment to 24 weeks following treatment completion[33].

EFFECT OF DAA ON THE INCIDENCE OF HCC

Several studies examined the effect of SVR from interferon-based therapies for hepatitis C on subsequent development of HCC. A meta-analysis established with moderate level of certainty that SVR achieved with interferon-containing regimens reduced all-cause mortality and decreased the risk of HCC at any stage of fibrosis[34]. In fact, the estimated risk reduction of HCC after achieving SVR with interferon-based therapies in patients with HCV-induced fibrosis/cirrhosis was an impressive 76%[34]. However, the reduction in HCC risk was not uniform as risk persisted in some patients despite viral clearance, particularly among those older than 65 years and those with advanced fibrosis or cirrhosis[35].

Viral clearance induced by DAA has been shown to reduce liver and non-liver related critical events and overall mortality. In a retrospective review of 467 patients (409 with decompensated cirrhosis) treated with DAA, viral clearance was achieved in 381 (82%) patients[36]. MELD scores improved in treated patients while they worsened in untreated patients. The authors concluded that viral clearance was associated with improvement in liver functions within 6 months compared to untreated patients. In a prospective study of patients with compensated cirrhosis, the effects of SVR on patient outcomes was studied[37]. Patients were treated with interferon or with DAA. Among 1323 patients included, 668 (50%) achieved SVR after a median follow up of 58 months. Patients with SVR had reduced incidence of HCC and hepatic decompensation. In addition, SVR was associated with reduced mortality and risk of death from liver and non-liver related causes.

However, several reports cast doubt on the beneficial effect of DAA induced SVR on the development of HCC. In a study of 103 patients, 58 with treated HCC and complete radiologic response had DAA induced SVR or HCV RNA negativity[38]. At a median follow-up of 5.7 months, 3 patients died and 16 (28%) developed

radiologic tumor recurrence. Those results implied that DAA therapy increased the recurrence rate of treated HCC. In another study of 344 cirrhotic patients without HCC (59 with treated HCC and complete response) who received DAA, 91% achieved SVR[39]. During a follow-up period of 24 weeks, 26 (8%) were noted to have HCC - 17/59 (29%) with previous HCC and 9/285 (3%) without previously diagnosed HCC. The rate of HCC recurrence was higher compared to historical controls. In a retrospective study of HCV patients with cirrhosis and treatment with DAA, the development of *de novo* HCC was examined[40]. *De novo* HCC was noted in 9% of the patients during or within 6 months of DAA therapy with new indeterminate lesions in another 3%. The authors concluded that as this rate exceeded the previously reported rate of 3% within 6 months of completing treatment, DAA appeared to increase the risk of *de novo* HCC development. In contrast, an analysis of data from three French prospective multicenter cohorts did not show an increased risk of HCC recurrence following DAA therapy[41]. The cohorts included more than 6000 patients treated with DAA. Among patients with previously treated HCC, the rate of HCC recurrence was similar in patients who received DAA *vs.* those who did not receive DAA.

More recently, two large retrospective studies provided more definitive evidence of the effect of SVR induced by DAA on the development of HCC. In a study of 22,500 patients treated with DAA at any of the 129 US Veterans Health Administration (VHA) hospitals, 39% were noted to have cirrhosis[42]. New HCCs were noted in 271 patients including 183 with SVR. Overall, annual HCC incidence was 1.19/100 person-years with significant reduced risk of HCC among patients with SVR compared to those without SVR (0.9 *vs.* 3.45/100 person-years). Although, patients with cirrhosis had the highest annual incidence of HCC after SVR (1.82 *vs.* 0.34 in patients without cirrhosis), the protective effect of SVR was similar among patients with or without cirrhosis. The second study was conducted by our group at Veterans Affairs Healthcare System Pittsburgh using the "Electronically Retrieved Cohort of HCV Infected Veterans (ERCHIVES)" database that is populated with a wide range of clinical information pertaining to veterans seropositive for HCV[43]. We identified 17,836 patients without prior HCC - 3534 received interferon-based therapy, 5734 received DAA and 8468 patients constituted the control untreated group. SVR was achieved by 67% of the interferon treated group and 96% of the DAA treated group. Among patients with cirrhosis who achieved SVR, HCC-free survival was similar in the interferon treated and DAA treated groups. Both groups had improved HCC-free survival compared to the untreated group. The two studies established that DAA induced SVR reduced the risk of HCC development; however, absolute HCC risk remained high among patients with cirrhosis.

The divergence of conclusions reached in the studies is intriguing. Earlier reports of increased HCC recurrence and *de novo* HCC following DAA induced viral clearance were based on smaller cohorts which were likely affected by selection bias. The reported increase in HCC was explained on the basis of changes in hepatic microenvironment. It was postulated that rapid viral clearance induced by DAA stunned immune surveillance that was characteristic of chronic hepatitis C. The resulting disruption in immunomodulation allowed niches of dormant neoplastic cells to proliferate unchecked. A direct effect of DAA on cancer cell growth was also proposed[44]. In contradistinction to those studies, the two VHA studies reported beneficial effects of DAA induced SVR. Despite the limitations of retrospective design, the considerable size of the study cohorts provided a more definitive evidence of the beneficial effect of DAA induced SVR on development of HCC.

SUMMARY

Patients with advanced hepatic fibrosis or cirrhosis due to hepatitis C are at considerable risk of HCC. Viral clearance induced by interferons was noted to effect significant risk reduction for HCC development. In contrast, an increase in *de novo* HCC and HCC recurrence was reported following SVR achieved with DAA. More recently, two large studies provided convincing evidence for the beneficial effect of DAA induced SVR

on subsequent development or recurrence of HCC; however, absolute risk of HCC remained high among such patients. Patients with advanced fibrosis or cirrhosis therefore require continued HCC surveillance irrespective of SVR.

DECLARATIONS

Authors' contributions

Critically reviewed available information: Moghe A, Shaikh OS
Wrote the manuscript: Moghe A
Planned, reviewed and finalized the manuscript: Shaikh OS

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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