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Chapter

Hepatocellular Carcinoma and Antiviral Therapies in HCV Chronic Infection

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Abstract

The development of direct-acting antiviral (DAA) therapies in chronic HCV infection has been associated with increased expectations regarding the prognosis of this infection in the medical community, as the possibility of HCV eradication is now in sight. While the cure of the HVC infection has been associated with a dramatic decrease in its systemic complications, the impact on the progression of the liver disease, especially in patients with cirrhosis, is still controversial. Furthermore, the risk of developing hepatocellular carcinoma (HCC) after direct-acting antiviral therapy is debatable, with studies presenting an increased prevalence of HCC early after the introduction of these therapies, as well as newer contradicting studies. This chapter aims to examine the current literature data available regarding the impact of new HCV therapies in the incidence and prognosis of hepatocellular carcinoma.

Keywords: hepatocellular carcinoma, hepatitis C virus, direct-acting antiviral agents

1. Introduction

Hepatitis C virus (HCV) chronic infection is one of the leading causes of morbidity and mortality, with over 71 million people infected worldwide. [1] Its natural evolution comprises liver cirrhosis and its complications, including hepatocellular carcinoma (HCC). HCV infection is the leading factor associated with HCC in Western European countries and USA, with an increased risk of up to 20 times greater than the general population. [2] The association between HCC and HCV occurs in cirrhotic patients; an estimated 20% of patients with HCV chronic infection develop cirrhosis within 20–30 years of infection, and, of those, 1–4% develop HCC each year. [3] The risk of developing HCC in the course of HCV infection is related not only to the presence of the virus, but also to viral genotype, concurrent liver disease or metabolic syndrome (diabetes mellitus, obesity) and lifestyle factors. [4]

HCV genotypes 3 and 6 are associated with higher HCC risks [5, 6]. Furthermore, co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) doubles the risk of developing HCC in younger HCV infected patients. [7] Smoking and alcohol abuse are associated with an increased risk of HCC in HCV infected patients as follows: a relative risk of HCC of 23 in smoking patients, as opposed to 7.7 in non-smokers [8] and a 2 fold increase in the risk of HCC in patients with an alcohol intake over 60 g daily. [9] On the other hand,

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coffee-drinking has beneficial effects on both the progression of liver disease and the HCC development. [10]

Diabetes mellitus is an important cofactor in the development of HCC associated with the HCV infection. On the one hand, the presence of HCV is an important risk factor for the development of type 2 diabetes. [11] HCV has a direct action against beta-pancreatic cells [12] and also a systemic pro-inflammatory action, inducing the expression of TNF-α and IL-6 which promote insulin-resistance. [13] On the other hand, the development of diabetes is associated with an increased risk of HCC of up to 3 fold, due to insulin resistance, increased inflammation, inhibition of apoptosis and the generation of pro-oncogenic mutations. [14] Obesity is also a risk factor for the development of HCC, due to increased production of pro-inflammatory cytokines and insulin resistance which mediate carcinogenesis.

2. Relationship between HCV and HCC

There are two main mechanisms of carcinogenesis in HCV chronic infection: the carcinogenetic hepatic environment produced by the HCV infection per se and the direct carcinogenetic effect of several HCV proteins, both structural (core, E1, E2) and non-structural (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B). [15]

Experimental studies have revealed the impact of the viral protein expressions on cellular proliferation. For example, over-expression of core proteins, NS3, NS5A promotes cellular proliferation and tumor transformation in mice, via oncogenic molecular pathways. [16, 17] The core protein also inhibits tumor suppressor genes (TP53 TP73) and negative regulation factors of the cell cycle. [18] Aggressive phenotypes of HCC are associated with the activation of cellular proliferative pathways (RAF/MAPK/ERK kinase) by the HCV core protein as well as by NS5A and NS5B. [19] Furthermore, HCV core protein stimulates the production of oxygen reactive species, with an important role in the pathogenesis of HCC, and also inhibits the tumor suppression activity of TGF- beta. [20, 21] NS5A protein inhibits caspase-3 enzyme (thus stimulating evasion from apoptosis) and prevents nuclear translocation of Smad proteins, inhibiting TGF beta signaling with the final outcome of down-regulating tumor suppressor cyclin-dependent kinase inhibitor 1. [22, 23] NS5A also induces chromosomal instability and mitotic dysregulation as well as apoptosis mediated by TNF-alpha. [24, 25]

Alterations of the host genomic DNA are described in HCV infection (oncogenic mutations, deletion of tumor suppressor genes), with an important impact on HCC carcinogenesis. The core protein inhibits mitotic spindle checkpoint function, increases chromosomal polyploidy, while the chronic oxidative stress induces mitochondrial and chromosomal DNA alterations. [20, 26]. HCV induces endoplasmic reticulum perturbations and prolonged stress, which leads to accumulation of DNA mutations and a predisposition to carcinogenesis. [27]

Chronic inflammation also plays a part in HCC development. In support of the inflammatory model of carcinogenesis, it has been shown that inhibition of cyclooxygenase 2 prevents HCC in experimental models. [28] The core protein of HCV inhibits immune responses mediated by the nuclear factor kappa-B (NF- kB), involved in the progression of initiated tumor clones. [29] Extracellular core protein may inhibit antigen-presenting cells via the IL-6 pathway. [30] NS5A interacts with TNF receptor-associated factor 2 and activates the JNK pathway (c-Jun N terminal kinase) generating an inflammatory environment in the liver that is the basis for HCC carcinogenesis. [31] Other viral proteins also affect immune mechanisms and promote carcinogenesis; for instance, NS3 has an immune suppressive effect by cleavage of mitochondrial

antiviral signaling proteins and E2 viral protein contributes to immune evasion by inhibiting natural killer cells. [32, 33]

HCV is an important factor in the dysregulation of normal liver metabolism and a promoter of steatosis. [34] It has been shown, in experimental animal models, that the expression of HCV core protein is associated with progressive steatosis and HCC, as well as insulin resistance and suppression of the assembly and secretion of very low density lipoproteins. [35–37] HCV core protein modulates cell differentiation and proliferation, accentuates steatosis and oxidative stress via peroxisome activated receptor alpha. [38]

Normal hepatocellular senescence is also impaired in HCV infected patients. In the stage of cirrhosis, after regeneration cycles, cellular senescence is stimulated by telomere shortening, which decreases hepatocyte proliferation and prevents carcinogenesis. [39] In the HCV infection, hepatocyte senescence is inhibited and somatic mutations of the telomerase reverse-transcriptase promoter stimulate carcinogenesis. [40]

Fibrosis is the most important background in the development of hepatocellular carcinoma, as it stimulates genetic aberrations. [41] There is a direct correlation between the degree of liver fibrosis and the increased risk of HCV associated HCC in some patients, which may persist despite obtaining sustained virologic response by antiviral treatments, as there is still progression of liver fibrosis and its associated HCC risk. [42, 43] HCV core and other non- structural proteins stimulate profibrogenic, mitogenic and pro-inflammatory cytokines (TGF-beta, platelet-derived growth factor, IL-8, Il-32). [15] In addition, HCV infected apoptotic cells may amplify fibrogenic signals. [44] Portal hypertension secondary to liver cirrhosis increases gut mucosa permeability and bacterial translocation, resulting in increased circulatory bacterial lipopolysaccharides, an important stimuli of fibrogenesis and carcinogenesis. [45] The interaction between the HCV protein E2 and CD81 (pertaining to the complex responsible for HCV internalization) stimulates an inflammatory response resulting in liver damage. [46] Experimental studies have suggested the role of renin-angiotensin system in carcinogenesis, as administration of angiotensin-converting enzymes inhibitors inhibits angiogenic factors and decreases insulin-resistance related carcinogenesis. [47]

Different host-specific mechanisms have been incriminated in the development of HCV associated HCC. For example, is has been demonstrated that the epidermal growth factor (EGF) pathway is activated in hepatic stellate cells, stimulating cellular growth, proliferation, differentiation and carcinogenesis, and its inhibition via EGF receptor inhibitor, erlotinib, diminishes fibrosis and reduces the risk of HCC. [48] In other trials, erlotinib has proven effective in preventing HCV infection, by inhibiting HCV cellular entry. [49] In addition, gefitinib (another EGF inhibitor) has proven effective in experimental animal models in suppressing HCC growth in subjects with established HCC lesions. [50] Sorafenib, a multi-kinase inhibitor, inhibits angiogenesis and has beneficial roles in portal hypertension as well as HCC by blocking the response to vascular endothelial growth factor. [51] Host related factors predicting response to antiviral therapy appear to play a role in HCV associated HCC risk. Il28B variants CT or TT, used to predict virologic response to interferon therapy, also increases the risk of developing HCC. [52] Molecules pertaining to the major histocompatibility complex class I are involved in fibrogenesis and carcinogenesis by inflammatory mechanisms. [53] Metabolic disturbances, such as those involved in the iron metabolism leading to hepatic iron overload, stimulate steatosis, mitochondrial alterations and carcinogenesis, especially in HCV-based models. [54] The presence of HCV infection dysregulates the activity of microRNAs in a distinct pattern. [55]

3. Hepatocellular carcinoma in the setting of DAA treatments

Currently, the most important international panels recommend using direct acting antiviral (DAA) therapies for all degrees of liver fibrosis, customized for all HCV genotypes, with significant advantages: very high response rates (over 90%), short treatment duration and few adverse effects [56–58] These options are summarized in **Table 1**.

Not only do all guidelines recommend antiviral treatment in chronic HCV infection regardless of degree of liver fibrosis or other comorbidities, but they also indicate that the presence of HCV associated comorbidities is a strong argument in favor of antiviral therapy. The use of DAA in patients with HCC is still under debate. The European guidelines recommend that HCV treatment in patients with HCC should be administered after curative (ablation, resection) or palliative procedures (transarterial chemoembolisation). [59] The reasoning behind this recommendation is that patients with HCC have lower response rates to DAA. [60] A recent meta-analysis on over 5500 patients with HCC revealed a SVR rate of 88%, with higher rates reported in patients who received curative HCC treatment compared to those with non-curative therapies or not treated. [61] Furthermore, patients with HCC awaiting liver transplantation who received DAA had a lower risk of dropout caused by tumor progression or death. [62] Strong recommendations are made in favor of treating HCV associated HCC patients after liver transplantation. [63] In HCV patients with treated HCC, without indication for liver transplantation, the indication of DAA treatment is uncertain. Large cohort studies show that obtaining SVR is associated with lower risks of de novo HCC and liver-related mortality in the mid and long term. [64, 65] On the other hand, a large study has shown that the high HCC risks persist up to 10 years after SVR in patients with advanced fibrosis. [66] There is no clear conclusion regarding the impact of DAA treatment on the risk of HCC recurrence following curative procedures, as shown by a review and meta-analysis on 13000 patients. [67] Another retrospective cohort study on 797 patients with HCV infection and a history of HCC with complete response to ablation, resection, transarterial chemo- or radioembolisation concluded that DAA therapy decreases the incidence of overall deaths. [68] A recent expert literature review states that DAA treatment decreases the risk of de novo HCC in patients with and without cirrhosis, while the presence of active HCC significantly decreases SVR rates. [69] There was no association between antiviral therapy and the baseline risk, aggressiveness, time of progression of HCC.

	Genotype 1a	Genotype 1b	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6
SOF/VEL							
GLE/PIB							
SOF/VEL/ VOX							
SOF/LDV							
GZR/ EBRGZR/ EBR							
OBV/ PTV/r + DSV							

SOF sofosbuvir; VEL velpatasvir, GLE glecaprevir, PIB pibrentasvir VOX voxilaprevir, LDV ledipasvir, GZR grazoprevir, ERB elbasvir, OBV ombitasvir, PTV paritaprevir, r ritonavir, DSV dasabuvir.

Table 1.
Direct acting antiviral agents currently in use (regimens marked with orange are not indicated in the respective genotypes.

The guidelines presented by the American Association for the Study of Liver Diseases in 2019 recommend screening for HCC in patients with advanced fibrosis before any antiviral therapy and elaborate simple treatment strategies for non-cirrhotic patients including diagnosis, pre-therapeutic evaluation and follow-up so as to be accessible to a broad range of health care professionals. [57] In patients with decompensated cirrhosis or cirrhosis complications, a case-based decision is required. [70] An interesting study presented in the APASL consensus statements and recommendations on treatment of hepatitis C shows that, in patients with compensate cirrhosis and HCC, DAA treatment (sofosbuvir and ribavirin) administered at least 4 weeks prior to liver transplantation reduced the risk of allograft recurrence by 50%. [71]

4. SOF/VEL

SOF/VEL is a pan-genotypic all oral treatment regimen, consisting of a NS5B polymerase inhibitor (sofosbuvir) and a NS5A inhibitor (velpatasvir). [72] In a real life study of over 2800 HCV infected patients, this regimen showed an efficacy of 94.6% in the general population, with an SVR rate of 88,6% in cirrhotic patients. Notably the number of cirrhotic patients included was significantly low. [73] In a trial on 102 Japanese patients with decompensated cirrhosis, HCC was diagnosed in 3 patients after the completion of antiviral therapy with SOF/VEL (in days 1, 70 and 124 respectively). Four other patients had a history of HCC resolved for more than 2 years prior to therapy and did not experience recurrence. [74] Another prospective multicenter trial studied the efficacy of SOF/VEL in 71 patients with decompensated cirrhosis; among those, 22 patients (31%) had a history of treated HCC (by resection, ablation, transarterial chemoembolization, chemotherapy, heavy ion therapy, proton therapy), during a timeframe ranging from 2 months to 13 years prior to DAA treatment. None of the patients had evidence of active HCC at the initiation of DAA therapy; however, the maximum level of alpha-fetoprotein noted at initiation was over 2000 ng/ml. 90.9% of patients with a history of HCC obtained SVR (compared to 94.4% in the entire study population); 4 patients presented HCC recurrence; no de novo HCC cases were reported. [75] 16 patients in a large trial involving 729 Chinese patients infected with genotype 2 HCV were given SOF/VEL, among which one had a history of HCC; all the patients obtained SVR and there was no recurrence in the HCC patient.

5. SOF/VEL/VOX

This is a pan-genotypic regimen, containing a NS5B polymerase inhibitor (sofosbuvir), a NS5A inhibitor (velpatasvir) and a NS3/4A protease inhibitor (voxilaprevir), with over 90% SVR rates in treatment naïve patients but especially in DAA- experienced patients and hard-to-treat categories, for which this regimen is currently reserved. [76, 77] One adverse reactions report has been filed regarding a treatment experienced patient developing HCC after treatment with SOF/VEL/VOX. [78] Another case report considers the undiagnosed presence of HCC as the cause of non-response to antiviral therapy re-treatment in a patient with HCV genotype 1b. [79] A large multicenter clinical trial reports HCC (alongside the presence of cirrhosis) as the only cause of treatment resistance in 179 patients with various degrees of fibrosis. [80]

6. GLE/PIB

The combination between Glecaprevir (a NS3/4A protease inhibitor) and Pibrentasvir (a NS5A inhibitor) is another pan-genotypic antiviral option in patients without cirrhosis or with compensated cirrhosis. [81] It has shown response rates of up to 100% and a rate of discontinuation due to severe adverse events of 0.7% in clinical trials (SURVEYOR-I and SURVEYOR-II, comprising 449 patients). [82] Furthermore, newer trials reveal excellent response rates with a lower duration of therapy (8 weeks instead of 12 weeks) even in patients with compensated cirrhosis, without the identification of post-baseline cases of HCC. [83] An interesting study performed in Japan (a country with one of the highest rates of HCV infection and HCC incidence) evaluates the cost-effectiveness of GLE/PIB compared to other DAAs. [84] This study revealed a lower lifetime risk of HCC in patients treated with GLE/PIB or SOF/LDV (3.66%) compared to EBV/GRZ (4.99%). However, in a study evaluating safety and efficacy of GLE/PIB in DAA experienced patients, which enrolled 177 subjects (17 with a history of HCC but no active disease 6 month prior to treatment initiation) one death from HCC was reported, occurring after the end of the treatment but before the SVR12 evaluation. This was a non- cirrhotic patient, without history or proof of HCC at baseline, diagnosed with advanced HCC shortly before the end of treatment. Virologic failure occurred in 17.7% of patients with a history of HCC. [85] A large real-life cohort study evaluated the efficacy of several antiviral regimens in patients with and without HCC in Taiwan. [86]. Among the 1237 patients, 193 received GLE/PIB; 9 of them had a history of HCC and one had active disease. The study notes no differences regarding SVR in patients with or without HCC. The same conclusion was drawn in regard to OBV/PVT/r + DVS (5 patients with active HCC), SOF/LDV and ELB/GZR (each with one patient with active HCC).

7. SOF/LDV

This is one of the first used all oral regimens, combining the well-known sofosbuvir (NS5B polymerase inhibitor) with an NS5A inhibitor (ledipasvir). It is one of the few therapeutic regimens suited for patients with decompensated cirrhosis. [87] In a real life observational trial, SOV/LDV demonstrated a rate of SVR of 86%, in patients with cirrhosis Child A, B or C and transplant recipients, with a significant improvement in MELD score. Out of 200 patients, only one HCC was newly diagnosed, while out of 35 patients with a history of HCC, 17 developed recurrence, depending on the previous (curative or non-curative therapies). [88] A retrospective analysis evaluating 62,354 patients treated for HCV chronic infection, either by interferon, DAA (including SOV/LDV) or both, revealed that achievement of SVR is associated with a 61% reduction in the risk of HCC. A higher incidence of HCC was noted after DAA only therapy (compared to interferon alone or interferon and DAA) but, after evaluating risk factors for HCC, analysis showed that the presence of cirrhosis, impaired liver function and diabetes (more prevalent in the DAA subgroup) were responsible for the differences. [89] Another trial comparing the HCC risk after DAA with the risk after interferon-based therapy (819 patients treated with DAA, 380 treated with SOV/LDV), found that 9/380 patients developed new HCCs. The patients were older and had Child A or Child B cirrhosis; most of them were interferon-experienced. [90] Notably, in the same cohort, out of 120 patients treated with OBV/ PTV/r + DSV, 3 patients developed HCC. Failure to achieve SVR was the strongest risk factor associated with de novo HCC. In contrast, in the historical cohort of patients treated with interferon 19/283 patients developed HCC;

11 patients had no signs of cirrhosis at the time of therapy. A prospective multicenter trial studied the risk of de novo HCC after DAA therapies, including 158 cirrhotic patients and 31 patients with advanced fibrosis receiving SOF/LDV. Newly diagnosed HCC was reported in 35/985 patients after 48 weeks of surveillance. [91] Risk factors for HCC included male gander, failure to obtain SVR, presence of cirrhosis and hepatocytolytic syndrome; DAA therapy was not associated with an increased risk of HCC. In another retrospective trial, 1082 HCV patients receiving DAA or interferon-based therapies were monitored for de novo HCC; during follow-up 33% developed HCC. The patients received different antiviral therapies, among them: SOF/LVD 41 patients, GLE/PIB 49 patients, GZR/EBR 44 patients and OBV/PTV/r + DSV 41 patients. None of the antiviral therapies represented risk factors for HCC. [92]

8. GZR/EBR

This treatment regimen contains an NS3/4A protease inhibitor (grazoprevir) and an NS5A inhibitor (elbasvir) and can only be used in patients with genotypes 1 and 4 HCV infection, with SVR rates of 92–99% in patients with chronic hepatitis and compensated cirrhosis. [93] In a real life retrospective study, out of 149 patients, 27 of with had a history of HCC, no new or recurrent cases of HCC were reported. [94] According to a recent model, in patients with chronic HCV infection and renal disease, the estimated incidence of HCC was 1,2% in the GZR/ EBR group, 21,64% in the no-treatment group and 8,9% in the interferon group. [95] Furthermore, in a prospective report on 40 hemodialysis patients with genotype 1b infection, there was one documented case of HCC at week 4 of therapy. [96] A trial of 349 patients treated with DAA, including 45 patients with a history of HCC, found 15 cases of HCC recurrence and 3 cases of de novo HCC, after a median surveillance of 22 months after DAA (for recurrent HCC) and 16 months (for de novo HCC). 2 cases of recurrence occurred in the 19 patients treated with GZR/EBR. The most important risk factor for recurrence was the previous HCC management. [97]

9. OBV/PTV/r + DSV

This is a genotype 1 specific DAA combination including an NS5A inhibitor (ombitasvir) an NS3/4A protease inhibitor (paritaprevir) and an NS5B polymerase inhibitor (dasabuvir), while ritonavir acts as a pharmacokinetic enhancer. [56] A prospective analysis on 24 patients with HCV associated compensated cirrhosis and history of HCC revealed a decrease in HCC recurrence rate, as well as survival without recurrence, when compared to a control group. Patients had been previously managed with resection, radiofrequency ablation, and trans-arterial chemoembolization, had a history of 6 month of disease free survival and were monitored by CT scan or MRI every 6 months. The SVR rate in the study group was 87% (lower than that recorded in patients without HCC). [98] Another prospective study on 278 patients with HCV related advanced fibrosis (F3-F4), without HCC history, revealed 11 cases on newly diagnosed HCC (5 during antiviral therapy, 2 at the end of therpy and 4 at 3 months after the end of therapy). The overall incidence of HCC did not surpass the general incidence. Notably, patients presented an infiltrative type HCC, difficult to observe on abdominal ultrasonography or even CT scan, requiring MRI. [99] In a multicenter trial in Brazil, out of 222 patients with advanced fibrosis, one patient was diagnosed with HCC at the end of therapy, despite initial screening, was not evaluated for SVR and subsequently died. [100]

A large real world cohort study of 941 patients including 131 patients with concomitant HCC (79 without viable tumors and 52 with viable tumors) evaluated safety and efficacy of OBV/PTV/r + DSV. There were no differences in SVR between patients with and without HCC; risk factors for no response were Child Pugh A 6 and low serum albumin. One patient died during treatment due to HCC rupture. [101] On the other hand, one of the first studies of HCC recurrence in the setting of DAA therapy which was performed in 4 Spanish hospitals, revealed a recurrence rate of 27.6% (16/58 patients); notably, initial evaluations showed no active disease for more than 6 months prior to DAA therapy. One of the 15 patients treated with OBV/PTV/r + DSV developed "non-characterized" nodules on liver imaging. [102]

10. Conclusion

The benefits of DAA therapy in patients with HCC have been proven by a propensity-matched trial on 1239 patients, with HCC managed by curative options or palliation. The results showed a decrease in 5-years all- cause mortality and liver related mortality in both groups. [103] However, the current opinion is that the risk of HCC may persist up to 10 years after obtaining SVR; the HCV infection appears to leave behind an epigenetic scar, inducing carcinogenesis. [104] Therefore, the international consensus is that HCC surveillance should continue after antiviral therapy, and its duration and periodicity should be based on the general risk of HCC of the patient, even deciding on a case to case basis. [105] Besides, the reduction of HCC risk in patients with decompensated cirrhosis is also controversial, thus stimulating further debate regarding the best timing for liver transplantation in these patients. [106]

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