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Review

Role of antiviral therapy in patients with chronic hepatitis B or C virus in preventing the development of hepatocellular carcinoma

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ABSTRACT

Patients with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are at significant risk for hepatocellular carcinoma (HCC). The most important risk factor associated with HCC is liver cirrhosis, which is again predominantly caused by chronic HBV or HCV infection. The most effective approach to avoid HCC development is to prevent HBV and HCV infection through vaccination. Indeed, HBV vaccine is the first vaccine demonstrated to prevent cancers. However, a vaccine for HCV is not available. Thus, the prevention of HCV-related HCC and to a large extent HBV-related HCC (among persons who are already chronically infected) will rely on antiviral therapy to prevent progressive liver disease. The evidence that these patients can effectively be protected against HCC risk by the treatment with antiviral therapy is rather controversial, due to the lack of randomized controlled trials (RCTs) that are ideally needed to establish the effi cacy, but are logistically and ethically challenging. Although the strongest evidence to support that antiviral therapy can prevent HCC should be derived from RCTs with HCC as an endpoint, it should be emphasized that clinical trials showing the efficacy of antiviral therapy on virus suppression or eradication, and/or improvement in liver histology can be considered indirect evidence that antiviral therapy can prevent HCC because high virus levels (in the case of HBV infection) and cirrhosis (in both HBV and HCV infection) are the most important risk factors for HCC.

Key words: Antiviral therapy; cirrhosis; hepatitis B virus; hepatitis C virus; hepatocellular carcinoma; nucleos(t)ide analogs; pegylated interferon; ribavirin

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INTRODUCTION

The World Health Organization estimates that over 350 million persons are infected with hepatitis B virus (HBV) and about 250 million people are chronically infected with hepatitis C virus (HCV).[1] This population is constantly exposed to an increased risk of developing cirrhosis, hepatocellular carcinoma (HCC), liver decompensation,

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and esophageal variceal bleeding, ultimately explaining why HBV and HCV infection are currently the leading causes of liver-related death and the main indication for liver transplantation in developed countries.[2] There is no clear evidence about the role of antiviral therapies in HCC prevention in patients with chronic hepatitis B (CHB) and hepatitis C.[3]

Reanalysis of studies with antivirals suggested that virus-induced HCC was more likely to be prevented in younger patients with mild liver inflammation rather than in older patients with advanced liver fibrosis or cirrhosis, who in fact, were at higher risk of developing liver cancer.[4] In this review, we will address the possible role of antiviral therapy in reducing the risk of HCC in patients affected by HBV and HCV.

We reviewed in PubMed database reports published in English language up to January 2015, using the following keywords: "HCC", "hepatocellular carcinoma", "hepatitis B", "HBV", "hepatitis C", "HCV", "antiviral therapy", and "cirrhosis". We selected the pivotal randomized controlled trials (RCTs) and meta-analysis on this issue. In addition, a manual search for American Association for the Study of Liver Diseases and European Association for the Study of the Liver 2012-2014 conference abstracts were performed using the same search terms.

HBV

HBV is one of the most etiologic agent of HCC in the world, in particular, in areas prevalent for HBV infection such as Asia, Africa, Southern part of Eastern and Central Europe, and the Middle East.[5] A report published in 2006 showed that HBV infection accounted for about 60% of the total liver cancer occurrence in developing countries and about 23% in developed countries.[6]

There are viral and host factors that are associated with an increased risk of HCC among patients with HBV.[7] Although a majority of liver cancers develop from cirrhotic livers, a significant fraction of HBV-related HCCs occurs in a background of CHB in the absence of liver cirrhosis. The lower rate of underlying cirrhosis in HBV-related HCCs as compared to other etiologies argues for a more direct role of HBV in the oncogenetic process.[8]

The molecular and genetic features of HBV chronic infection involving cancer development could be summarized into (1) Pre-core and basal core promoter mutations, genotype B and C[9-13] and (2) integration of HBV DNA into the host genome and the expression of HBV proteins such as surface proteins and the X protein.[14-16]

Studies on the natural history of chronic HBV infection have shown that active HBV replication contributes to the development of acute hepatitis flare, hepatic decompensation, cirrhosis, and HCC.[17] A prospective cohort study with 11 years of follow-up observed that there was a significant increase in HCC-related mortality across viral load categories, with a relative risk (RR) for HCC mortality in the low viral load group of 1.7 [95% confidence interval (CI): 0.5-5.7] when compared with 11.2 (3.6-35.0) in the high viral load group.[18] In the REVEAL-HBV study, serum HBV DNA levels, and HCC risk correlate in a linear relationship, independently of hepatitis B early antigen (HBeAg) status, serum alanine aminotransferase level, and the presence or absence of liver cirrhosis.[19] In addition to these viral factors, older age, male gender, heavy alcohol consumption, and exposure to carcinogens such as aflatoxin B, a family history of HCC, and more recently, the elevated levels of quantitative hepatitis B surface antigen, as well as metabolic syndrome, associated with obesity and diabetes mellitus have been established as the risk factors for HBV-related HCC.[17,20-22]

The primary prevention of HBV-related HCC concerns in the prevention of the population exposure to HBV, treatment of HBV infection itself, elimination of those factors which contribute to the progression of liver disease and risk scores have also been established to estimate the risk of developing HCC in < 10 years after presentation. Such scores based on age, gender, HBV DNA levels, core promoter mutations, and cirrhosis, can be used to identify high-risk patients.[23-25] However, these models were found lacking accuracy for the prediction of HCC in Caucasian patients, for whom different models are, therefore, deemed necessary.[26] The implementation of universal hepatitis B vaccination program has reduced the incidence rates of childhood HCC in several countries including Taiwan.[11] Prompt treatment is the only strategy to prevent end-stage liver disease, incidence, and mortality for HCC in unvaccinated adults with chronic HBV infection.

Current therapeutic options for patients with CHB infection are treatment with interferon-alpha (IFN-α), pegylated interferon-alpha (Peg-IFN-α), lamivudine, adefovir, entecavir, telbivudine, and tenofovir. IFN-α has antiviral, immunomodulatory and perhaps antitumoral activities. It has been used in the treatment of CHB for decades and beneficial effects, including HBeAg/HBV-DNA, clearance the reduction of HCC development, and better complication free survival have been documented. However, the effect on the prevention of cirrhosis and HCC development was controversial. Colombo and Iavarone[3] have recently reviewed the six meta-analysis published to date: The administration of IFN decreased the rate of HCC

development in three meta-analyses, but it appeared to be unchanged in another three. The effect is more evident in Asian than in European studies possibly related to the lower incidence of HCC in European patients.[27-32] These controversial results can be explained by extrapolating HCC chemoprevention through the retrospective scrutiny of the studies that were originally designed to assess the antiviral efficacy of IFN therapy. The reanalysis of these studies was biased by the lack of a separate analysis of the treatment outcomes between sustained responders and non-responders, who represent a majority of all patients with CHB receiving IFN.[3] Therefore, proving a direct anti-HCC effect of IFN-based therapy with clinical trial data beyond what is currently available will be difficult if not impossible. However, IFN still has a role as an effective antiviral for HBV, with finite treatment duration and the potential for a durable effect. Theoretically, the promotion of immune control of viral replication by IFN may have a more solid rationale in terms of HCC prevention unless HBV DNA levels have a direct carcinogenic effect, in which case nucleos(t)ide analog therapy is likely more effective.[33]

The role of nucleos(t)ide analog therapies in preventing HCC has already been widely investigated. The first data date back to the first antiviral agent chronically administered to reduce viral load in patients with the chronic HBV-related liver disease. In 2004, a large RCT conducted in Asia in patients with chronic hepatitis B, who had histologically confirmed cirrhosis or advanced fibrosis, proved that lamivudine was effective in reducing rates of progression of disease and hepatic decompensation as well as the incidence of HCC.[22] Further studies confirmed these results. Papatheodoridis *et al*.[31] showed that long-term therapy with nucleos(t)ide analogs (NUCs) starting with lamivudine monotherapy did not eliminate the HCC risk in HBeAg-negative patients with CHB, especially those with pre-existing cirrhosis. A recent meta-analysis reported that lamivudine treatment significantly reduced the incidence of HCC when compared with no treatment. However, HCC still develops at a rate of 1.3 per 100 patient years in CHB patients receiving an oral antiviral agent.[34] Recent paper on a nationwide study in Greece indicates that the HCC risk remains increased in entecavir-treated HBeAg-negative CHB patients with cirrhosis, in particular, of older age, at least for the first 5 years. The HCC risk does not seem to be significantly reduced with entecavir when compared with antiviral therapy starting with lamivudine.[31] This finding highlights the need for continued HCC surveillance, particularly in CHB patients with inadequate viral suppression, older age, and cirrhosis.

Maintenance of virological remission is also important for the reduction of HCC risk. Among treated patients, HCC incidence is significantly higher among those who do not achieve virologic response than in those who do, with a significant treatment effect observed in the subgroup of cirrhotic patients.[35-38] This observation provides further evidence that older nucleos(t)ide analogs are not an optimal first-line treatment for chronic hepatitis B, as they are associated with very high rates of drug resistance during the long-term treatment, especially in cirrhotic patients. The nucleos(t)ide analogs entecavir and tenofovir, currently recommended as first-line options for the treatment of chronic hepatitis B, maintain long-term viral suppression in over 95% of patients and improve liver histology.[39-41] Treatment with entecavir and tenofovir can reduce the risk of HCC.[42-45] The treatment effect was significant in patients with cirrhosis,[36] whereas a significant HCC risk reduction in non-cirrhotic patients was noticeable only in some reports.[45,46]

Finally, there is an increasing evidence to suggest that antiviral therapy may reduce recurrence and also improve survival on post-hepatectomy outcome for hepatitis B-related HCC. A registry-based study from Taiwan showed that of 4569 HBV-related HCC patients who received curative liver resections, patients treated with lamivudine, telbivudine, or entecavir had a significantly lower risk of HCC recurrence as compared to those who received no antiviral therapy (hazard ratio 0.67, 95% CI: 0.55-0.81, $P < 0.001$).[46] Another study by Chan *et al*.[47] demonstrated that antiviral therapy with lamivudine or entecavir improves the prognosis of HBV-related HCC: The 1-, 3-, and 5-year overall survival rates in the treatment group were 88.1%, 79.1%, and 71.2%, respectively; in the control group, 76.5%, 47.5%, and 43.5%, respectively ($P = 0.005$). Huang *et al*.[48] in a recent RCT showed that, in patients with hepatitis B-related HCC treated with adefovir, antiviral therapy leads to a reduction of late HCC recurrence and significantly improves overall survival after hepatic resection when compared with no treatment. IFN treatment as tertiary prevention of HBV-HCC-related recurrence remains controversial according to the findings in systematic reviews. Furthermore, the use of IFN is burdened by several side effects, including liver decompensation.

HCV

Increasing incidence of HCC in many countries, especially in the United States, is the result of an increase in the prevalence of HCV infection. HCV has been the dominant viral cause of HCC in North America, some Western countries, and Japan.[49] The incidence of HCC in HCV-infected patients amounts to 1-3% at 30 years after the infection.[50]

The molecular mechanism of a malignant transformation of hepatocyte induced by HCV infection is still unclear.[51] The pathogenesis of HCC is generally accepted as chronic inflammation and injury, which leads to fibrosis with eventual progression to cirrhosis and subsequent development of HCC.[52] In this setting, the prevention of HCC could be achieved by preventing cirrhosis and chronic liver inflammation and injury. The most effective approach to prevent HCC is averting HCV infection by vaccination. Unfortunately, despite researcher's efforts, HCV vaccine is not yet available.[53] When infection is acquired the only way to preventing cancer and progression of liver disease depends on antiviral therapy.

Not all patients with chronic hepatitis C (CHC) progress to cirrhosis and not all patients with HCV-related cirrhosis develop HCC, and the risk factors involved are still unknown. Furthermore, the progression from chronic hepatitis to cirrhosis occurs over several decades thus implying that for RCTs to assess efficacy of antiviral therapy to preventing HCC as a primary endpoint, need to enroll large sample size of patients and long-term follow-up. These limitations ensure that evidence to support the role of antiviral therapy to prevent cancer is based mainly on cohort follow-up, retrospective analysis, and meta-analysis.

In the 2000s, the standard therapy of HCV was Peg-IFN and ribavirin; many reports in this period showed a benefit of treatment, even though only a few of these were RCTs, and most of these studies were retrospective or cohort studies.[54-57] The protective effect of antiviral therapy was seen in most studies when patients achieved sustained virological response (SVR).[58,59] These data have recently been confirmed by Moon *et al*.[60] in a retrospective analysis including 494 CHC patients: Among the group of patients who did not achieve SVR, the incidence of HCC was significantly higher (5.5%) *vs*. the group of patients with SVR (1%, $P = 0.005$). In this study, the clinical factors associated with SVR were non-cirrhosis, age younger than 40 years, HCV genotype 2 or 3, low HCV RNA level, and low body weight, as reported in the previous studies. This suggests that the main chemoprotective effect is achieved for younger patients without cirrhosis and non-advanced liver disease.

The strength of these data are enforced by three meta-analyses suggesting that IFN therapy reduces the incidence of HCC in patients with CHC with an RR among treated patients of 0.43 (95% CI: 0.33-0.56, $P < 0.00001$).[58,61,62] Some studies report that the risk of HCC is reduced in these patients independent of fibrosis stage, while among cirrhotic patients that achieve SVR incidence of HCC is reduced by 20%.[63-65] In the group of patients with chronic hepatitis treated with IFN ± ribavirin, the incidence rate of HCC is markedly reduced, while in the group of cirrhotic patients data are not sufficient to support the efficacy of therapy to preventing cancer.[64-66] A meta-analysis in 2010 compared 20 studies with 4,700 patients overall; the risk in treatment group of HCC was reduced (RR: 0.43, 95% CI: 0.33-0.56).[58] Pinzoni *et al*.[67] showed that the risk of developing HCC after achieving SVR persisted in patients with HCV-related cirrhosis: among 598 patients with CHC who underwent a complete course of treatment with Peg-IFN and ribavirin, 221 (37%) patients obtained a SVR and throughout the 10-year post-treatment follow-up, 5.8% of these 221 patients developed HCC. Authors conclude that these patients should continue to undergo long-term surveillance for HCC, to ensure the early detection and treatment. Standard therapy can decrease the risk of HCC, but the patients with this benefit are those who achieve SVR and who have not yet progressed to cirrhosis or advanced fibrosis.

The risk of HCC is reduced but not eliminated also in patients with SVR: these patients are older, thus reflecting a long duration of infection or increased prevalence of cirrhosis and other risk factors for HCC in aged population.[68,69] In addition, non-viral carcinogenic factors such as diabetes, obesity, and alcohol abuse may explain the failure of HCC prevention in SVR patients.[70] Although this calls for a reassessment of current strategies of patient prioritization to antiviral therapies, which are mostly dictated by cost-utility criteria and, therefore, target the most in need patients with advanced liver disease, we became progressively aware that uncertainty regarding rates and the pattern of HCC chemoprevention by antiviral regimens is mainly the consequence of methodological flaws generated by the retrospective scrutiny of the literature. Because of its chemopreventive and antifibrotic effects, IFN monotherapy has been adopted as a long-term maintenance therapy to prevent HCC development.

Three large RCTs of long-term (3-4 years), low-dose Peg-IFN in patients with advanced fibrosis or cirrhosis showed no benefit of treatment on overall clinical outcomes or HCC.[71-73] A subsequent report of the HALT-C Trial focusing on HCC development with a slightly longer duration of follow-up also showed no difference in the incidence of HCC between the patients that were randomized to the maintenance IFN or no treatment.[74] The same results were observed even when the duration of follow-up in these studies was more prolonged.[75] Even after radical treatment, tumor recurrence of de novo second primary HCC was extremely frequent (70% after 5 years of surgical resection) and treatment options available,

especially for advanced-stage liver disease, including liver transplantation were limited.[76] In a meta-analysis of ten studies including eight RCTs conducted in 1029 subjects: 528 HCC patients were treated with adjuvant treatment with IFN and 501 patients with placebo. When compared to the control group, the recurrence rates of HCC in IFN group was significantly lower [odds ratio (OR): 0.66, 95% CI: 0.50-0.86, $P = 0.02$], especially after TACE treatment according to subgroup analysis (OR: 0.73, 95% CI: 0.52-1.01, $P = 0.06$ for surgical resection; and OR: 0.54, 95% CI: 0.33-0.86, $P = 0.01$ for TACE).[77] In another meta-analysis of 10 controlled studies conducted in 655 patients undergoing local ablation or resection of a HCC, the 2-7 years pooled estimated risk reduction of HCC recurrence in SVR patients to IFN based regimens, was 74% and a 60% pooled risk reduction of mortality was observed in parallel. The study showed no correlation between SVR and risk of local recurrence (12.6% *vs.* 21.3%, $P = 0.22$), whereas the prevalence of recurrent tumors was greater in untreated patients and non-responders (79% and 61.3%) than in responders (35.6%). Finally, these findings support tertiary chemoprevention of hepatitis C-related HCC by IFN, even though applicability of IFN treatment is limited by its toxicity profile in most cirrhotic patients with a previous resection or tumor ablation.[78]

DISCUSSION

The actual public health measures for preventing HCV/HBV transmission, including testing blood donors for HBV and HCV, needle exchange programs, lifestyles preventing alcohol abuse, uncontrolled sexual behaviors, and surveillance of high-risk individuals, could allow a significant decline of the disease in future generations.[79] Successful treatment of HBV and HCV could decrease the risk of HCC, but does not completely eliminate it.

Regarding HBV, the protective effect of IFN-α is likely to be limited to patients with cirrhosis who are sustained responders, which represented a relatively small proportion of all their patients. The effect of IFN-α in patient without cirrhosis is unclear. Treatment with nucleos(t)ide analogs appears more effective in lowering the risk of HCC development, probably through more powerful and long-standing suppression of viral replication, though the effect may be blunted with the occurrence of resistance.[80] Risk scoring systems for HCC in CHB should be useful to identify the high-risk patients and also to encourage all available prevention measures targeting adjustable HCC risk factors. However, these models need to be applied and validated in worldwide patients setting.

Furthermore, the current therapeutic options do not eradicate HBV infection and in spite of adequate treatment, the virus remains indefinitely latent in the host genome, representing a continuous threat of reactivation and an oncogenic HCC booster should be mandatory to start viral suppression in patients with active chronic liver disease, in particular with those who have already developed advanced hepatic disease, to avoid future complications, blackout the liver damage and hopefully reducing some degree of inflammation and fibrosis.[32]

In HCV setting, new direct antiviral therapies seem to be more effective to achieve a complete sustained virological response, and these new results will be compared with those of patients treated with IFN or Peg-IFN and ribavirin. Some patients who achieved an SVR with IFN-α based therapy also develop the complications of cirrhosis including HCC years after they have been cleaned from HCV.[81] Although nearly all patients will be cured of HCV by the new therapeutic approach, many of these cannot achieve a restorage of the underlying liver damage if yet established. Thus, it is essential that HCV should be identified and eradicated in all patients, despite the presence of symptoms and different severity grasses of liver disease.

CONCLUSION

The risk of HCC in patients with chronic HBV or chronic HCV infection is not avoided if the treatment is started after cirrhosis is established. These data indicate that treatment could be useful if administrated earlier in the course of CHB or CHC.

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Conflicts of interest
There are no conflicts of interest.

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