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Persistent Risk for Hepatocellular Carcinoma in Patients on Antiviral Treatment: Desperate Need for HBV Cure

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Keywords

HBV; Antiviral drugs; HCC; HBV cure

Commentary

During the past 20 years, with the advent of highly effective antiviral drugs for Hepatitis B Virus (HBV), we have witnessed successful viral suppression as well as the delay and prevention of progressive liver disease leading to cirrhosis and Hepatocellular Carcinoma (HCC).

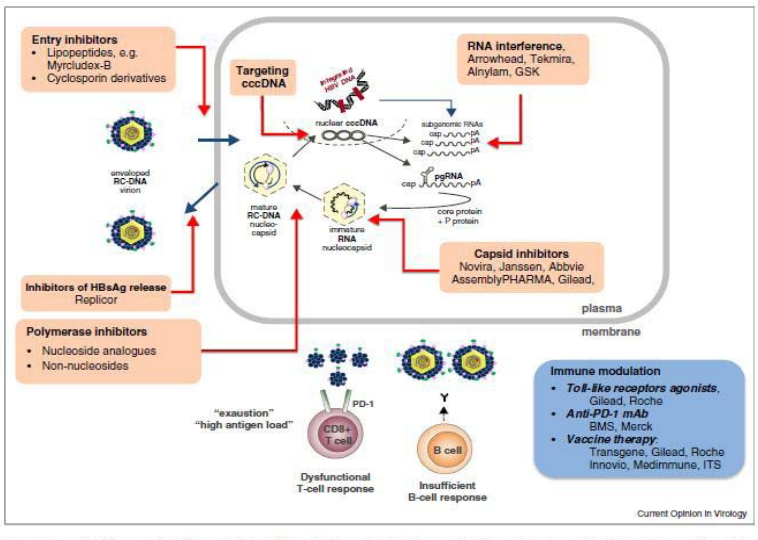
In the past, reduced incidence of HCC with antiviral treatment has been well documented with lamivudine, entecavir and tenofovir [1-4].

Furthermore, prevention of recurrent HCC was observed by numerous investigators including ours following initial tumor ablation when patients received combined antiviral treatment [5-10].

Nonetheless, as reported previously, we are observing a persistent risk for HCC in patients who have maintained successful suppression of viral replication with undetectable serum HBV DNA and normal liver function, even in patients who have been on anti-HBV therapy for greater than 18 years [11]. The result of the observation is shown below (Table 1) [11].

In addition, among patients who are on antiviral therapy and post first tumor ablation, some of them continue developing new HC or recurrent HCC several years (5 yr to 10 yr) after the first HCC (personal communication). In most cases, however, continued antiviral therapy and additional tumor ablation has been successful and patients remain well on continued antiviral treatment.

These persistent risks for new and recurrent HCC among patients with successful control of



The landscape of HBV cure efforts. All steps of the HBV replication cycle (viral entry, cccDNA formation, chromatinization and transcription, viral mRNAs, envelope protein secretion, core proteins and the capsid, Pol enzymatic activities), the intrahepatic innate immune responses and the deficient adaptive HBV specific B and T cell responses are currently being explored as potential new therapeutic targets.

Figure 1:

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Table 1: Development of HCC in patients with cirrhosis on long-term antiviral therapy.

Patient #	Treatment start	Change in Child class on treatment	HCC diagnosis	Size (cm) and site of HCC	Sex and age (yr) at HCC diagnosis	Years on anti-HBV therapy at HCC diagnosis	HBV DNA at HCC diagnosis	Years with undetectable HBV DNA before HCC diagnosis	Anti-HBV treatment	Status
1	May 1998	A→A	February 2008	1.8 × 0.9 Lt	76 F	9.8	UD	6.7	LAM+TDF	Alive
2	February 2004	A→A	June 2013	2.5 Lt	57 M	9.3	UD	7.7	TDF	Dead
3	February 1996	A→A	July 2013	1.6 × 1.4 Rt	73 M	17.4	UD	9.7	TDF	Alive
4	May 1996	A→A	October 2014	3.4 Rt	74 M	18.4	UD	10.4	LAM+TDF	Alive
5	February 2000	A→A	April 2015	3.4 × 3.4 Rt	62 M	15.2	UD	12.4	TDF	Alive

HCC: Hepatocellular Carcinoma; HBV: Hepatitis B Virus; LAM: Lamivudine. TDF: tenofovir disoproxil fiimarate.
Average years on antiviral therapy: average 14 years with a median of 15.2 years (93-18.4 years): average years with undetectable HBV DNA: median 9.7 years (6.7-12.4 years).

HBV are attributed to the incomplete control of HBV, namely due to the presence of cccDNA in the host's hepatocytes.

While we are able to achieve a functional cure, a complete cure that is able to eliminate the cccDNA has not yet been possible. Therefore, even though HBV is not actively replicating, cccDNA remains in the nucleus of the hepatocytes and continues hepatocarcinogenic process including HBV and host DNA integration.

While we are grateful for the current management of HBV associated HCC, there is a desperate need for the drugs that can eradicate the virus. Due to the complexity of HBV replication, It has not been easy, potential strategies include preventing the entry of the virus by blocking the receptor of hepatocytes, preventing the replication of new HBV DNA from the pregenomic RNA (successful with currently available nucleoside/nucleotide analogues), enhancing the host innate immunity (such as small molecule agonists of toll-like receptors), developing a therapeutic vaccine engineered to activate an HBV-specific T cell immune response, and directly targeting cccDNA, in addition to other strategies.

Recent update of the development of potential HBV cure drugs was recently illustrated by Levrero et al. [11] and Block et al. [12]. The lucidly illustrated "the landscape of HBV cure efforts" by Levrero et al. (Figure 1) [12].

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