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Short Communication

Are we Close to Achieving HBV Cure? Risk for Hepatocellular Carcinoma Persists Despite Successful Suppression of Hepatitis B Virus for Over a Decade

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Short Communication

Since the discovery of the Hepatitis B Surface Antigen in 1965 by Blumberg et al [1] and recognition of the antigen linked with post-transfusion hepatitis by the same group and others, significant progress on our understanding of the Hepatitis B Virus (HBV) has followed. Such advances include the illustration of the HBV virion [2], identification of Hepatitis B e-Antigen [3], and discovery of the first HBV plasma vaccine in 1982, which was named the first anti-cancer vaccine by WHO. Soon after, the Bloomberg group noted that in endemic regions, the majority of liver diseases including Hepatocellular Carcinoma (HCC) was associated with chronic infection of HBV [4]. Furthermore, a strong family aggregation was noted and this observation was confirmed by the discovery of vertical transmission from the mother to the newborn at the time of delivery.

In the following decades the HBV epidemiology, hepatocarcinogenesis, genome and replication cycle were further elucidated. In 1998, lamivudine - a nucleoside analogue - became the first anti-HBV drug for treatment of Chronic Hepatitis B (CHB). This breakthrough was followed by the development of more Nucleos(t)ide Analogues (NAs) including adefovir (2002), entecavir (2005), telbivudine (2006), tenofovir disoproxil fumarate (2008), and tenofovir alafenamide (2016) most recently. The efficacy in terms of viral sup pression of these NAs has well been documented by multiple studies as reviewed by Halegoua – DeMarzio et al [5].

HBV is a significant hepatocarcinogen. Currently HCC is the 5th most common cancer in men and the 7th most common cancer in women [6,7]. In 1985, 85% of HCC was associated with HBV infection globally and by 2015, 50% of HCC was attributed to HBV [7-10]. The decline of HBV association with HCC worldwide can likely to be attributed to multiple factors including widespread use of HBV vaccination [9]. particularly for younger generations in hyper-endemic regions, improved sanitation, knowledge of how HBV infection is spread, and most importantly due to the treatment of HBV with the NAs, which suppress the viral replication to delay or prevent the development of HCC.

Therapeutic strategies have focused on affecting the various stages of the replication cycle of HBV. However, currently available NAs are only able to target the reverse transcription of HBV RNA, thereby halting the transcription of HBV DNA [11]. The six approved NAs are highly effective in suppressing the HBV replication by the inhibition of reverse transcription; there has been high success in halting inflammation of the liver and delaying the progression to cirrhosis

and ultimately to HCC. Since 1998 the treatment with NAs - initially with lamivudine [12], then entecavir [13] and finally tenofovir [14] - for CHB, has resulted in the aforementioned decreased incidence of HCC.

Despite successful viral suppression with NAs, the risk for developing HBV associated HCC has remained persistent especially in patients with underlying cirrhosis [15-21]. In our series at the Liver Disease Prevention Center as depicted in Table 1, the presence of HCC - although at low rates - has appeared in patients whose HBV DNA levels have remained undetectable even for over a decade with NA therapy [20].

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

pt	Date startTx	Chang in Child Class on Tx	Date HCC Dx	Yrs on anti-HBV Tx at HCC Dx	Yrswith HBV DNA(-)	Age(yr) at HCC Dx	Size(cm) and site of HCC	HBVDNA at HCC Dx	Anti-HBV Tx	Status
1	4/1998	B→A	7/2007	9.3	3.4*	53	1.1 Junction	UD#	LAM+TDF	alive
2	6/2002	A→A	8/2007	5.2	4.7	70	1.0 Rt	UD	LAM+TDF	alive
3	1/1998	B→A	3/2008	10.2	8.2	68	2.8x2.5	UD	LAM+TDF	dead
4	5/1998	A→A	2/2008	9.8	6.7	76	1.8x0.9 Lt	UD	LAM+TDF	alive
5	7/2004	B→B	9/2009	5.2	4.7	52	3.9 Rt	UD	LAM+TDF	alive
6	7/2001	B→B	9/2010	9.2	4.1	54	2.8 Rt	UD	LAM+TDF	dead
7	2/2004	A→A	6/2013	9.3	7.7	57	2.5 Lt med	UD	TDF	dead
8	2/1996	A→A	7/2013	17.4	9.7	73	1.6x1.4 Rt	UD	TDF	dead
9	8/1997	A→A	6/2014	16.8	5.9	54	2.2x1.9 Lt lat	UD	ETV	alive
10	5/1996	A→A	10/2014	18.4	10.4	74	3.4 Rt	UD	LAM+TDF	dead
11	2/2000	A→A	4/2015	15.2	12.4	62	3.4x3.4 Rt	UD	TDF	alive
12	2/2000	B→A-	5/2015	15.3	12.2	65	3.8 Rt	UD	TDF	alive

LAM, Iamivudine, TDF, Tenofovir disoproxil fumarate #UD: undetectable
*pt has been DNA (-) until 3 yrs before HBV DNA became detectable (22 IU/ml) when TDF was added

*Table 1 above is from reference (20).

It is well understood that the persistent HCC risk is largely attributed to the inability of current NAs to eradicate HBV DNA in the hepatocytes. While NAs are effective in suppressing HBV replication, they do not eliminate intra-nuclear covalently closed circular DNA (cccDNA) which is the template for viral replication and a key mechanism for HBV chronicity [22].

As described by Levrero et al [23] in figure 1 below, multiple steps for eradication of HBV include: 1) Entry inhibition of the virus through the specific receptor (heparin sulfate proteoglycans); 2) Inhibition of the relaxed circular (rcDNA) from entering the hepatocyte nucleus to become cccDNA; 3) interference of transcription to form multiple mRNAs including pre-genomic RNA (pgRNA), core proteins, P protein; 4) inhibition of immature nucleocapsid formation; 5) inhibition of reverse transcription of the pgRNA to form the new partially double-stranded viral DNA, and finally release of mature enveloped virions to blood from the hepatocytes.

Efforts to enhance the innate and adaptive immunity of the host is in progress with development of drugs including an HBV specific T cell vaccine and anti-PD1 monoclonal antibody amongst other treatments.

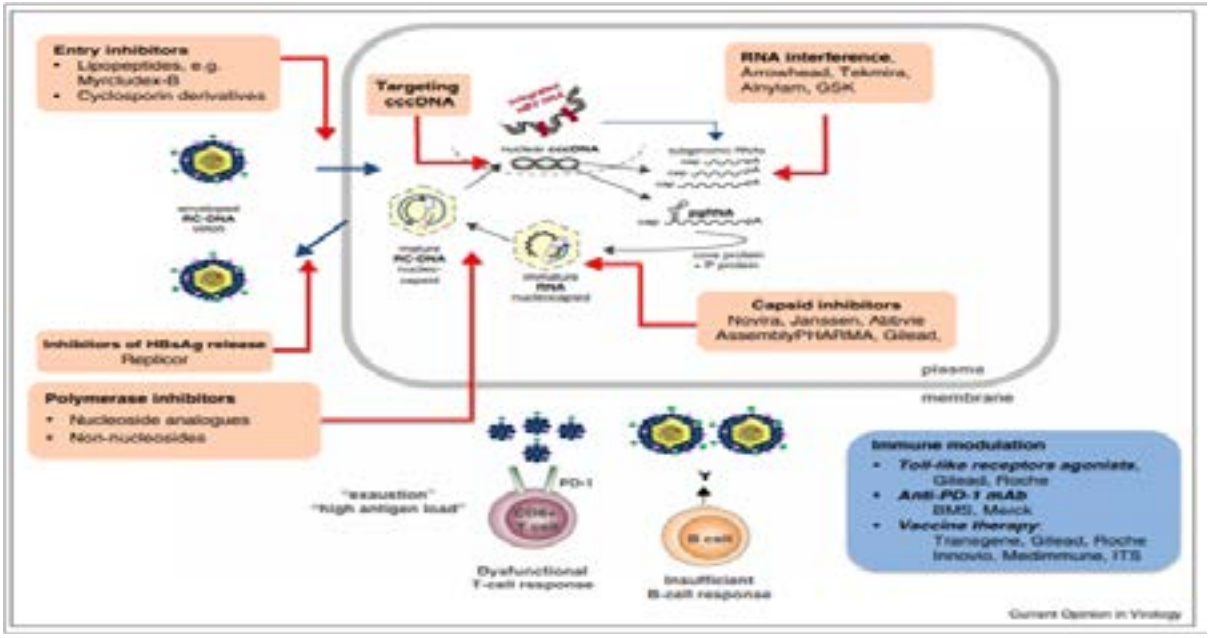

Figure 1: The landscape of HBV cure efforts [23].

Current anti-HBV drugs including all NAs have been successful in inhibition of only one stage of the viral replication process - the reverse transcription from pgRNA to HBV DNA. There is need for medication to affect the multiple steps as described above, ideally with elimination of cccDNA. As shown in Table 2 below which is summarized by Block et al and Hepatitis B Foundation [24], multiple phase I and II studies are currently in progress. Such phase II trials focus on the inhibition of hepatocyte entry, interference of transcription of mRNAs and inhibition of capsid formation.

Table 2. HBV Cure Watch (24)	
Direct Acting Antivirals	**Phase of Trial**
Targets the virus and interferes with specific steps of HBV lifecycle to prevent replication	
Entry Inhibitors (Mycludex)	II
Silencing RNAs (siRNAs)	I, I/II, Preclinical
Capsid Inhibitors	I, II, Preclinical
HBsAg Inhibitors	II
Antisense molecules	I
Indirect Acting Antivirals	**Phase of Trial**
Targets the human immune system to attack HBV	
Therapeutic Vaccines	I, II, Preclinical
Innate Immune Defense Pathway	I, II
Host Acting Pathway	I, Preclinical

Recently there was a new report of a core protein inhibitor activity presented at 2019 AASLD meeting as shown in Figure 2 [25]. This core protein inhibitor, ABI-HO731 has been known to interfere with viral capsid formation and entry of the relaxed circular DNA into the nucleus which results in formation of cccDNA. In a phase II trial with this core protein inhibitor the investigators found that in addition to the activities described above, it also interfered mRNA transcription, notably the pregenomic RNA.

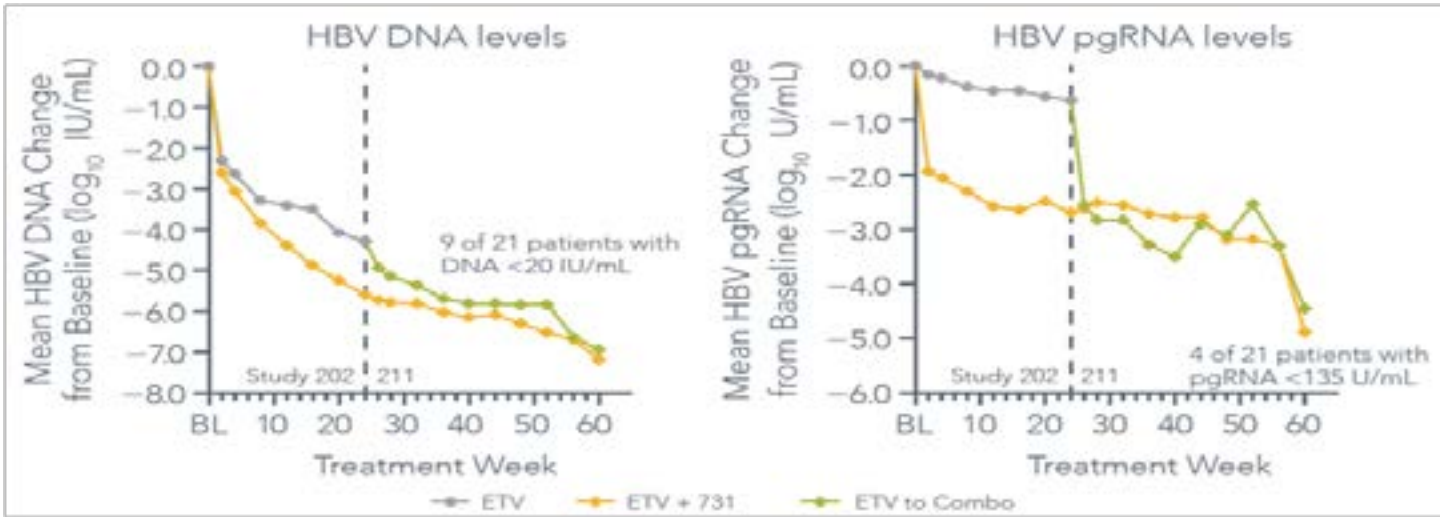

Figure 2: In Study 202, Entecavir alone and Entecavir+ABI-H0731 (Core Protein Inhibitor) and in Study 211, Entecavir alone was switched to ABI-H0731+ Entecavir [25].

The combination of ABI-H0731 +Nucleoside anaglogue (Entecavir) demonstrated faster and greater reductions in viral nucleic acid levels than Entecavir therapy alone, with decrease of pgRNA. Switch from ETV to ABI-H0731 + ETV resulted in immediate and enhanced declines in both HBV DNA and pgRNA levels, confirming the contribution of ABI-H0731 to the combination. The mean HBV DNA and pgRNA declines from baseline at Week 48 were 6.3 logs and 3.0 logs, respectively, for patients treated with ABI-H0731 + ETV • Continued HBV DNA declines are observed on combination therapy • The observed acceleration in second phase decline of HBV pgRNA levels likely reflects reductions of cccDNA pools [25].

While a cure for HBV has not yet been achieved secondary to the complexity of the HBV replication cycle, there is continued worldwide effort in the eradication of this infection. With multiple phase I and phase II clinical trials in process, we are optimistic that we are on the horizon of finding a cure.

References

1. Blumberg BS, Alter HJ, Visnich S. A "new" antigen in leukemia sera. JAMA. 1965; 191: 541-6.
2. Dane DS, Cameron CH, Briggs M. Virus-like particles in serum of patients with Australia-antigen-associated hepatitis. Lancet. 1970; 1: 695-8.
3. Magnius LO, Espmark JA. New specificities in Australia antigen positive sera distinct from the Le Bouvier determinants. J Immunol. 1972; 109: 1017-21.
4. Hann HWL, Kim CY, London WT, Whitford P, Blumberg BS. Hepatitis B virus and primary hepatocellular carcinoma: Family studies in Korea. Int. J. Cancer. 1982; 30:47-51.
5. Halegoua-De Marzio D, Hann HW. Then and now: the progress in hepatitis B treatment over the past 20 years. World J Gastroenterol. 2014; 20: 401-13.
6. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin, DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int. J. Cancer. 2010; 127: 2893-917.
7. Jemal A, Bray F, Center M.M, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: A Cancer Journal for Clinicians. 2011; 61: 69-90.
8. Perz JF, Armstrong GL, Farrington LA, Hutin YJF, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006; 45: 529-38.
9. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. Gastroenterology. 2004; 127: S27-S34.
10. Ha J, Yan M, Aguilar M, Bhuket T, Tana MM, Liu B, et al. Race/ethnicity-specific disparities in cancer incidence, burden of disease, and overall survival among patients with hepatocellular carcinoma in the United States.Cancer. 2016; 122: 2512-23.
11. Pollack JR, Ganem D. Site-specific RNA binding by a hepatitis B virus reverse transcriptase initiates two distinct reactions: RNA packaging and DNA synthesis. J Virol. 1994; 68: 5579-87.
12. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med. 2004; 351: 1521-31.
13. Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology. 2013; 58(1): 98-107

14. Kim WR, Loomba R, Berg T, Aguilar Schall RE, Yee LJ, Dinh PV, et al. Impact of long-term tenofovir disoproxil fumarate on incidence of hepatocellular carcinoma in patients with chronic hepatitis B. Cancer. 2015; 121(20): 3631-8.

15. Papatheodoridis GV, Manolakopoulos S, Touloumi G, Vourli G, Raptopoulou-Gigi M, Vafiadis-Zoumbouli I, et al. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. Gut. 2011; 60: 1109-16.

16. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol. 2010; 53: 348-56.

17. Vlachogiannakos J, Papatheodoridis G. Hepatocellular carcinoma in chronic hepatitis B patients under antiviral therapy. World J Gastroenterol. 2013; 19: 8822-30.

18. Dargan A, Wong SY, Coben R, Conn MI, Prieto J, Kroop H, et al. Persistent risk for hepatocellular carcinoma after more than a decade of successful hepatitis B virus suppression. Minerva Gastroenterol Dietol. 2017; 63: 74-6.

19. Ando Y, Ishigami M, Ishizu Y, Kuzuya T, Honda T, Hayashi K, et al. Cumulative incidence and risk factors for the development of hepatocellular carcinoma in patients with chronic hepatitis B who achieved sustained disappearance of viremia by nucleos(t)ide analogue treatment. Hepatol Res. 2017; 48: 240-51.

20. Yoo J, Hann HW, Coben R, Conn M, DiMarino AJ. Update Treatment for HBV Infection and Persistent Risk for Hepatocellular Carcinoma: Prospect for an HBV Cure. Diseases. 2018; 6: 27.

21. Shinn BJ, Martin A, Coben RM, Conn M, Prieto J, Kroop H, et al. Persistent risk for new, subsequent new and recurrent hepatocellular carcinoma despite Successful anti-hepatitis B virus therapy and tumor ablation: The need for hepatitis B virus cure. World J Hepatol. 2019; 11: 65-73.

22. Allweiss L, Dandri M. The Role of cccDNA in HBV maintenance. Viruses. 2017; 9: 156.

23. Levrero M, Testoni B, Zoulim F. HBV cure: why, how and when? Curr Opin Vir. 2016; 18: 135-43.

24. Block TM, Alter H, Brown N, Brownstein A, Brosgart C, Chang KM, et al. Antiviral Research priorities for the discovery of a cure for chronic hepatitis B: Report of a workshop. Antiviral Res 2018; 150: 93-100.

25. Sulkowski MS, Agarwal K, Fung S, Yuen MF, MA X, Lalezari J, et al. Continued Therapy with ABI-H0731+NrtI Results in Sequential Reduction/Loss of HBV DNA, HBV RNA, HBeAg, HBcrAg and HBsAg in HBeAg Positive Patients. AASLD 2019. Poster. LP1.