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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1. Short Communication

Since the discovery of the Hepatitis B Surface Antigen [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 Blumberg 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), telbivirusine (2006), tenofovir disoproxil fumarate (2008), and tenofovir alafenamide (2016) most recently. The efficacy in terms of viral suppression of these NAs has well been documented by multiple studies as reviewed [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 be attributed to multiple factors including widespread use of HBV vaccination - 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].

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 [23] in the (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-PDI monoclonal antibody amongst other treatments.

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 tran-

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

<table>
<thead>
<tr>
<th>pt</th>
<th>Date startTx</th>
<th>Chang in Child Class on Tx</th>
<th>Date HCC Dx</th>
<th>Yrs on anti-HBV Tx at HCC Dx</th>
<th>Yrs with HBV DNA(+</th>
<th>Age(yr) at HCC Dx</th>
<th>Size(cm) and site of HCC</th>
<th>HBVDNA at HCC Dx</th>
<th>Anti-HBV Tx</th>
<th>Status</th>
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<tr>
<td>2</td>
<td>6/2002</td>
<td>A→A</td>
<td>8/2007</td>
<td>5.2</td>
<td>4.7</td>
<td>70</td>
<td>1.0 Rt</td>
<td>UD</td>
<td>LAM+TDF</td>
<td>alive</td>
</tr>
<tr>
<td>3</td>
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<td>B→A</td>
<td>3/2008</td>
<td>10.2</td>
<td>8.2</td>
<td>68</td>
<td>2.8x2.5</td>
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<td>LAM+TDF</td>
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<td>A→A</td>
<td>2/2008</td>
<td>9.8</td>
<td>6.7</td>
<td>76</td>
<td>1.8x0.9 Lt</td>
<td>UD</td>
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<tr>
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<td>9/2009</td>
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<td>4.7</td>
<td>52</td>
<td>3.9 Rt</td>
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<tr>
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<td>9/2010</td>
<td>9.2</td>
<td>4.1</td>
<td>54</td>
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<td>6/2013</td>
<td>9.3</td>
<td>7.7</td>
<td>57</td>
<td>2.5Lt med</td>
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<td>9.7</td>
<td>73</td>
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<td>UD</td>
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<tr>
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<td>6/2014</td>
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<td>2.2x1.9 Lt lat</td>
<td>UD</td>
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<td>10.4</td>
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<td>3.8 Rt</td>
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Figure 1: The landscape of HBV cure efforts [23].

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].

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-H0731 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.

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

2. Dane DS, Cameron CH, Briggs M. Virus-like particles in serum of


