Evolving Scenarios in HBV Therapy

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First, let me say that many academic laboratories, biotech and pharmaceutical companies nowadays are investing considerable resources to develop new "curative" treatments for CHB [1]. These treatments not only involve approaches that directly target HBV but also approaches that either target specific cellular functions required by the virus or that affect the host immune response. Of note, the scientific community has long recognized that a "sterilizing" cure - defined as the long-lasting elimination from the liver of the covalently closed circular (ccc) DNA that functions as the viral transcriptional template - will be difficult to attain in the foreseeable future [2]. In its place, the concept of "functional" cure – defined as the loss of detectable serum hepatitis B surface antigen (HBsAg) with or without seroconversion to anti-HBs antibody – has taken hold [2]. The idea is that serum HBsAg loss may serve as a surrogate marker for long-term suppression of HBV replication and immune control, thus representing a more attainable goal for future curative strategies allowing cessation of nucleos(t)ide analogue (NUC) treatment [2].

What is the landscape of new direct acting antivirals (DAAs)?

Several new DAAs have already reached the clinic and - among them – agents that inhibit either the encapsidation of pregenomic RNA (the so-called Capsid Assembly Modulators or CAMs) or the expression/function of viral transcripts (e.g. siRNAs and antisense oligonucleotides) are significantly advanced in their development and deserve further discussion. As orally available and well tolerated drugs that interfere with pregenomic RNA packaging and – possibly - cccDNA biogenesis, CAMs appear particularly attractive and suited for enduring treatments in combination with NUCs [3]. Success at promoting a functional cure may well depend on their relative capacity of zeroing the levels of viremia long term, thus reducing the infectivity potential of the extremely low-abundant infectious material (< 10 virions/ml) that is thought to still circulate in the blood of NUC-treated patients [4]. Prolonged CAM treatment, therefore, may significantly suppress the overall viral replication capacity of the liver and this could eventually lower the levels of serum HBsAg by directly reducing the cccDNA-dependent production of this antigen (note that CAMs would not impact serum HBsAg coming from integrated forms of HBV DNA). A limitation in the efficacy of CAMs may result from the emergence of naturally occurring and/or treatment-induced HBV variants that are intrinsically resistant to their mechanism of action (i.e. CAMs bind to a pocket at the HBV core dimer-dimer interface and induce the formation of empty or aberrant capsids [3]). Development and progression of CAMs with high potency, however, should mitigate this effect. Another limitation relies on the possibility that blocking the capacity of the few residual circulating virions to replenish or de novo establish the hepatocellular pools of cccDNA molecules may not be sufficient, as the persistence of cccDNA in the liver of NUC-treated patients might reflect a very long lifespan of this molecule and/or the capacity of HBV to directly spread from hepatocyte to hepatocyte. The results on ongoing and future clinical studies involving different CAMs may shed some light on these important issues.

Non-orally available agents that target overlapping HBV transcripts such as siRNAs and antisense oligonucleotides have recently gained attention as they showed capacity to lower the viremia and the levels of circulating viral antigens (including HBsAg) in CHB patients [1]. Besides their intrinsic antiviral potential (ultimately limiting the release of infectious virions from infected hepatocytes), much of the expectation for these approaches relies on

the idea that reducing the viral antigen burden in the liver or blood could result in a sort of "awakening" of otherwise dysfunctional HBV-specific adaptive immune responses. Unfortunately, definitive data about this latter concept are missing and, indeed, recent preclinical work (where the levels of intracellular and circulating HBV antigens have been experimentally reduced in animal models of HBV infection) seems to disagree with such idea [5, 6]. Again, ongoing and future clinical studies may provide useful information on this topic. Finally, it is worth reminding that other potentially interesting DAAs that, for instance, tackle viral entry or the biogenesis and maintenance of cccDNA are under development [1]. We will see in the next few years if and how these approaches progress to the clinical stage.

How about combining DAAs with immunotherapeutic approaches?

This is an attractive concept that the scientific community is actually embracing as necessary strategy to achieve functional cure in a significant percentage of CHB patients (> 30% of them). Problems are that still we do not know which is the best combination therapy and, just as importantly, which are the best cohorts of patients that may benefit from it.

Therapeutics stimulating the innate immune response such as TLR7 and TLR8 agonists have been and are being clinically evaluated in monotherapy studies and time will tell whether they could also be considered in DAA combination studies [1]. As per stimulators of HBV-specific adaptive immune responses that have already entered the clinic (e.g. therapeutic vaccinations and anti-PD-1 treatments) or that are supposed to do so in the future (e.g. anti-PDL-1 treatments, CAR- T cells or TCR-redirected T cells) is just too early to express an opinion and much should be done before considering combination or add-on strategies with approved or yet to be approved DAAs. Talking about patient selection, much should also be done as per the identification of predictors of immunological responses and this may involve quantitative/qualitative analyses of HBV-specific B and T cell responses at baseline and the development of assays quantitatively measuring circulating HBs-anti-HBs immune-complexes. Not to mention that patient selection would greatly benefit from intrahepatic analyses aimed, for instance, at defining the relative percentage of HBV-expressing hepatocytes or the overall amount of ccc-DNA and discussions among academic and non-academic scientists and physicians about the cost/benefit of re-introducing the possibility of performing liver biopsies are certainly warranted.

References

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