Combination treatment of a TLR7/8 dual agonist with an antisense oligonucleotide bepirovirsen and entecavir leads to additive HBsAg decline in the AAV-HBV mouse model

Ke Qiu1, Zhiling Deng1, Taiyu He1, Zhi-Wei Chen1, Taichang Yuan2, Guozhi Tang2, Ming-Li Peng1, Hong Ren1

1Key Laboratory of Molecular Biology for Infectious Diseases (Ministry of Education), Institute for Viral Hepatitis, the Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, 2Shanghai Visonpharma Co., LTD, Shanghai, China

Email: renhong0531@vip.sina.com

Background and Aims: Achieving high levels of functional cure of chronic hepatitis B (CHB) will likely require a combination regimen that blocks viral replication, reduces antigen load, and activates host immune responses to control residual virus. Bepirovirsen is a promising antisense oligonucleotide (ASO) against HBV which can significantly reduce hepatitis B surface antigen (HBsAg) but the duration is limited. TLR7 and TLR8 agonists induced durable antiviral efficacy in preclinical studies. However, the effect of single-acting TLR agonists in reducing HBsAg in clinical studies is limited. Recently, TLR7/8 dual acting agonists have been reported can induce broad cytokines which may provide novel opportunities towards functional HBV cure. This current work describes the investigation of combinations of a TLR7/8 dual acting agonist (VE03702) with bepirovirsen (ASO) and entecavir (ETV) in a mouse model of HBV infection. Sequential and concomitant treatment of these agents were explored and the results may inform future clinical combination trial design.

Method: C57BL/6 mice infected with rAAV8-1.3HBV were treated ETV and ASO for three weeks then stopped treatment or switched to VE03702 or Peg-IFN treatment for four weeks. ETV was orally administered at 0.1mg/kg daily, and ASO was dosed at 50 mg/kg, subcutaneously once a week. VE03702 was dosed at 0.05 mg/kg, subcutaneously once a week, and Peg-IFN was dosed at 30g/kg, subcutaneously twice a week. HBsAg was the key viral endpoint measured for these studies. Additionally, two potential clinical treatment paradigms were tested where both ASO and Peg-IFN were administered concurrently or ASO preceding treatment with Peg-IFN sequentially.

Results: In the first three weeks, concomitant treatment of ASO and ETV resulted in an up to 1.67 log reduction in HBsAg levels. After stopping treatment of ASO, serum HBsAg rapidly rebounded to pretreatment levels within 4 weeks while HBV DNA was still below the lower detection limit. When switching to VE03702 treatment after stopping ASO administration, additional decreases reaching 4.5 logs in HBsAg were observed. After 4 doses of VE03702, HBsAg loss was observed and anti-HBs antibodies in the serum were detected. For the sequential treatment of ASO followed by Peg-IFN, rapid rebound in HBsAg occurred after discontinuation of ASO resulting in no added benefit in this regimen. There is no significant difference between the sequential and concurrent treatment paradigms of Peg-IFN and ASO.

Conclusion: Combinations of a TLR7/8 dual agonist (VE03702) and bepirovirsen (ASO) and ETV provide additional reduction in HBsAg when dosed sequentially in the AAV-HBV mouse model of HBV. VE03702 showed more effectiveness than Peg-IFN in terms of avoiding HBsAg rebound after ASO discontinuation, suggesting the potential for clinical translation.