

DEEP SEQUENCING SHOWS THAT THE PRESENCE OF HBV BCP/PC VARIANTS REDUCES THE RATE OF HBSAG LOSS AMONG HBEAG-POSITIVE CHB PATIENTS TREATED WITH LONG-TERM TENOFOVIR DF THERAPY

Littlejohn M¹, Yuen L¹, Wong D^{1,2}, Bayliss J¹, Rosenberg G¹, Jackson K¹, Sozzi V¹, Edwards R¹, Gaggar A³, Kitrinis K³, Subramanian M³, Marcellin P⁴, Buti M⁵, Janssen H^{6,7}, Gane E⁸, Thompson A², Locarnini S¹, Revill P¹.

¹Molecular Research and Development, Victorian Infectious Diseases Reference Laboratory, Peter Doherty Institute for Infection and Immunity, Melbourne, Australia

²Department of Gastroenterology, St. Vincent's Hospital, Melbourne, Australia

³Gilead Sciences, Foster City, California, USA

⁴Hôpital Beaujon, University of Paris, Clichy, France

⁵Liver Unit, Valle d'Hebron (Ciberehd) University Hospital, Barcelona, Spain

⁶Toronto Center for Liver Diseases, Toronto Western and General Hospital, University Health Network, University of Toronto, Toronto, Canada

⁷Department of Gastroenterology and Hepatology, Erasmus MC University Hospital, Rotterdam, The Netherlands

⁸Auckland City Hospital, Auckland, New Zealand

Background: HBsAg loss, or functional cure, is now an important treatment endpoint for novel antiviral agents in clinical development however this is a rare event. Basal core promoter (BCP) and precore (PC) variants are immune escape variants selected during the development of HBeAg-negative CHB. We hypothesized that the presence of BCP/PC variants will reduce the probability of HBsAg loss during long-term NA therapy, and that conversely, individuals with WT virus would be most likely to achieve HBsAg loss.

Methods: GS-US-174-0103 evaluated the efficacy of tenofovir for the treatment of HBeAg-positive CHB. We used next generation sequencing (NGS) to identify the presence of BCP and PC variants at baseline in this study population (detection threshold 1%). We tested for an association between the presence of BCP/PC variants and HBsAg loss at week 192, adjusting for relevant co-variables including age, gender, HBV genotype, HBV DNA levels, HBsAg levels and HBeAg levels.

Results: Baseline serum samples from 157 CHB patients were analyzed by NGS. BCP/PC variants were common and presence varied by genotype. HBsAg loss was more common in the presence of WT vs. BCP/PC variants (41% vs. 3%, $P < 0.0001$). The utility of BCP/PC sequence for predicting HBsAg loss was most useful among individuals with Gt A and D HBV (Gt A, HBsAg loss 50% vs. 8% for WT vs. BCP/PC; Gt D, 40% vs. 3%; $P < 0.05$). Only 1 case of HBsAg loss was observed in individuals with Gt B/C HBV, with BCP/PC variants detected in almost all individuals. The presence of WT virus was independently associated with HBsAg loss in multivariable models.

Conclusion: Patients with detectable BCP/PC mutants, even at low frequency using NGS, have a lower probability of HBsAg loss. Strategies to achieve functional cure of HBV infection through antiviral therapy should consider stratifying patients according to BCP/PC sequence.

Disclosure of Interest: This research was funded by Gilead Sciences.