Phase 1b/2a study of heterologous ChAdOx1-HBV/MVA-HBV therapeutic vaccination (VTP-300) as monotherapy and combined with low-dose nivolumab in virally suppressed patients with CHB on nucleos(t)ide analogues

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INTRODUCTION: Induction of a CD8+ T cell response to HBV is considered to be a needed mechanism to achieve a functional cure of chronic hepatitis B (CHB). The highest magnitude CD8+ T cell responses achieved to date in man have used replication incompetent adenoviral vectors followed by attenuated poxvirus vector boosts.

AIM: The goal of this study is to assess the immunogenicity and activity of the ChAdOx1-HBV/MVA-HBV regimen in CHB patients.

METHODS: Vaccitech has developed an HBV immunotherapeutic using a chimpanzee adenovirus vector [ChAdOx1-HBV] and a heterologous Modified vaccinia Ankara boost (MVA-HBV), both encoding the inactivated polymerase, core, and the entire E region from a consensus genotype C virus (HBV-300). A Phase 2b/2a trial has enrolled 55 patients with virally suppressed CHB (on antivirals for a minimum of one year with viral load undetectable and HBsAg <4,000 IU/L) in Taiwan, South Korea and the UK (NCT047795).

As of May 2022, the study had closed recruitment, having exceeded enrolment at n=55 patients. An amendment closed Groups 1 and 4 early due to interim HBsAg data. Visits were conducted at days 0, 7, 28, and months 3, 6, and 9. HBsAg data shown were collected through May 9, 2022. Individual plots show results for those patients with data through at least month 3.

Immunologic assays are performed with peptide pools encompassing core, Pol (4 pools pre-51, pre-52, 5 for the gamma IFN ELISPOT) and 4 pools (Core, Pol1, Pol2, S) for the gamma IFN ELISPOT assay. The CS assay was used to examine the magnitude of responses with stimulation ex vivo without intracellular expansion. The CS used the following phenotypic and activation markers: CD3, CD4, CD8, IFN-γ, IL-2, TNFα, CCR7, CD45RA, CD27, CD154.

Construct Design

Study Design

Group 1 (n=18)
MVA-HBV (1 x 10^5 pfu); MVA-HBV (1 x 10^7 pfu)

Group 2 (n=18)
ChAdOx (1.5 x 10^9 pfu); MVA-HBV (1 x 10^5 pfu)

Group 3 (n=18)
ChAdOx (1.5 x 10^9 pfu); MVA-HBV (1 x 10^7 pfu) + LD nivolumab (0.3 mg/kg)

Group 4 (n=9)
ChAdOx (1.5 x 10^9 pfu) + LD nivolumab (0.3 mg/kg); MVA-HBV (1 x 10^5 pfu); MVA-HBV (1 x 10^7 pfu)

Major enrollment criteria
• On effective antiviral treatment for one year
• HBV DNA<40 copies/mL
• HBsAg<4,000 IU/L

Safety

• To date no vaccine-related SAEs
• Two patients with mild, non-serious reactogenic events
• Local reactions have been mild or moderate

Figure 1: Surface antigen responses by group and individual

Figure 2: Decline in relation to starting HBsAg levels

Figure 3: T cell immune responses

CONCLUSIONS: VTP-300 as monotherapy and in combination with LD nivolumab was safely administered, with no treatment-related SAEs, and infrequent transient transaminis.

Significant, durable reductions of HBsAg were seen in patients in the MVA monotherapy group (Group 2).
• 3 patients had 0.7, 0.7 and 1.4 log10 declines 2 mos post last dose
• These dramatic declines are persisting in all 3 patients at latest follow-up 5 or 8 months after the last dose of VTP-300
• The mean reduction in HBsAg was over 1 log10 at 6 months
• This effect persisted with a mean decline of 1.15 log10 at 8 months after the last dose
• Effect most prominent with starting values HBsAg < 1,000 IU/mL
• One patient in group 3 developed a non-detectable HBsAg level, which continued 8 months after last dose
• The lowering of HBsAg persisted until the last measurement in all patients with >0.5 log10 reduction. This compares favorably to the lack of durability seen with direct acting agents to date
• No reductions ≥1 log10 were seen in Group 1 patients who received 2 doses of HBV or in patients who received low-dose nivolumab with both doses of VTP-300 (Group 4). These groups were discontinued after interim analysis
• A robust T cell response against all encoded antigens is observed following VTP-300, notable for marked CD8+ T cell predominance, which had never been achieved by any other immunotherapeutic
• A trial to look at timing of low dose nivolumab and additional doses of the HBV boost to VTP-300 has been implemented, with first patient dosed expected by Q2 2023 (NCT05343841)

These results portend well for the collaborative study with Arbutus 725 siRNA, in which HBsAg is expected to be lowered to <200 IU/mL in the majority of the patients prior to receiving VTP-300

Trial Recruiting Patients: Kaohsiung Medical University Chung-Ho Memorial Hospital, 2National Taiwan University Hospital, 3King’s College Hospital NHS Foundation Trust (K Agarwal), 4Nottingham University Hospitals NHS Trust (S Ryder), 5Faulk University, 6Pusan National University JongAng Hospital, 7Kyoungpook National University Hospital (B Jang); 8Seoul National University Hospital (YS Lim); 9Hoseo University College of Medicine (S Ryder); 10Chia-Yi Christian Hospital (C Y Chen); 11E-Da Hospital (WY Su); 12Dalain Tsu Chi General Hospital (K Agarwal); 13King’s College Hospital NHS Foundation Trust (K Agarwal); 14Nottingham University Hospitals NHS Trust (S Ryder), 15Faulk University, 16Pusan National University JongAng Hospital (B Jang); 17Kyoungpook National University Hospital (B Jang); 18Seoul National University Hospital (YS Lim); 19Hoseo University College of Medicine (S Ryder); 20Chia-Yi Christian Hospital (C Y Chen); 21E-Da Hospital (WY Su); 22Dalain Tsu Chi General Hospital (K Agarwal)

Design and Development of a Multi-HBV Antigen Encoded in Chimpanzee Adenoviral and Modified Vaccinia Ankara Viral Vectors; A Novel Therapeutic Vaccine Strategy against HBV. Vaccines. 2020 Apr 18;8(4):222

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