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IMMUNE-MODULATORY EFFECTS OF PEVIFOSCORVIR SODIUM IN HBEAG-POSITIVE PATIENTS WITH CHRONIC HEPATITIS B INFECTION

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INTRODUCTION

- **Pevifoscorvir sodium (PEVY, ALG-000184)** is a prodrug of a novel Type E Capsid Assembly Modulator (ALG-001075), which demonstrated potent on-treatment viral antigen suppression in the Phase 1 study ALG-000184-201 (NCT04536337) in participants with chronic hepatitis B infection who received oral, once daily 300 mg PEVY for 96 weeks.[1]
- After the end of the PEVY treatment (EOT), these antiviral effects were sustained in a cohort of 9 HBeAg+ participants for 24-48 weeks of follow-up (FU) while on entecavir (ETV).[2]
- Here, we report the immunological changes during and after PEVY 300 mg treatment.

AIM

To characterize the immunomodulatory effects in the peripheral compartment in 9 HBeAg+ participants patients with chronic hepatitis B infection during and after PEVY 300 mg treatment.

METHOD

- 9 of 10 HBeAg+ participants from study ALG-000184-201 were recruited for 24-48 weeks (wks) of ETV-only FU.
- Peripheral blood was collected at baseline, wks 48 and 96 of PEVY 300 mg, and FU 24-48 wks after EOT.
- Plasma cytokine levels were determined by ProcartaPlexTM multiplex kits.
- PBMCs were evaluated ex vivo by multicolor flow cytometry for CD4+, CD8+, regulatory T cells (Tregs), NK cells, and coinhibitory markers. Higher viability was observed in the PBMC from the last time point compared to baseline, week 48 and week 96.
- HBV-specific T cell function was assessed by Fluorospot assay for IFNγ, TNFα, and IL-2 after co-culturing synthetic HBV peptide (envelope [env] and polymerase [pol]) using the ImmunoSpot® Software.

RESULTS

PEVY 300 mg 96 weeks (10 HBeAg+, 11 HBeAg-) → Follow-up (NA) 8 weeks (10 HBeAg+, 11 HBeAg-) → LTFU (ETV) 24-48 weeks (9 HBeAg+)

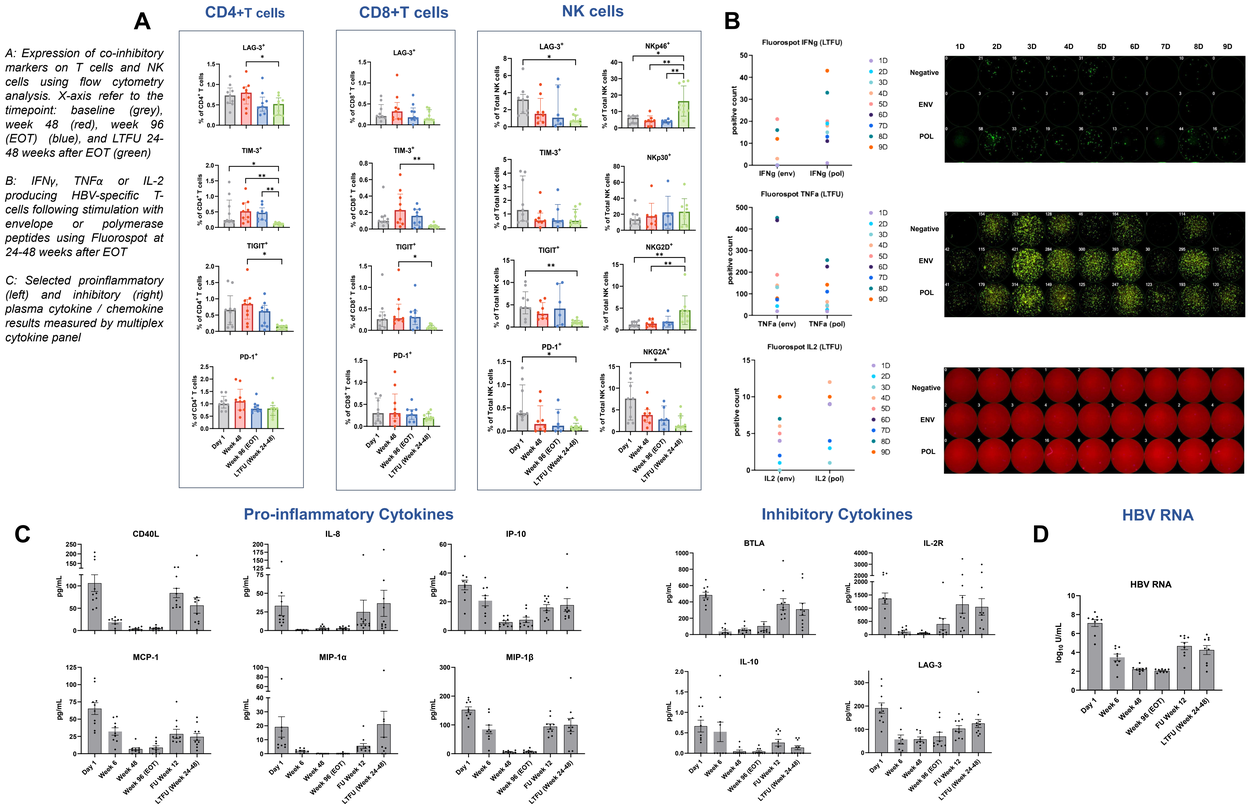
ALG-000184-201 Part 4 Cohort B | **REG26-1185**

- Expression of co-inhibitory markers (≥2 among LAG-3, TIM-3, TIGIT, PD-1) on CD4+T, CD8+T and NK cells, and proportion of Treg were significantly reduced at 24-48 wks after EOT compared to earlier timepoints (Figure A).
- Expression of activating NK receptors (NKG2D, NKp46) increased over time, while expression of inhibitory NK receptor (NKG2A) was reduced on NK cells (**Figure A**).
- No apparent correlation of baseline qHBsAg levels with the PBMC phenotypes, but baseline TIGIT expression on CD4+T was positively correlated with week 96 HBsAg level and HBsAg change at week 48, week 96, and at FU
- Baseline TIGIT expression on CD8+T cells was positively correlated with week 96 HBsAg level.
- Fluorospot analysis showed presence of HBV-specific T cells [env or pol] producing IFN-γ, TNF-α, and IL-2 (**Figure B**) at 24-48 wks after EOT.
- The frequency of IL-2 producing HBV-specific T cells (pol) were negatively correlated with TIM-3 on CD4+T and TIGIT on CD8+T at FU.
- IFN-γ-producing HBV-specific T cells [pol] were also negatively correlated with LAG-3 on CD4+T cells at FU.
- IFN-γ-producing T cells were positively correlated with LAG-3 and TIGIT on NK cells, suggestive of involvement of NK cells in modulating HBV-specific T cell function.
- Plasma cytokine analysis revealed significant reduction of both pro-inflammatory cytokines (CD40L, IL-8, IP-10, MCP-1, MIP-1α and MIP-1β) and inhibitory cytokines (BTLA, CTLA, IL-2R and LAG-3) (**Figure C**).
  - Suppression of these cytokines during PEVY 300 mg treatment phase and partial rebound during ETV FU indicate that cytokines levels mirror the relative concentrations of viral RNA (**Figure D**).
  - Induction of pro- and anti-inflammatory cytokines is suggestive of complex immunomodulatory effects associated with PEVY which persisted partially after EOT.

A: Expression of co-inhibitory markers on T cells and NK cells using flow cytometry analysis. X-axis refer to the timepoint: baseline (grey), week 48 (red), week 96 (EOT) (blue), and LTFU 24-48 weeks after EOT (green)

B: IFNγ, TNFα or IL-2 producing HBV-specific T-cells following stimulation with envelope or polymerase peptides using Fluorospot at 24-48 weeks after EOT

C: Selected proinflammatory (left) and inhibitory (right) plasma cytokine / chemokine results measured by multiplex cytokine panel



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CONCLUSIONS

In a cohort of 9 HBeAg+ participants, potent suppression of HBsAg during and after PEVY treatment was associated with immunological changes in the peripheral compartment, favoring enhancement of immune control of chronic HBV infection.