Intrahepatic CD8+ T cells correlate with significant declines in HBV viral load and S antigen following a single vaccination with VRON-2020 in an AAV mouse model

INTRODUCTION

Despite HBV genotype a vaccine, chronic HBV infection remains a high unmet need. Most of the 257 million people who are living with HBV are undiagnosed and untreated. In the United States, the estimated number of people who have chronic HBV (CHC) is unknown. Chronic HBV infection is characterized by impaired clearance and the accumulation of infected hepatocytes, which leads to hepatic inflammation.

A Aim

To evaluate the immunogenicity and correlations between intrahepatic CD8+ T cell responses and HBV viral load and S antigen decline in a mouse model following a single injection of a genotype B therapeutic vaccine.

METHODS: IMMUNOGENICITY

A A therapeutic vaccine (VRON-2020) was used to induce an immune response.

- Hourly: placebo
- Vaccine: placebo + adeno-associated virus (AAV).

B Antigenic expression

- Adenoviral carriers: Ad5 and Ad26 (AAV, adeno-associated virus).

C B and T lymphocyte cell mediated immune responses

- CD8+ T cells: Cell-mediated immune responses were measured using ELISPOT and IFN-γ ELISA.

METHODS: EFFICACY

A AVON-2020 virucidal activity

- HBV viral load reduction: HBV viral clearance was determined using qPCR and ELISA.

B Correlation between intrahepatic lymphocytes and splenic virus and viral dynamics

- The relationship between intrahepatic CD8+ T cell and viral load was assessed using serologic analysis and HBV DNA quantification.

RESULTS

IMMUNOGENICITY: NON-AAV-TREATED ANIMALS

- Ad5-gDHBV2-vaccinated animals showed significantly higher frequencies of vaccine-induced IFN-γ producing CD8+ T cells in blood (Fig. 2A).

- Ad5-gDHBV2-vaccinated animals showed a significant increase in the number of IFN-γ producing CD8+ T cells in liver (Fig. 2C).

IMMUNOGENICITY: AAV-TREATED ANIMALS

- No significant difference in the number of IFN-γ producing CD8+ T cells was observed in the liver of Ad5-gDHBV2- and Ad5-gDHBV2-vaccinated animals treated with AAV virus (Fig. 2C).

- Ad5-gDHBV2-vaccinated animals showed a significant increase in the number of IFN-γ producing CD8+ T cells in liver (Fig. 2C).

ANTIVIRAL ACTIVITY

- Following a single injection, AAV-gDHBV2-vaccinated mice showed a 3-4 fold increase in IFN-γ production, and a 10-fold increase in the number of IFN-γ producing CD8+ T cells in the spleen (Fig. 3A).

- AAV-gDHBV2-vaccinated mice showed a significant decrease in the number of IFN-γ producing CD8+ T cells in liver (Fig. 3B).

CORRELATIONS BETWEEN INTRAHEPATIC AND SPLenic Virology and CD8+ T cell Dynamics

- Correlations between viral load and CD8+ T cell frequencies were observed in different mouse models.

CONCLUSIONS

- These are the first preclinical HBV vaccine candidates that show correlations between intrahepatic CD8+ T cells and HBV viral load declines in serum.

- Intravenous administration of Ad5-gDHBV2 correlates with lower HBsAg levels.

- The addition of gD, a novel checkpoint modulator of early T cell activation:
  - Markedly enhanced the breadth of CD8+ T cell responses.
  - Significantly improved T cell frequency within the liver.

- A Phase 1b clinical trial of Ad5-gDHBV2 for HBV functional cure is scheduled to begin in Q3 2023.