Achievement of surface antigen clearance in the liver by combination therapy with REP 2139-Ca and nucleoside analogues against chronic hepatitis B
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BACKGROUND

- Nucleic acid polymers (NAPs) are a promising new therapy for chronic hepatitis B treatment since they inhibit HBsAg release from infected hepatocytes.
- The clinical NAP compound, REP 2139-Ca, was shown to achieve the elimination of circulating HBsAg in human subjects with chronic HBV infection.

OBJECTIVES

- The aim of this preclinical study was to assess the antiviral effect of REP 2139-Ca in combination with tenofovir disoproxil fumarate (TDF) and entecavir (ETV) on makers of chronic DHBV infection in vivo.
- We focused on the ability of this novel combination therapy to clear viral surface antigen in the liver.

MATERIALS & METHODS

- Chronic DHBV-carrying ducks, infected as neonates, were randomized into 4 groups (n=10).
- NS (control); monotherapy REP 2139-Ca + TDF; combination therapy REP 2139-Ca + TDF + ETV.

RESULTS

- Antiviral treatment started in 26 days-old animals and lasted for 4 weeks using the following dosing regimens:
  - REP 2139-Ca daily via 10mg/kg IP injection (REP 2139 formulated as a calcium chelate complex).
  - TDF: 1 mg/day /oral gavage
- Importantly, all animals were followed during additional 8 weeks after treatment cessation.

- Antiviral activity was assessed by monitoring serum DHBsAg and anti-DHBpreS (anti-DHBsAg) antibodies by ELISA and serum DHBV DNA by qPCR, liver DHBV DNA and cccDNA by qPCR.

- Sustained functional control of infection (FC) was defined as stable suppression of serum HBsAg and DHBV DNA during 2 years off-therapy.

- Immunostaining of surface antigen (DHBsAg) was performed using primary 1H1 Mab and secondary HRP-conjugated sheep anti-mouse IgG.

CONCLUSIONS

- Combination therapy led to sustained functional control (FC) of infection as demonstrated by a significant decrease of total viral liver DNA and cccDNA in a large majority of animals.
- Importantly, combination therapy resulted also in the clearance of surface Ag in the liver of all animals exhibiting FC.
- IFN-free regimen combining REP 2139-Ca with TDF or TDF & ETV led to dramatic reduction or clearance of all markers of viral infection, including liver HBsAg.
- Synergistic antiviral effects were observed when REP 2139-Ca was combined with TDF or TDF & ETV.

REFERENCES


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