Background

Nucleic acid polymers (NAPs) block the release of HBsAg from infected hepatocytes appearing therefore of particular interest for chronic hepatitis B therapy. Two current NAPs compounds (REP 2055 and REP 2139), effectively clear the bloods of HBsAg in human subjects with chronic HBV infection and when used in combination with immunotherapy have been able to achieve higher SVR rates in patients than when immunotherapy is used alone.

Objectives

The goal of this preclinical study was to examine the effect of various nucleic acid modifications on the tolerability, liver accumulation and antiviral effect of NAPs in vivo, in chronic DHBV infection model.

Materials & Methods

Three-day-old Pekin ducklings were infected with 2x10^11 VGE/ml of DHBV from infectious duck serum. NAP treatment was started in 14 days-old animals and consisted of dosing via intraperitoneal injection with 10mg/kg of NAPs (formulated as calcium chelate complexes) 3 times / week for three weeks followed by autopsy analysis. All five NAPs used (REP 2055, REP 2139, REP 2163, REP 2165 and REP 2166) had the same sequence composition [(dC)4] but each comprised different nucleic acid modifications known to impact the tolerability and stability of oligonucleotides (see Fig. 1). NAP stability in neutral and acidic (modeling intracellular endonuclease activity) human plasma and in duck liver was assessed by fluorescence-HPLC using a fluorescent RNA probe-based hybridization assay. Tolerance was assessed by monitoring weight during treatment, injection site reactivity and findings at autopsy. Antiviral activity was assessed by monitoring serum DHBsAg and anti-DHBsAg (anti-DHBsAg) antibodies by ELISA and serum and liver DHBV DNA by quantitative PCR.

Conclusions

- The liver accumulation of NAPs can be modulated significantly without affecting their overal antiviral activity.
- All NAPs reduced serum DHBsAg and elicit other important antiviral responses in the blood and liver.
- The NAP REP 2165 may be of clinical benefit owing to its comparable antiviral activity compared to REP 2139 with significantly lower liver accumulation.

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