REP 9AC' (REP 2139-Ca) – INDUCED HBsAg CLEARANCE POTENTIATES RESPONSE TO IMMUNOTHERAPY IN PATIENTS WITH CHRONIC HBV INFECTION

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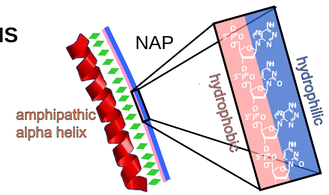
INTRODUCTION

The secreted HBV surface antigen (HBsAg) plays a critical role in suppressing host immunity which permits chronic maintenance of HBV infection. REP 2139 is a nucleic acid-based amphipathic polymer (NAP) which inhibits the release of subviral particles (SVPs) from infected hepatocytes. Previous interim clinical data has shown that NAPs rapidly clear serum HBsAg in infected patients and allows patients to regain immunological control over their HBV infection. New data demonstrating the efficacy of NAPs in restoring the immune response to HBV as well as the response to immunotherapeutic agents is presented.

THE PHARMACOLOGY OF NAP INTERACTIONS

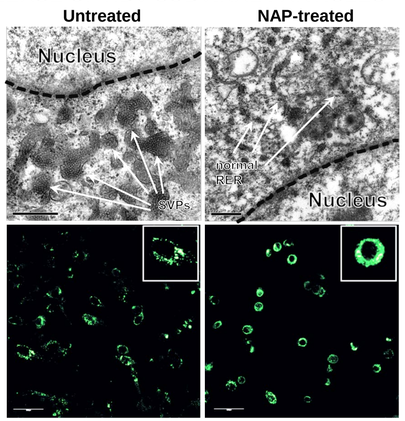
NAPs are amphipathic polymers synthesized using phosphorothioate oligonucleotide chemistry. NAPs interact with amphipathic targets in a size dependent but sequence independent fashion via multiple lateral interactions with the target interface. NAPs are engineered to minimize immunostimulatory properties, interactions with the host genome and to retain their amphipathic nature in the intracellular compartments where subviral particles are formed.



NAPS BLOCK THE FORMATION AND RELEASE OF HBV SUBVIRAL PARTICLES

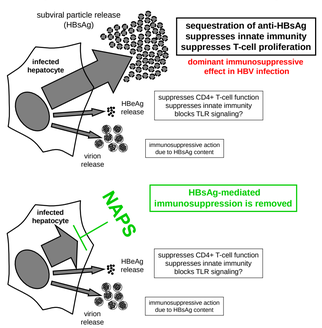
Expression of sHBsAg in BHK-21 cells results in the formation of SVPs in perinuclear vesicles (upper left) similar in morphology to those observed in human infection. HBsAg expression in the cells (bottom left) exhibits the normal punctate distribution consistent with SVP transit through the constitutive secretory pathway. NAPs block the assembly of SVPs (upper right) and result in the retention of HBsAg in the perinuclear space (bottom right), preventing its transit through the secretory pathway.

(TEM and immunofluorescence data from Romuald Patient and Philippe Roingeard, Francois Rabelais University, Tours, France)



NAPS CAN RESTORE THE EXISTING HOST IMMUNE RESPONSE TO HBV INFECTION WHERE OTHER HBV TREATMENTS FAIL

HBV infection is an immunological disorder where the host immune response (both innate and adaptive) are inhibited by circulating HBsAg protein (1-5). By blocking the release of SVPs, NAPs can provide an effective mechanism for clearing HBsAg from the blood of patients, allowing the host immune response to recover its ability to fight the HBV infection.



Immunotherapy

HBsAg suppresses cytokine signalling response to interferon based therapy

Direct acting antivirals

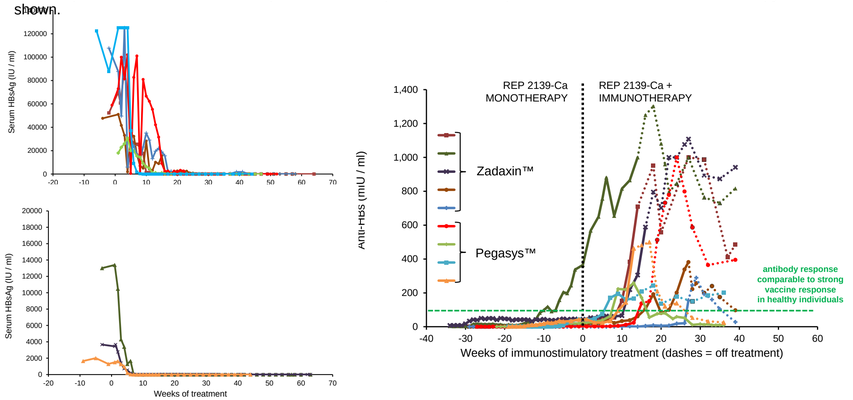
HBsAg (SVP) production is mostly unaffected by long term HBV polymerase inhibition

Restoration of a competent immune control over HBV infection is rarely achieved

Existing immune response is "unmasked" and now responsive to stimulation by immunotherapy

REP 2139-Ca PROOF OF CONCEPT CLINICAL TRIAL

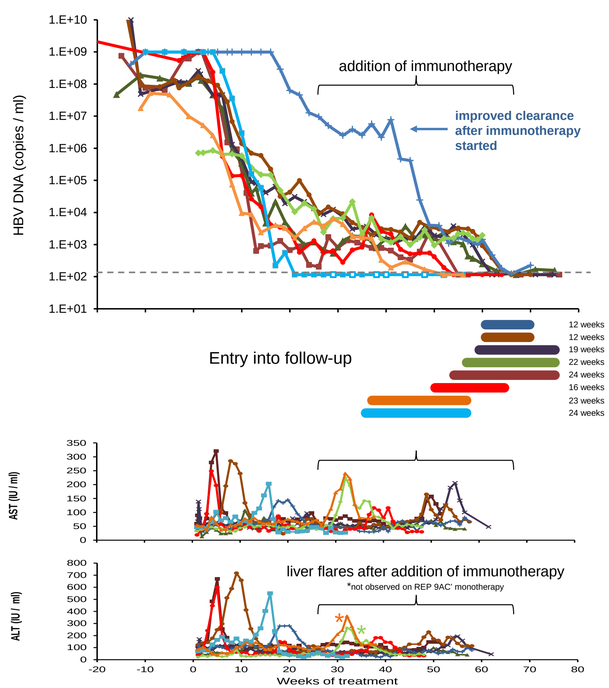
REP 2139 is currently undergoing testing in human patients with chronic HBeAg+ HBV in a proof of concept clinical trial where patients were treated with REP 2139-Ca. Virologic monitoring included HBV DNA (Roche Cobas™), HBsAg, anti-HBs, HBeAg and anti-HBe (all by Abbott Architect™). The effects of REP 2139-Ca treatment on reduction of HBsAg in the blood of infected patients is shown below. Improved anti-HBs production in the presence of concomitant immunotherapy is also shown.



EFFECT OF ADD-ON IMMUNOTHERAPY WITH REP 2139-Ca ON VIRAL CLEARANCE

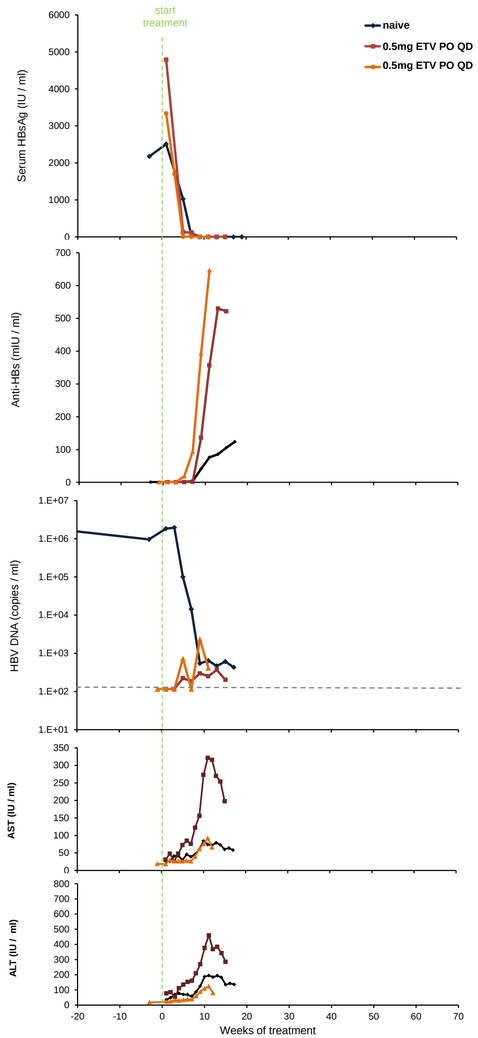
Clearance of serum HBV DNA with HBsAg clearance achieved with REP 2139-Ca monotherapy followed by combination therapy with either Zadaxin® or Pegasys®. All patients (except where noted) achieved robust clearance of HBV DNA prior to the start of add-on immunotherapy. The delayed clearance of HBV DNA in one patient was rescued with the start of add-on immunotherapy. Liver flares are of a defined nature and occur concomitantly with elimination of serum viremia.

8 / 8 patients off treatment have experienced persistent control of infection 12 – 24 weeks off treatment. (line segments below HBV DNA graph indicate off treatment duration)



EFFECT OF COMBINATION REP 2139-Ca / PEGASYS AT START OF TREATMENT

Patients are now receiving REP 2139-Ca 500mg once weekly) in combination with 180ug of Pegasys® at the start of their treatment. One patient is treatment naïve and two patients started combination treatment while continuing previous therapy with ETV. The effects of REP 2139-Ca / Pegasys® combination treatment virologic response in the blood of infected patients is shown below. Combination therapy achieves very rapid clearance of HBsAg and rapid development of substantial anti-HBs titers. Serum HBV DNA levels fall rapidly in the naïve patient. The HBsAg and anti-HBs response are comparable in the naïve and ETV patients.



CONCLUSIONS

- **NAP mediated HBsAg reduction / clearance appears to improve anti-HBs response with immunotherapy.**
- **HBsAg persistence during traditional immunotherapy may inhibit immune response.**
- **Combination NAP / immunotherapy may elicit a durable immunological control in most patients with chronic HBV with short term exposure to immunotherapy.**

REFERENCES

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4. Xu et al., 2009 Molecular immunology, 46: 2640-2646.
5. Wu et al., 2009 Hepatology, 49: 1132-1140.