CYTOKINE RESPONSES IN CHRONIC HEPATITIS B PATIENTS DOSED WITH THE NUCLEIC-ACID POLYMER REP 2139-CA

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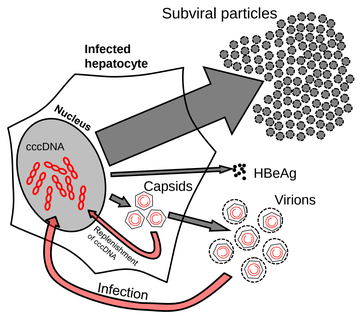
BACKGROUND AND AIM

Current treatment regimens for patients with chronic hepatitis B (CHB) are only successful in eradicating HBsAg (considered functional cure) in a minority of patients. REP 2139-Ca may be a promising new treatment option for CHB patients. By blocking the assembly of HBV subviral particles and their release from the hepatocyte (figures 1, 2), treatment with REP 2139-Ca can lead to clearance of HBsAg in the serum. As HBsAg is considered one of the drivers of HBV-specific T cell exhaustion, the clearance of HBsAg could be the key to restoring the immune response against the hepatitis B virus. Here, we have analysed immunologic activity in response to treatment with REP 2139-Ca. Furthermore, we have compared patients who responded to REP 2139-Ca therapy to those who did not.



Subviral particles represent the bulk of circulating HBsAg

HBsAg may have a direct immunosuppressive function:

- **Sequestration of anti-HBs**
- **Suppression of innate immunity**
  Woltman *PLoSone* 2011; Wu Hepatology 2009
- **Suppression of T-cell function**
  OpDenBrouw *Immunity* 2009; Cheng et al 2005
- **Suppression of cytokine signaling**
  Cheng, *J Hep* 2005; Shi, *PLoSone* 2012

Figure 1. Subviral particles in HBV infection.

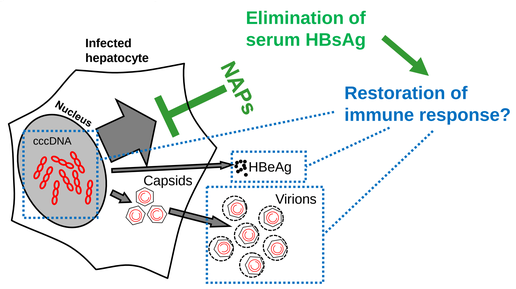


Figure 2. Mechanism of action of NAPs and their proposed antiviral effect.

MATERIALS & METHODS

12 Patients with HBeAg positive CHB (mean HBV DNA 8.21 $\log_{10}$ IU/ml) participating in a phase 2 study, were dosed with REP 2139-Ca for 20-38 weeks. The 9 responders to REP 2139-Ca (defined as clearance of serum HBsAg) subsequently received add-on immunomodulatory agents (peginterferon alfa-2a and/or thymosin alpha-1) and all therapy was withdrawn during follow-up. The 3 non-responders (no change in serum HBsAg) were given standard NUC therapy during follow-up. Serum samples were collected at baseline (BL), during REP 2139-Ca treatment (week 5, 12, 24), during add-on immunomodulatory treatment (add-on) and follow-up (FU, 12-39 weeks after cessation of therapy). Cytokine and chemokine levels were measured using a Luminex 27-plex immunoassay (Affymetrix eBioscience, San Diego, USA). Statistical analyses were done using a paired T-test/Wilcoxon signed rank test.

RESULTS

1. Changes in Serum Cytokines upon REP 2139-Ca Treatment.

11/27 Cytokines met the criterion for detection. Of all cytokines analysed, IFNγ, TNFα, IP-10, IL-1α (not shown) and IL-18 significantly increased during treatment with REP 2139-Ca. IL-7 and IL-8 serum concentration decreased. Add-on immunomodulatory treatment did not further influence cytokine levels as there were no significant differences at week 24 of REP 2139-Ca treatment and the first time point during add-on immunomodulatory therapy. (For IL-1RA, IL-31, IL-6 and IL-10 no changes were observed, not shown)

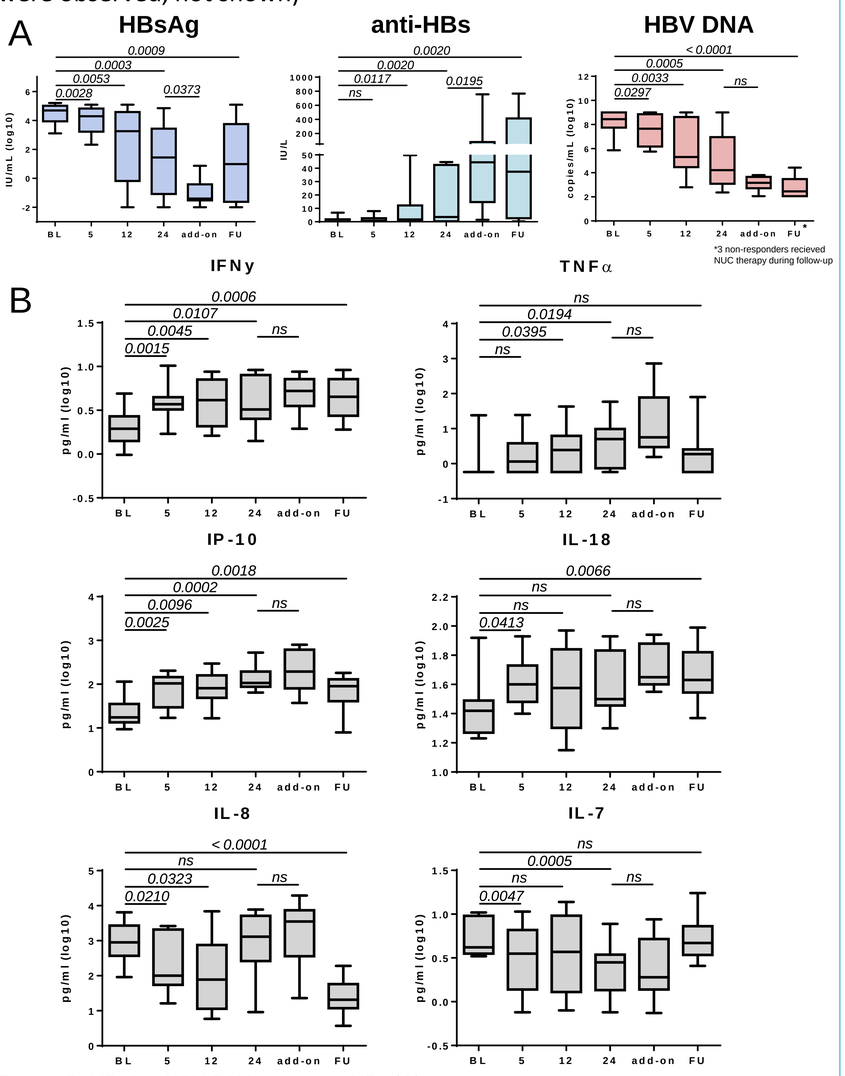


Figure 3. HBsAg, HBV DNA and anti-HBs (A) and serum concentration of several cytokines/chemokines (B) in patients dosed with REP2139-Ca. (add-on; during add-on immunomodulatory therapy.)

2. REP 2139-Ca Responders vs. Non-responders.

No differences were observed in serum cytokine concentrations between responders (with HBsAg loss) and non-responders (without HBsAg loss) to REP 2139-Ca treatment.

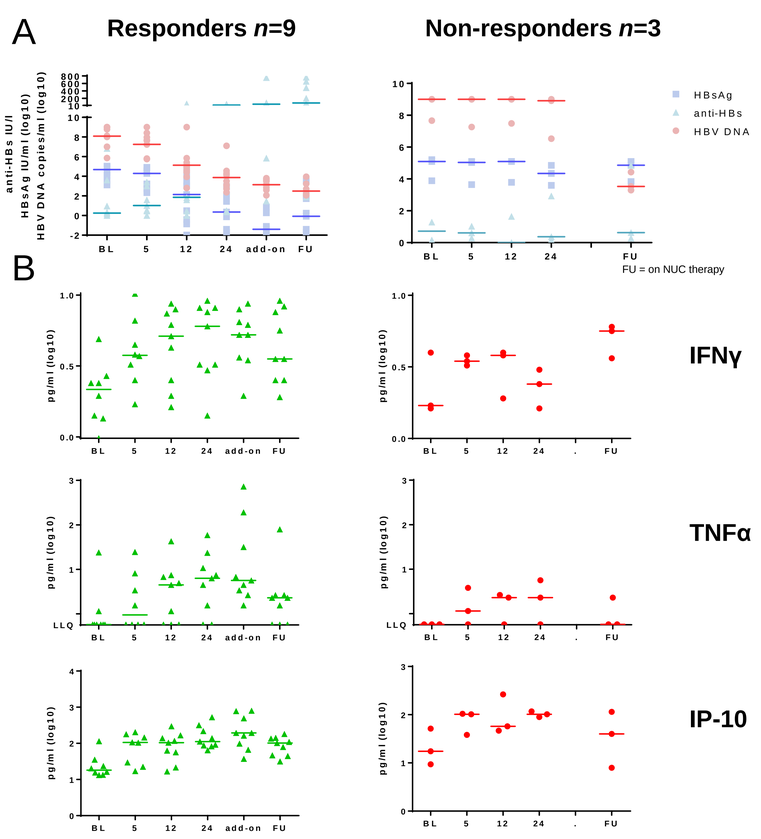


Figure 4. HBsAg, HBV DNA, anti-HBs (A) and serum cytokine concentrations (B) in responders versus non-responders to REP-2139-Ca. Bars indicate median.

CONCLUSIONS

- REP 2139-Ca can induce significant changes in serum chemokine and cytokine levels.
- Chemokine / cytokine responses were not significantly correlated with antiviral response to REP 2139-Ca and were not altered with add-on immunotherapy.
- The observed serum chemokine / cytokine responses may result from residual PAMP activity of REP 2139-Ca, distinct from its antiviral effect in blocking HBsAg release.

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