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 immunomodulatory 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:
- Suppression of anti-HBs
- Suppression of innate immunity
- Suppression of T-cell function
- Suppression of cytokine signalling

Figure 1. Subviral particles in HBV infection.

Elimination of serum HBsAg
Restoration of immune response?

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 log10 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received add-on immunomodulatory agents (peginterferon alfa-2a and/or thymosin alpha-1) and all therapy was withdrawn during follow-up.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 Lumexin 27plex 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, TNFa, 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).

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.

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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