Therapeutic vaccination of chronically HBV infected patients with low-level of HBsAg using a combination of a third generation PreS/S vaccine (Sci-B-Vac™) and a nucleoside analogue

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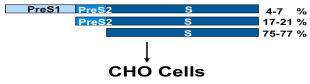
Background and Aim

Treatment regimens for chronic hepatitis B virus (HBV) infection are efficient in suppressing viral load and improving hepatocellular injury and its complications. However, current anti-viral agents such as NUCs or IFN alpha are inefficient to reconstitute immunologic control of persistent HBV infection or clearance of HBVcccDNA. It was hypothesized that high levels of circulating HBV surface antigens (HBsAg) lead to immune tolerance against HBV and contribute to persistence of chronic HBV infection. Hence, low-level HBsAg in some patients may create a window for the reconstitution of an HBV-specific immune response and control of infection. Previous studies in non-responders to classical HBV vaccines with a third generation PreS/S vaccine (Sci-B-Vac™), lead to 95% anti-HBs seroconversion at high protective levels. The present report describes an attempt to evaluate the potential role of Sci B Vac™, the preS/S HBV vaccine in a therapeutic maneuver to clear persistent HBV.

Krawczyk A, Roggendorf H, et al Liver Transplantation 2013 and Vaccine 2014
Shouval D, Roggendorf H, Roggendorf M. Med Microbiol Immunol. 2015 Feb;204(1):57-68
Roggendorf,H Deutsches Ärzteblatt, 112, 39, 2015

Materials and Methods

3rd Generation Sci-B-Vac™ (PreHevBri,VBI Vaccines)



Design of therapeutic vaccination (n = 4)

- ✓Antiviral Therapy for > 2 years
- ✓HBV-DNA in the serum below detection level
- ✓HBsAg< 500 IU/ml, GOT/GPT< 50 (U/L), HBeAg neg.
- ✓5-16 vaccinations with Sci-B-Vac™ (10µg /20µg)

Read-out

- ➢Anti-HBs IU/ml
- ➢HBsAg
- ➢IFNγ-ELISpot
- ➢Proliferation assay

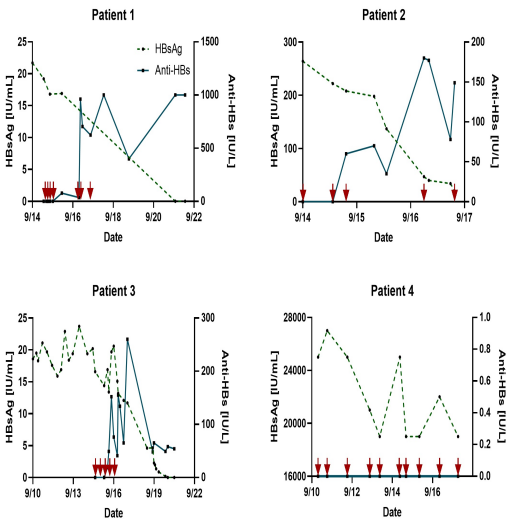
Table 1

	age	gender	HBsAG IU/ml	ALT	NUC	Drug
Sci-B-vac					(Treatment)	
Pat#1	40	male	20.2	wnl**	>2years	Viread
Pat#2	62	male	268	wnl	>2years	Barclude
Pat#3	37	female	19.2	wnl	>2years	Viread
Pat#4	63	male	19865.0	wnl	>2years	Viread
Control						
Pat#A	69	male	450.0	wnl	>2years	Barclude
Pat#B	33	female	2.0	wnl	>2years	Barclude
Pat#C	66	female	52.0	wnl	>2years	Barclude
Pat#D	56	male	250.0	wnl	>2years	Viread

Baseline characteristics (age, gender, HbsAg status) of 3 vaccinated patients (Pat.1-3) with low level HBsAg and one control (Pat.4) with high level HBsAg. 4 patients without vaccination (controls), who where treated with NUCs over a period of at least 2 years and had HBV DNA below detection level. ** within normal limits.

Results

Figure 1



Three low-level HBsAg carriers (with pretreatment levels of HBsAg 268, 20.2 and 19.2 IU/L, respectively), were vaccinated **5 to 16** times with 20 µg Sci-B-Vac™. All three vaccinated patients seroconverted to Anti-HBs. Two years after completion of the vaccination series, anti-HBs titers were 100, 260 and 623 IU/L, respectively (Fig.1). Patient #4 with high level of HBsAg did not seroconvert to AntiHBs. Ongoing vaccination in two patients (#1 and #3) led to complete elimination of HBsAg and persistence of anti-HBs (> 100 UI/L)). One year after stopping NUC treatment, these two patients were still HBsAg negative and anti-HBs positive (58 and >1000 IU/L, respectively).

Controls: HBsAg concentrations in non-vaccinated patients measured at least at seven time points showed no substantial changes or spontaneous loss of HBsAg (Fig.2)

The determination of HBsAg concentrations in two cohort of patients (Essen n= 1131 und Munich n= 351) indicated that about 30% of patients showed low level concentrations HBsAg below 500 IU (Fig.3). These patients maybe good candidates for a therapeutic vaccination.

Figure 2

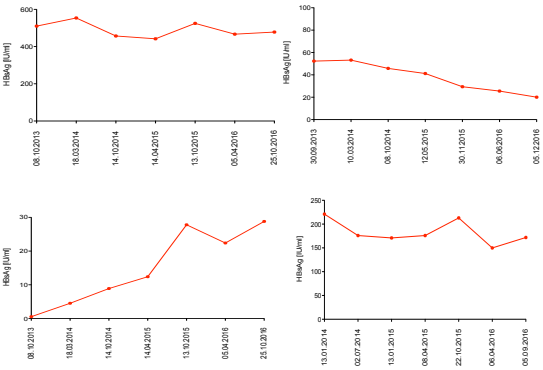
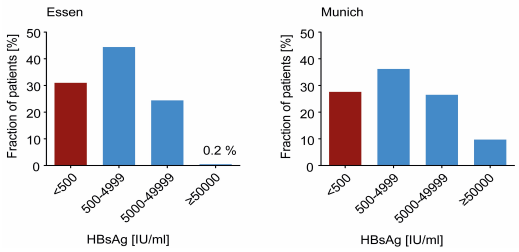


Figure 3



Conclusion

All three HBV carriers with low-level HBsAg concentrations (<500 IU) and negative results for HBV DNA under NUC treatment receiving therapeutic vaccination with the third generation PreS/S vaccine (Sci-B-Vac™) seroconverted to anti-HBs and showed declining concentrations of HBsAg. Two Patients 1 and 3 completely lost HBsAg indicating functional cure. This treatment may be effective only in low level HBsAg carriers with a low tolerizing effect of HBsAg. Further studies with a larger cohort including long-term observation are needed to determine whether HBV cccDNA may be reduced or even eliminated in these patients resulting in additional option for treatment of chronic hepatitis B.

This PreS/S vaccine against HBV infection has recently been approved by the FDA and EMEA for prevention of HBV. Based on our preliminary observation, there is a rational to further evaluate a potential role of this vaccine as a therapeutic agent, possibly in combination with one or more of new antiviral agents against HBV.

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