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Brief report

Immunogenicity of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared with a licensed hepatitis B vaccine in subpopulations of healthy adults 18–70 years of age☆

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ABSTRACT

Background: Immunologic response to a complete vaccine regimen of currently licensed alum-adjuvanted hepatitis B vaccines is reduced in several subpopulations, including older adults, men, obese persons, and smokers. Two phase 3 trials in healthy adults demonstrated that 2 doses over 1 month of an investigational hepatitis B vaccine (HBsAg-1018) induced superior seroprotection rates (SPRs) to 3 doses over 6 months of the licensed vaccine Engerix-B® (HBsAg-Eng).
Methods: An exploratory analysis of immunogenicity was conducted in subpopulations from pooled data for the 2 phase 3 trials.
Results: In each subpopulation, the peak SPR in the HBsAg-1018 group was statistically significantly higher than the peak SPR in the HBsAg-Eng group. Peak HBsAg-1018 SPRs ranged from 91.6% to 99.7%, while peak HBsAg-Eng SPRs ranged from 67.7% to 92.9%.
Conclusion: In these exploratory analyses, 2 doses of HBsAg-1018 induced statistically significantly higher rates of seroprotection than 3 doses of HBsAg-Eng across all subpopulations.

1. Introduction

The World Health Organization estimates that 2 billion people have been infected with hepatitis B virus (HBV) worldwide, resulting in over 780,000 deaths each year [1,2]. With the more widespread availability and use of hepatitis B vaccines, there has been a decrease in the prevalence of hepatitis B infection over the last 25 years; however, the global burden of disease is still high [3]. Several subpopulations, including older adults, men, obese persons, and smokers have been reported as hyporesponsive to currently licensed alum-adjuvanted hepatitis B vaccines and thus may not be protected from hepatitis B infection by routine vaccination [4–12].

A more potent hepatitis B vaccine could represent an important advance in hepatitis B prevention by improving seroprotection in subpopulations that may remain at risk for infection with HBV after vaccination. An investigational hepatitis B vaccine, HBsAg-1018, (HEPLISAV™, Dynavax Technologies Corporation, Berkeley, California) contains 20 mcg of recombinant hepatitis B surface antigen (rHBsAg) and 3000 mcg of a synthetic phosphorothioate oligodeoxynucleotide, 1018. Results of 2 phase 3 trials in healthy adults demonstrated that 2 doses over 1 month of HBsAg-1018 met the primary objective of noninferiority as well as superiority to 3 doses over 6 months of HBsAg-Eng (Engerix-B®, GlaxoSmithKline Biologicals, Rixensart, Belgium) with a similar safety profile [13,14].

Here we present an exploratory analysis of participants enrolled in the 2 phase 3 trials of healthy adults by age, sex, body mass index (BMI), and smoking status.

2. Materials and methods

2.1. Study design and participants

Details of the study methods for both phase 3 trials have been previously described [13,14]. The 2 phase 3 trials (HBV-10 and HBV-16) were similar in study design. Briefly, 2415 persons 18 to 55 years of age (HBV-10) and 2452 persons 40 to 70 years

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of age (HBV-16) with no history of hepatitis B vaccination or infection were enrolled. Inclusion and exclusion criteria were similar. Randomization was stratified by age in both studies and, additionally, by site in HBV-16. Participants were randomly assigned 3:1 (HBV-10) or 4:1 (HBV-16) to receive 2 doses of HBsAg-1018 at 0, 4 and 24 (placebo) weeks or 3 doses of HBsAg-Eng (20 mcg rHBsAg combined with 500 mcg alum adjuvant) at 0, 4, and 24 weeks. Data from samples collected at weeks 8, 12, 24, and 28 were used for immunogenicity analyses. The peak SPRs were measured at week 24 for the HBsAg-1018 group and week 28 for the HBsAg-Eng group. The same assay was used to assess the serum concentration of antibody against hepatitis B surface antigen (anti-HBs). Anti-HBs serum concentrations were measured using the Ortho Vitros® enhanced chemiluminescence immunoassay (Ortho Clinical Diagnostics, Rochester, NY). Seroprotection was defined as anti-HBs serum concentration ≥10 mIU/mL.

The data from HBV-10 and HBV-16 were pooled to create a larger sample size to explore immunogenicity results in subpopulations of participants by age, sex, BMI, and smoking status. The SPRs in the only age group (40–55 years of age) enrolled in both HBV-10 and HBV-16 were similar across the studies, supporting the pooling of SPR results from the 2 trials (data not shown).

2.2. Statistical methods

Post hoc exploratory analyses were conducted to evaluate the immune response to HBsAg-1018 compared to HBsAg-Eng in each subpopulation as measured by comparison of peak SPRs. The difference in SPRs between the HBsAg-1018 and HBsAg-Eng groups (HBsAg-1018 minus HBsAg-Eng) and its two-sided 95% CIs were computed using the Wilson score method with continuity correction [15]. Results were considered statistically significant if the lower bound of the 95% CI of the difference in rates was greater than 0.

Immunogenicity analyses used the modified intent to treat (mITT) analysis population defined as all participants who received at least one study injection and had an immunogenicity evaluation.

No imputations were made for missing immunogenicity data. All data analyses were performed using SAS® version 9.3.

3. Results

3.1. Study participants

In total, the trials randomized 4867 participants (HBsAg-1018: 3778; HBsAg-Eng: 1089) 18 to 70 years of age across sites in the US, Canada, and Germany, of which 4815 participants were included in the mITT population (HBsAg-1018: 3736; HBsAg-Eng: 1079). In the pooled analysis of participants in both trials, demographics and baseline characteristics were balanced between the 2 treatment groups (Table 1).

3.2. Immunogenicity

The peak SPR in the HBsAg-1018 group was statistically significantly higher than the peak SPR in the HBsAg-Eng group in each

Table 1
Demographics and baseline characteristics (mITT population).

Characteristics	Treatment group		
	HBsAg-1018 (*N* = 3736)	HBsAg-Eng (*N* = 1079)	Total (*N* = 4815)
Sex *n* (%)			
Male	1775 (47.5)	495 (45.9)	2270 (47.1)
Female	1961 (52.5)	584 (54.1)	2545 (52.9)
Age strata (years)			
18–29	317 (8.5)	103 (9.5)	420 (8.7)
30–39	495 (13.2)	171 (15.8)	666 (13.8)
40–49	1276 (34.2)	395 (36.6)	1671 (34.7)
50–59	1105 (29.6)	280 (25.9)	1385 (28.8)
60–70	543 (14.5)	130 (12.0)	673 (14.0)
Age (years)			
n	3736	1079	4815
Mean (SD)	47 (11.2)	46 (11.0)	47 (11.1)
Median	48	46	48
Min, Max	18, 70	18, 70	18, 70
BMI[a] *n* (%)			
N	3731	1077	4808
Mean (SD)	28.8 (6.20)	28.6 (6.39)	28.7 (6.24)
Median	27.8	27.6	27.8
Min, Max	14.2, 67.4	16.4, 63.2	14.2, 67.4
BMI stratum[a] *n* (%)			
<30 kg/m^2	2425 (64.9)	709 (65.7)	3134 (65.1)
≥30 kg/m^2	1311 (35.1)	370 (34.3)	1681 (34.9)
Race *n* (%)			
White	3282 (87.8)	951 (88.1)	4233 (87.9)
Black	327 (8.8)	86 (8.0)	413 (8.6)
Asian	66 (1.8)	26 (2.4)	92 (1.9)
Other[b]	61 (1.6)	16 (1.5)	77 (1.6)
Ethnicity[c] *n* (%)			
Hispanic or Latino	162 (4.3)	56 (5.2)	218 (4.5)
Not Hispanic or Latino	3572 (95.7)	1023 (94.8)	4595 (95.5)
Smoking status[d] *n* (%)			
Yes	1067 (28.6)	336 (31.1)	1403 (29.1)
No	2669 (71.4)	743 (68.9)	3412 (70.9)

BMI = body mass index; mITT = modified intent-to-treat; *N* = number of participants in the study population in the treatment group; *n* = number of participants with characteristic; SD = standard deviation.

[a] There was insufficient information to calculate the BMI of 7 participants.
[b] Other race includes American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, and other race.
[c] Two participants did not report their ethnicity.
[d] Implies regular smoking within 1 year before enrollment in the trial.

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