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Safety and immunogenicity of a recombinant hepatitis B vaccine manufactured by a modified process in renal pre-dialysis and dialysis patients

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ABSTRACT

Background: Patients with renal insufficiency are hyporesponsive to vaccination, including to hepatitis B vaccines. A manufacturing process modification for a hepatitis B vaccine (mpHBV) was studied in renal pre-dialysis and dialysis patients.
Methods: This randomized, open-label, multicenter, estimation study enrolled previously unvaccinated, HBV-seronegative adult dialysis and pre-dialysis patients ($N = 276$, median age 72.0 years). At 0, 1, 6, and 8 months, group 1 received a 1 mL intramuscular dose of mpHBV (containing 40 μg HBsAg) as a single injection, while group 2 received a 1 mL intramuscular dose of a licensed hepatitis B vaccine as two injections (each containing 20 μg HBsAg; 40 μg HBsAg total). Serum antibody to HBsAg (anti-HBs) was measured predose 1, and 1 month postdose 3 and 4. Anti-HBs geometric mean concentration (GMC) and seroprotection rate (SPR, % of subjects with anti-HBs titer ≥10 mIU/mL) were estimated at months 7 and 9.
Results: For group 1, month 7 SPR was 48.5% (49/101, 95% CI: 38.4%, 58.7%); with an additional dose, month 9 SPR increased to 66.7% (66/99, 95% CI: 56.5%, 75.8%). For group 2, month 7 SPR was 57.7% (64/111, 95% CI: 47.9%, 67.0%); with an additional dose, month 9 SPR increased to 69.2% (72/104, 95% CI: 59.4%, 77.9%). group 1 GMCs at months 7 and 9 were 27.5 mIU/mL (95% CI: 15.7, 48.0) and 61.7 mIU/mL (95% CI: 34.2, 111.5), respectively. group 2 GMCs at months 7 and 9 were 48.7 mIU/mL (95% CI: 28.7, 82.7) and 115.8 mIU/mL (95% CI: 65.2, 205.5), respectively. There were 22 serious adverse events; none were considered related to study vaccine.
Conclusions: Both formulations were immunogenic in this population but required more vaccinations to reach seroprotective levels than comparable regimens in healthy individuals, as expected. The relatively reduced SPRs seen in this population support the need for routine screening and re-dosing in this population.

1. Introduction

Individuals with chronic kidney disease (CKD) and end stage renal disease (ESRD) comprise a special population which has historically been at high risk for hepatitis B infection [1–4]. Hepatitis B is a highly transmissible blood-borne virus, which leads to acute and chronic hepatitis, cirrhosis, hepatocellular carcinoma (HCC) and liver failure [1–4]. The relative stability of hepatitis B virus, which can remain infectious for up to 7 days at room temperature, and the repeated potential exposure to body fluids as required by routine hemodialysis increases the risk of environmental transmission in the dialysis setting [1–4]. The prevention of hepatitis B is particularly important for ESRD patients as they are more likely to progress to chronic infection, which leads to HCC and liver failure

Abbreviations: AEs, adverse experiences; ANOVA, analysis of variance; anti-HBs, serum antibody to HBsAg; CI, confidence interval; GMC, geometric mean concentration; HBsAg, hepatitis B surface antigen; mpHBV, modified process hepatitis B vaccine; SPR, sseroprotection rates.

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[1–4]. The implementation of rigorous infection control standards, routine screening of blood derived products, and hepatitis B vaccination have helped to significantly reduce the risk of acquisition of hepatitis B for CKD patients [1–4].

The modified process hepatitis B vaccine (mpHBV) was manufactured using a higher phosphate content [5], and was developed to optimize the manufacturing consistency and the immunogenicity of hepatitis B vaccine. The phosphate component of the alum-based antigen-adjuvant facilitates desorption and may improve ligand exchange to antigen presenting cells [6,7], which should facilitate antibody production [7]. The mpHBV showed adequate immunogenicity and safety in healthy infants, young adults, and older adults [8–11]. Therefore, this study was conducted to describe the mpHBV in pre-dialysis and dialysis patients to represent the use of mpHBV in a high-risk population that routinely receives hepatitis B vaccination under general vaccination approaches. This study was purely descriptive, with no direct comparisons pre-specified for any of the study groups.

2. Methods

2.1. Study design

This study evaluated the safety, tolerability, and immunogenicity of four doses of mpHBV administered as a 1.0-mL intramuscular injection (deltoid muscle) at Day 1, Month 1, Month 6, and Month 8 following study entry. All subjects were followed for safety for Days 1–15 after each dose (date of vaccination considered Day 1), with subjects recording any adverse experiences (AEs) using a vaccination report card (VRC). Subjects were also instructed to record in the VRC daily oral temperatures for the first 5 days following each vaccination.

A blood sample was collected at Day 1 (prior to Dose 1), at Month 7 (1 month Postdose 3), and at Month 9 (1 month Postdose 4). Day 1 screening serum samples were tested at local laboratories for each study site to ensure baseline negative results for hepatitis B surface antigen (HBsAg), antibodies against hepatitis B core antigen (anti-HBc), and antibodies against HBsAg (anti-HBs) prior to study enrolment. Both Month 7 and Month 9 samples were tested for anti-HBs using the VITROS ECi Immunodiagnostic anti-HBs Assay (Merck Research Laboratories, West Point, PA). Immunogenicity was evaluated with respect to seroprotection rate (SPR), defined as the percent of subjects with an anti-HBs titer $\geq$10 mIU/mL, and as anti-HBs geometric mean concentration (GMC). The quantifiable range of the standard curve was 5 to 1000 mIU/mL. Titers <5 mIU/mL were not reported because the assay does not reliably discriminate between very low anti-HBs responders (1 to 3 mIU/mL) and true negatives; for values reported below the detection threshold, half the threshold was imputed for determining the GMC.

This randomized, double-blind (subject, investigator, sponsor, and laboratory) clinical trial was conducted at 23 sites (7 in Canada, 8 in the United Kingdom, 5 in Italy, and 3 in Spain) from December 2006 to May 2008. The protocol was approved by the ethical review committee of each country or site and conducted in conformance with applicable country or local requirements.

2.2. Study subjects

This study included pre-dialysis subjects (defined as having a creatinine clearance $\leq$30 mL/min as calculated according to the Cockroft-Gault formula [12]) or subjects who were receiving either hemodialysis or peritoneal dialysis. Subjects were required to be at least 18 years of age and HBV-seronegative at baseline. A negative urine pregnancy test for women was mandatory for inclusion. Exclusionary criteria included: recent (<72 h) history of febrile illness (oral temperature $\geq$37.8 °C/$\geq$100.0 °F); other than from renal disease, known or suspected impairment of immunologic function (e.g., HIV positivity, end-stage liver disease); use of systemic corticosteroids within 3 months prior to study entry; receipt of licensed inactivated (within 14 days) or live vaccines (within 30 days) prior to study entry or during the study; receipt of investigational drugs or vaccines within 3 months prior to entry or during the study; or receipt of hepatitis B immune globulin (HBIG), serum immune globulin, or any other blood-derived product within 3 months prior to study entry or during the study.

This study was designed to randomize approximately 276 subjects in a 1:1 ratio to either one of the two vaccination groups (mpHBV or licensed hepatitis B vaccine [group 2]). Subjects were allocated to vaccination group using a randomized schedule generated by the study statistician. All study personnel, including investigators, study site personnel, subjects, monitors, and central laboratory personnel, remained blinded to allocation throughout the study. This study was an estimation study with a clinical assumption that the true SPR in subjects receiving vaccination was at least 60% following three doses. Assuming a 10% non-evaluable rate, a sample size of 276 subjects enrolled (138 per group) was calculated to yield 125 evaluable subjects per group.

2.3. Vaccine descriptions

The group 2 vaccine, Engerix-B™ (hepatitis B vaccine [recombinant], GlaxoSMithKline, Rixensart, Belguim), is a noninfectious, particulate, viral subunit vaccine consisting of HBsAg produced in yeast cells [13]. To produce the mpHBV, the manufacturing process of the adjuvant in the HBsAg bulk intermediate of RECOMBIVAX HB™ (hepatitis B vaccine [recombinant], Merck, Sharp, & Dohme Corp., Whitehouse Station, NJ) was modified by providing additional phosphate during the co-precipitation step, which increases the phosphate-to-aluminum ratio of the adjuvant in the final product. Vaccine (mpHBV lot WL00021570; group 2 vaccine lot DL00008816) was packaged in single-dose glass vials. At each vaccination visit, subjects received either one injection of the mpHBV (40 μg/mL) or two separate injections of the group 2 20 μg/mL vaccine as specified by the manufacturer. Subjects in the mpHBV group received a total of 4 injections and subjects in group 2 received a total of 8 injections. For group 2, the schedule of vaccination used (0, 1 and 6 months) did not follow the manufacturer's recommendation of 0, 1, 2, and 6 months [13]; the schedule chosen was that of RecombivaxHB, upon which the mpHBV is based, and by which the mpHBV would be administered. Clinical material was stored at 2° to 8 °C.

2.4. Immunogenicity

The primary immunogenicity end point of this study was the SPR (percent of subjects with anti-HBs titer $\geq$10 mIU/mL) one month after the third or fourth dose of either vaccine. Descriptive summaries were performed for the GMCs; this study was not of adequate power to make statistical comparisons. A one-sample, two-sided 95% exact confidence interval (CI) was constructed for the SPRs and the GMCs.

2.5. Safety

The adverse experience (AE) profile following each vaccination, and for the entire 4-dose series, was described for each vaccination group. The key safety endpoints were the overall number of subjects reporting injection-site and systemic AEs Day 1 through