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Immunogenicity and safety of an adjuvanted hepatitis B vaccine in pre-hemodialysis and hemodialysis patients

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Background. Due to their impaired immune system, patients with renal insufficiency have a suboptimal response to hepatitis B (HB) vaccination and frequent boosters are needed to maintain protection. GlaxoSmithKline Biologicals has developed a HB vaccine containing a new adjuvant system AS04 for use in this immunocompromised patient population.

Methods. In an open, randomized clinical trial conducted in pre-hemodialysis (documented creatinine clearance ≤30 mL/min) and hemodialysis patients, over 15 years of age and naïve for HB, the immunogenicity and safety of single doses of HB-AS04 (Fendrix™, GlaxoSmithKline Biologicals) were compared to double doses of commercially available HB vaccine (Engerix™, GlaxoSmithKline Biologicals) administered at 0, 1, 2, and 6 months, and followed-up for 36 months.

Results. The HB-AS04 vaccine elicited a more rapid onset of protection than the currently licensed vaccine for this particular population, with 74% versus 52% of subjects seroprotected at month 3. After the vaccination course, seroprotection rates increased to 91% versus 84% in the HB-AS04 and standard vaccine groups, respectively. Differences persisted up to 36 months post-vaccination (73% vs. 52%, respectively). Antibody concentrations were higher following the HB-AS04 vaccine at all post-vaccination time points. During the follow-up, significantly fewer subjects primed with the HB-AS04 vaccine needed a booster dose as a consequence of anti-HBs loss below seroprotective levels (11/62 subjects in the HB-AS04 group vs. 22/57 subjects in the standard vaccine group, respectively, $P = 0.014$). The HB-AS04 was more locally reactogenic than the standard immunization regimen, with pain at the injection site occurring with 41% of HB-AS04 doses versus 19% of standard vaccine doses. The occurrence of grade 3 pain was less than 1% in both groups and all events resolved within the 4-day follow-up period.

Conclusion. The improved immunogenicity profile and clinically acceptable reactogenicity of HB-AS04 vaccine are of key importance to provide a more rapid, enhanced, and longer seroprotection to these immunocompromised patients at risk for HB infection.

Key words: hepatitis B, HB-AS04 vaccine, adjuvant, hemodialysis, immunogenicity, reactogenicity, immunization.

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Currently available hepatitis B (HB) vaccines have an excellent safety and immunogenicity profile, conferring seroprotection in more than 95% of the vaccinated population [1]. Nevertheless, certain population subgroups, such as some healthy people and immunocompromised subjects, do not respond adequately to vaccination. Among these groups, end-stage renal disease (ESRD) patients, comprising pre- and hemodialysis patients, are considered at high risk for HB infection due to cross-contamination to patients via environmental surfaces, disposables, or equipment during the process of hemodialysis [2–5]. Once infected, about 60% of hemodialysis patients will become chronic carriers of the HB surface antigen (HBsAg), increasing the risk of contamination for other hemodialysis patients, medical personnel, and family members [6], and leading to significant logistic and practical difficulties, including provision for separate medical devices and staff.

Attempts to overcome the impaired immune response in hemodialysis patients have produced mixed results. An increased dose strategy with additional injections was found to be necessary to improve the response rate in these subjects. Currently a 0-, 1-, 2-, and 6-month schedule with double doses hepatitis B surface antigen (2×20 μg HBsAg) of commercially available HB vaccine is recommended in hemodialysis patients, with regular monitoring of antibody levels to ensure that antibody concentrations remain above the protective level of 10 mIU/mL [7].

In order to improve the immunogenicity of existing HB vaccines, GlaxoSmithKline Biologicals (Rixensart, Belgium) has developed several adjuvant systems

containing immunostimulants. One of them was shown to significantly increase the immune response to the HBsAg and has been used in the formulation of an improved HB vaccine. The new adjuvant system, AS04, is composed of aluminium salt and 3-*O*-desacyl-4′-monophosphoryl lipid A (MPL®, Corixa, Seattle, WA, USA). In the case of pre-hemodialysis and hemodialysis patients, the impaired immune response observed in this group, including a diminished activation of helper T-cells, can in part be explained by a suboptimal costimulation by antigen presenting-cells due to a deficit of CD86. The hypothesis, therefore, is that, in these patients, the adjuvant system AS04 could stimulate cellular and humoral responses via an increased antigen-presenting capacity through up-regulation of the CD86 molecule and/or via an increased production of cytokines.

Several studies in which 3500 subjects received 8670 doses of different formulations of the candidate vaccine were performed and have shown that the HB-AS04 vaccine is safe and immunogenic in different populations [8–11].

To further characterize the immune response induced by the HB-AS04 vaccine, cell-mediated immunity (CMI) data were collected as exploratory measurements in several studies performed in healthy subjects. These data included measurement of lymphoproliferation (expressed as stimulation index) and lymphokines (IFNγ and IL-5) secretion in subgroups of subjects enrolled in these studies. The results indicated that when similar schedules were compared, the HB-AS04 vaccine tended to improve the cellular response and to increase IFNγ secretion, suggesting that part of the immune response follows a Th-1 pathway.

In this open, randomized clinical trial conducted in pre-hemodialysis and hemodialysis patients over 15 years of age, the immunogenicity and safety of HB-AS04 were compared to the currently recommended immunization regimen for these patients.

METHODS

Study population and design

In 1999, 165 ESRD patients were enrolled into this multinational study conducted at 6 study centers in Spain, Czech Republic, and Malaysia, respectively. The study was approved by the respective institutional ethics review boards, and was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines effective at study initiation. Written informed consent in the local language was obtained from the subjects or parents or guardians prior to entry into the trial.

Subjects were excluded if they had hepatomegaly, elevated serum liver enzymes, history of allergic disease likely to be stimulated by any vaccine component, a family history of congenital or hereditary immunodeficiency, received simultaneous vaccination or immunoglobulins and/or any blood products (with the exception of recombinant erythropoietin), or were receiving immunosuppressive therapy. Eligible pre-hemodialysis and hemodialysis (documented creatinine clearance $\leq$30 mL/min) subjects over 15 years of age and naive for HB were randomized to 1 of 2 groups to receive either single doses of HB-AS04 vaccine or the current standard of care [i.e., double doses (2×20 μg HBsAg) of commercial HB vaccine at 0, 1, 2, and 6 months] and followed-up for 36 months.

Materials. Both vaccines are commercially available and manufactured by GlaxoSmithKline Biologicals, Rixensart, Belgium. One dose (0.5 mL) of HB-AS04 (Fendrix™) contained 20 μg of recombinant HBsAg, 50 μg of MPL®, and 0.5 mg of aluminium as salt. One dose (1.0 mL) of the commercial HB vaccine (Engerix™-B) was composed of 20 μg recombinant HBsAg and 0.5 mg aluminium as salt; two 1.0 mL monodose vials of the vaccine were mixed and given as a single injection. In accordance with current standard of care for hemodialysis patients, both vaccines were administered at 0, 1, 2, and 6 months as an intramuscular injection in the deltoid region of the arm without the hemodialysis arteriovenous fistula.

Methods. Prevaccination blood samples obtained at screening and postvaccination blood samples obtained at months 1, 2, 3, 6, 7, and at months 12, 24, 30, 36 for persistence data, were assayed for the presence of antibodies against HBsAg (anti-HBs) using a commercial enzyme-immunoassay (EIA) produced by Abbott Laboratories (AUSAB, Abbott Laboratories, Abbott Park, IL, USA). The assay cut-off was 3.3 mIU/mL; antibody concentrations $\geq$ this cut-off were designated as seropositive. Seroprotection was defined as anti-HBs concentration $\geq$10 mIU/mL.

Local injection site symptoms (pain, redness, swelling) and general symptoms (headache, fatigue, gastrointestinal symptoms, fever) were solicited on the day of vaccination and for 3 subsequent days. The size of redness and swelling was obtained by measuring the largest diameter; a grade 3 event was defined as a diameter over 50 mm. Grade 3 injection site pain was defined as "spontaneously painful." Subjects were asked to record axillary temperature daily and any other findings on diary cards and to contact the investigator immediately if they felt any symptom was serious. Fever was defined as axillary temperature above 37.4°C; grade 3 fever was axillary temperature above 39°C. Any signs and symptoms that prevented normal daily activities were designated grade 3 in intensity. Serious adverse events, defined according to Good Clinical Practice guidelines, that occurred at any time throughout the study period up to at least 30 days after receiving the last vaccine dose were reported and described in detail.

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