

Immunogenicity and Safety of an Experimental Adjuvanted Hepatitis B Candidate Vaccine in Liver Transplant Patients

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Patients with chronic liver disease are at higher risk of hepatitis B (HB) virus infection before and after liver transplantation, and they commonly have a suboptimal immune response to HB vaccines. In this randomized trial, we compared the immunogenicity of primary vaccination with 2 doses of an experimental adjuvanted HB vaccine (adjuvant system 04 containing aluminium and monophosphoryl lipid A [HB-AS04]) to that of 3 double doses of a licensed HB vaccine in 93 liver transplant candidates. Depending on the waiting list for liver transplantation, a booster dose of HB-AS04 or double booster dose of the licensed HB vaccine was given before or after surgery, at 6 to 12 months after initiation of the vaccination course. The percentage of subjects with seroprotective anti-HB surface antibody concentrations 1 month after booster was twice as high in the HB-AS04 group (60.0%), vs. patients in the comparator group (32.0%) ($P = 0.035$). In subjects who did not undergo liver transplantation before administration of the booster, better immunogenicity results were obtained: 80% of subjects were seroprotected after HB-AS04 vaccination vs. 60% with the comparator ($P = 0.2302$). Despite a slightly higher reactogenicity, the safety profile of the HB-AS04 vaccine was clinically acceptable. In conclusion, an improved antibody response was observed in liver transplant candidates with 3 doses of HB-AS04, as compared to 4 double doses of a comparator. Liver transplant candidates could benefit from the use of this experimental adjuvanted HB vaccine to further increase their protection against HB infection. *Liver Transpl* 12:1489-1495, 2006. © 2006 AASLD.

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Patients undergoing liver transplantation have an increased risk of exposure to hepatitis B (HB) virus, mainly due to transmission of the virus from the donor

organ and, to a lesser extent, due to multiple transfusions of blood products.¹⁻⁴ To protect these patients against de novo HB infection acquired during or after

Abbreviations: HB, hepatitis B; HBsAg, hepatitis B surface antigen; anti-HBs, antibody to hepatitis B surface antigen; AS04, adjuvant system 04 containing aluminium and monophosphoryl lipid A; GMC, geometric mean concentration; SAE, serious adverse event. Supported by a grant from GlaxoSmithKline Biologicals, Rixensart, Belgium. Address reprint requests to Prof. F. Nevens, Dept. of Hepatology, University Hospital Gasthuisberg, Herestraat 49, Catholic University of Leuven, 3000 Leuven, Belgium. Telephone: 32 16 34 42 99; FAX: 32 16.34 43 87; E-mail: frederik.nevens@uz.kuleuven.ac.be

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TABLE 1. Patient Characteristics

| | Comparator HB Vaccine (N = 44) | HB-AS04 (N = 49) | Total (N = 93) |
|-----------------------------|-----------------------------------|---------------------|-------------------|
| Age (years \pm SD) | 52.7 \pm 8.3 | 50.6 \pm 11.2 | 51.6 \pm 9.9 |
| Gender (male/female) | 31/13 | 32/17 | 63/30 |
| Etiology of Liver Disease | n (%) | n (%) | n (%) |
| Alcoholic liver cirrhosis | 21 (47.7) | 22 (44.9) | 43 (46.2) |
| Hepatitis C virus infection | 16 (36.4) | 11 (22.4) | 27 (29.0) |
| Cholestatic liver disease | 6 (13.6) | 11 (22.3) | 17 (18.3) |
| Other | 7 (15.9) | 5 (10.2) | 12 (13.0) |
| Unknown | 3 (6.8) | 3 (6.1) | 6 (6.5) |
| Child-Turcotte-Pugh Score* | n (%) | n (%) | n (%) |
| Total | 41 (93.1) | 48 (97.9) | 89 (95.6) |
| A | 12 (29.3) | 15 (31.2) | 27 (30.3) |
| B | 16 (39.0) | 14 (29.2) | 30 (33.7) |
| C | 13 (31.7) | 19 (39.6) | 32 (36.0) |

NOTE: Five subjects (4 in comparator group and 1 in HB-AS04 group) had both hepatitis C virus infection and alcoholic liver disease; 2 subjects (1 in each group) had both hepatitis C virus infection and hepatocellular carcinoma; 2 subjects (1 in each group) had both alcoholic liver disease and hepatocellular carcinoma; 1 subject (comparator group) had both hemochromatosis and hepatitis C virus infection; 2 subjects (comparator group) had both hemochromatosis and alcoholic liver disease. "Other" includes hepatocellular carcinoma, hemochromatosis, liver polycystosis, parenteral nutrition, amyloidosis, and congenital liver fibrosis. "Unknown" includes cryptogenic liver cirrhosis.

*Calculated on total number of subjects with Child-Turcotte-Pugh score available.

liver transplantation, it is common practice to vaccinate against HB those patients waiting for transplantation. An accelerated HB vaccination schedule is frequently applied with the goal of obtaining protection as soon as possible before transplantation.⁵ Since a higher than regular dose of HB surface antigen (HBsAg, 20 μ g) has proven more effective in some immunodeficient patients,^{6,7} a double vaccine dose is usually administered in an attempt to increase the percentage of seroprotected liver transplant candidates. However, an accelerated schedule with double doses of a currently marketed HB vaccine followed by a booster dose provided seroprotection in only 25-40% of subjects.⁸⁻¹⁰

The poor antibody response of liver transplant candidates to classical HB vaccines is mainly attributed to impaired immunity associated with end-stage liver disease.^{11,12} Vaccination against HB is therefore recommended for these patients as soon as possible after the diagnosis of liver disease has been made, preferably at an early stage when the immune system is still functional.¹³⁻¹⁵

HB vaccines with novel or improved adjuvants have been developed to improve the immune response in vaccinees, such as immunocompromised patients. The adjuvant system 04 containing aluminium and monophosphoryl lipid A (MPL[®], Corixa, Seattle, WA), has been shown to improve the immune response to HBsAg and to be well tolerated in healthy subjects.^{16,17} The HB-AS04 vaccine might thus confer improved protection against HB in pre-liver transplant patients.

The aim of the present study was to explore the safety and immunogenicity of the HB-AS04 vaccine in patients with end-stage liver disease waiting for liver transplantation.

PATIENTS AND METHODS

Study Ethics and Approval

This study was conducted in accordance with Good Clinical Practice guidelines in operation at the time of initiation of the trial and with the amended version of the Declaration of Helsinki (1996). The study protocol was approved by the Ethical Review Committees of the respective study centers, and written informed consent was obtained from all patients.

Study Population

A total of 93 liver transplant candidates with advanced chronic liver disease were recruited at 13 different institutions in Belgium, France, Germany, Spain, and the United Kingdom. Patients were eligible for inclusion into the study if they were on a waiting list for liver transplantation and if they had no serological markers for persistent or past HB virus infection (antibody to HB surface antigen [anti-HBs] antibodies, anti-HB core antigen antibodies, and HBsAg negative). Subjects were excluded if they had previous vaccination against HB, previous administration of a vaccine containing monophosphoryl lipid A, history of allergic disease likely to be stimulated by any vaccine component, or a family history of congenital or hereditary immunodeficiency, or if they received immunoglobulins and/or any blood products, were receiving immunosuppressive therapy, or had acute or intercurrent disease at the time of enrollment. Characteristics of the patients are summarized in Table 1.

Study Design

The objective of this prospective, open, controlled, randomized (1:1 ratio; algorithm of pseudo random numbers given by RS/1 software from BBN, Cambridge, MA) trial was to evaluate the safety and immunogenicity of candidate HB-AS04 vs. a licensed HB vaccine. At least 40 evaluable subjects in each treatment group would provide 80% power to detect a 2-fold increase in anti-HBs seroprotection rates, using a 1-sided Fisher exact test (nQuery Adviser, Statistical Solutions, Saugus, MA). Subjects in the comparator group (Group 1) received 4 double doses of a licensed recombinant HB vaccine (Engerix-B, GlaxoSmithKline Biologicals, Rixensart, Belgium), each 2×1 -mL dose containing 2×20 μ g HBsAg and 2×0.5 mg of alum as salt, administered at Day 0, Day 7, and Day 21, with a booster dose at Month 6-12. Subjects in Group 2 received 3 doses of an experimental adjuvanted vaccine HB-AS04 (developed by GlaxoSmithKline Biologicals) containing 20 μ g HBsAg, 50 μ g of monophosphoryl lipid A, and 0.5 mg of alum as salt per 0.5-mL dose, administered at Day 0 and Day 21 with a booster dose at Month 6-12. The study vaccines were administered in the deltoid muscle.

Assessment of Immunogenicity

Anti-HBs quantification was performed using the enzyme immunoassay AUSAB (Abbott Laboratories, Chicago, IL) with a cutoff of 3.3 mIU/mL. Subjects with an anti-HBs concentration ≥ 10 mIU/mL were considered seroprotected. Serum was collected for measurement of anti-HBs antibodies at screening (Day -21 to -3), Day 21, Day 28, Day 56, Month 6-12 (before booster vaccination), and 1 month after booster vaccination. The geometric mean concentration (GMC) was calculated using the log-transformation of concentrations ≥ 3.3 mIU/mL for anti-HBs and taking the anti-log of the mean of these transformed values.

Assessment of Safety and Reactogenicity

The patients were observed closely for at least 15 minutes after each vaccination. The reactogenicity and safety of the vaccines were assessed by the subjects recording solicited local (pain, redness, swelling) and general (fatigue, fever, gastrointestinal symptoms, headache) adverse events on diary cards during a 4-day follow-up period after each vaccination. All local symptoms were considered as related to vaccination. Unsolicited adverse events occurring within 30 days after each vaccination regardless of attribution were also recorded as well as any serious adverse event (SAE) that occurred during the whole study period up to 30 days after the last vaccination.

Systemic and local reactions were scored as absent, grade 1 (easily tolerated), grade 2 (interfered with daily activity), and grade 3 (prevented normal daily activity). The size of redness and swelling was obtained by measuring the largest diameter and was scored as grade 1 (≤ 20 mm), grade 2 (>20 mm to ≤ 50 mm) or grade 3

(>50 mm). Fever was defined as oral/axillary body temperature $\geq 37.5^\circ\text{C}$ and was scored as grade 1 ($\geq 37.5^\circ\text{C}$ to $\leq 38^\circ\text{C}$), grade 2 ($>38^\circ\text{C}$ to $\leq 39^\circ\text{C}$) or grade 3 ($>39^\circ\text{C}$).

Statistical Analysis

Seroprotection rates (% of subjects with anti-HBs ≥ 10 mIU/mL) were compared between both groups using 1-sided Fisher exact test, at all time-points. A *P* value < 0.05 was considered statistically significant. GMCs were compared between groups using 1-way ANOVA (analysis of variance). Post-booster results were analyzed separately depending on whether subjects received their booster dose before or after the transplantation. All statistical analyses were done using SAS (SAS Institute Inc., Cary, NC) software.

RESULTS

Our study was conducted between January 2000 and May 2002. A total of 93 liver transplant candidates entered the study and were randomized into 2 groups. Group 1 consisted of 44 subjects who received the double dose of comparator HB vaccine, while Group 2 consisted of 49 subjects who received the HB-AS04 vaccine. The demographic profiles of the 2 groups were comparable with respect to mean age, gender, Child-Turcotte-Pugh score, and etiology of the liver disease (Table 1). The majority of patients needed liver transplantation for alcoholic liver cirrhosis (46.2%) and hepatitis C infection (29.0%). The primary analysis of immunogenicity was based on the total cohort; the results of the descriptive according to protocol analysis of immunogenicity were consistent with and very similar to those obtained from the analysis performed for the total cohort.

As illustrated in Figure 1, 75 subjects (35 in the comparator group and 40 in the HB-AS04 group) were eligible for per-protocol analysis of immunogenicity, as they met all the eligibility criteria and complied with study procedures. The population analyzed for reactogenicity was the according to protocol cohort (subjects who received at least 1 vaccine dose administered according to protocol procedures) and included 41 subjects receiving the comparator vaccine and 46 subjects receiving the HB-AS04 vaccine.

In the comparator HB vaccine group, 30 subjects completed the full vaccination course. Of these subjects, 15 did not undergo liver transplantation before receiving the booster dose, and 15 were transplanted before administration of the booster dose. In the HB-AS04 group, 33 subjects completed the full vaccination course. Of these subjects, 23 were not transplanted before receiving the booster vaccination, and 10 underwent transplantation before administration of the booster dose.

Immunogenicity

The anti-HBs immune response of the total cohort is detailed in Table 2. One week after the second vaccine

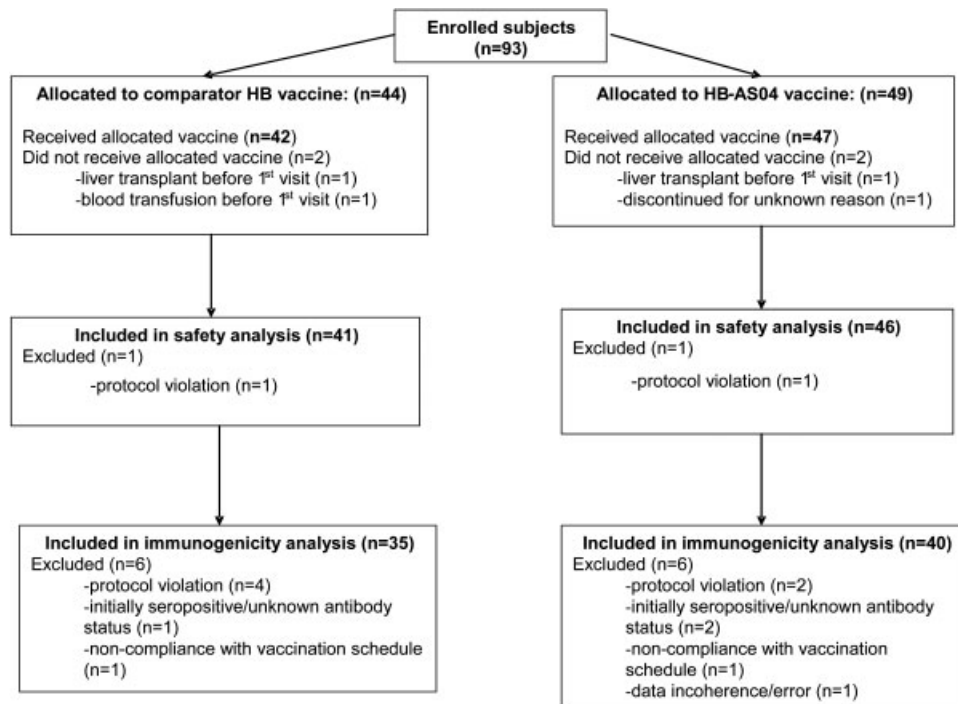


Figure 1. Flow of participants during the study.

TABLE 2. Immunogenicity of HB-AS04 and Comparator HB Vaccine in Liver Transplant Candidates (Total Cohort)

| | Time | N | SP | | GMC* | |
|-----------------------|------------|----|------|-----------|--------|-------------|
| | | | % | 95% CI | mIU/mL | Range |
| Comparator HB Vaccine | Day 21 | 38 | 13.2 | 4.4-28.1 | 66 | <3.3-5,152 |
| | Day 28 | 38 | 21.1 | 9.6-37.3 | 43 | <3.3-4,167 |
| | Day 56 | 35 | 14.3 | 4.8-30.3 | 67 | <3.3-6,341 |
| | Pre-boost | 30 | 10.0 | 2.1-26.5 | 73 | <3.3-1,025 |
| | Post-boost | 25 | 32.0 | 14.9-53.5 | 279 | <3.3-5,345 |
| HB-AS04 | Day 21 | 44 | 15.9 | 6.6-30.1 | 18.5 | <3.3-84 |
| | Day 28 | 41 | 31.7 | 18.1-48.1 | 19 | <3.3-387 |
| | Day 56 | 38 | 15.8 | 6.0-31.3 | 14 | <3.3-104 |
| | Pre-boost | 31 | 32.3 | 16.7-51.4 | 38 | <3.3-810 |
| | Post-boost | 30 | 60.0 | 40.6-77.3 | 481 | <3.3-44,060 |

Abbreviations: SP, seroprotection rate; CI, confidence interval; GMC, geometric mean concentration, calculated.
*Calculated in seropositive subjects (concentration ≥ 3.3 mIU/mL).

dose (at day 28), 31.7 % of the subjects in the HB-AS04 group were seroprotected (anti-HBs antibody concentration ≥ 10 mIU/mL) whereas at that time (1 week after the third vaccine dose) the seroprotection rate in the comparator group was 21.1 % ($P = 0.2076$, 1-sided Fisher exact test). GMCs were low in both groups: 19 mIU/mL in the HB-AS04 group and 43 mIU/mL in the comparator group.

At the time of booster dose administration (6-12 months after initiation of the vaccination course), significantly more subjects were seroprotected in the HB-AS04 group (32.3 %) as compared to the comparator HB vaccine group (10.0%) ($P = 0.0337$, 1-sided Fisher exact

test). GMCs stayed low and comparable in both groups (38 mIU/mL in the HB-AS04 group and 73 mIU/mL in the comparator group).

One month after administration of the booster dose, the seroprotection rate in the HB-AS04 group (60.0%) was significantly higher than the seroprotection rate in the comparator group (32.0%) ($P = 0.0354$, 1-sided Fisher exact test). The GMCs were 481 mIU/mL in the HB-AS04 group and 279 mIU/mL in the comparator group ($P = 0.6407$, 1-way ANOVA test).

The results of the protocol analysis of immunogenicity were consistent with those obtained from the total cohort analysis. At Day 28, a seroprotection rate of 28.2% was

TABLE 3. Immunogenicity of HB-AS04 and Comparator HB Vaccine in Subjects With Booster Dose Before or After Liver Transplantation (Total Cohort)

| | Time | N | SP | | GMC* | |
|--|------------|----|------|-----------|--------|-------------|
| | | | % | 95% CI | mIU/mL | Range |
| <i>Subjects With Booster Dose After Liver Transplantation</i> | | | | | | |
| Comparator HB vaccine | Day 21 | 17 | 17.6 | 3.8-43.4 | 24 | <3.3-80.4 |
| | Day 28 | 17 | 29.4 | 10.3-56.0 | 24 | <3.3-4,167 |
| | Day 56 | 14 | 7.1 | 0.2-33.9 | 30 | <3.3-115.4 |
| | Pre-boost | 16 | 0.0 | 0.0-20.6 | | |
| | Post-boost | 15 | 13.3 | 1.7-40.5 | 512 | <3.3-1,926 |
| HB-AS04 | Day 21 | 14 | 14.3 | 1.8-42.8 | 13 | <3.3-35.3 |
| | Day 28 | 14 | 42.9 | 17.7-71.1 | 19 | <3.3-52.2 |
| | Day 56 | 11 | 9.1 | 0.2-41.3 | 14 | <3.3-22.2 |
| | Pre-boost | 11 | 18.2 | 2.3-51.8 | 90 | <3.3-639.1 |
| | Post-boost | 10 | 20.0 | 2.5-55.6 | 166.5 | <3.3-7,301 |
| <i>Subjects With Booster Dose Before Liver Transplantation</i> | | | | | | |
| Comparator HB Vaccine | Day 21 | 21 | 9.5 | 1.2-30.4 | 875 | <3.3-5,152 |
| | Day 28 | 21 | 14.3 | 3.0-36.3 | 104 | <3.3-4,157 |
| | Day 56 | 21 | 19.0 | 5.4-41.9 | 92 | <3.3-6,341 |
| | Pre-boost | 14 | 21.4 | 4.7-50.8 | 73 | <3.3-1,025 |
| | Post-boost | 10 | 60.0 | 26.2-87.8 | 235 | <3.3-5,345 |
| HB-AS04 | Day 21 | 30 | 16.7 | 5.6-34.7 | 27 | <3.3-84 |
| | Day 28 | 27 | 25.9 | 11.1-46.3 | 20 | <3.3-387 |
| | Day 56 | 27 | 18.5 | 6.3-38.1 | 14 | <3.3-104 |
| | Pre-boost | 20 | 40.0 | 19.1-63.9 | 33 | <3.3-810 |
| | Post-boost | 20 | 80.0 | 56.3-94.3 | 574 | <3.3-44,060 |

Abbreviations: SP, seroprotection rate; CI, confidence interval; GMC, geometric mean concentration, calculated.

*calculated in seropositive subjects (concentration ≥ 3.3 mIU/mL).

observed in the HB-AS04 group and 20.0% in the comparator group. One month after administration of the booster dose, seroprotection was obtained in 58.6% of the subjects in the HB-AS04 group and in 33.3% of the subjects receiving the comparator HB vaccine.

A subanalysis was performed to evaluate the immune response in subjects who received the full vaccination course, including the booster dose, before transplantation, as compared to the immune response in subjects who were transplanted before administration of the booster dose. The results of this subanalysis are presented in Table 3. One month after administration of the booster dose, higher seroprotection rates were observed in subjects who received the booster dose before liver transplantation (80.0% in the HB-AS04 group and 60.0% in the comparator group), as compared to subjects who received the booster dose after liver transplantation (20.0% in the HB-AS04 group and 13.3% in the comparator group). The data obtained in the subset of subjects who did not undergo surgery before administration of the booster dose are thus in line with the higher seroprotection rates elicited by HB-AS04, as compared to the comparator HB vaccine, observed in the analysis of all subjects.

Reactogenicity

Data on the reactogenicity following administration of 124 doses of HB-AS04 and 151 doses of the comparator HB vaccine were collected and are presented in Table 4.

Overall, more doses of the HB-AS04 vaccine (73.3%) than of the comparator vaccine (57.1%) caused at least 1 solicited or unsolicited symptom. This increase in reactogenicity was mainly due to an increased local reactogenicity of the HB-AS04 vaccine. Pain at the injection site was the most frequently reported solicited local symptom in both groups, and the incidence was higher in the HB-AS04 group (39.3%) than in the comparator group (14.7%). However, only 3 solicited local symptoms were described as severe. Of these cases, 2 included pain at injection site (1 in each group), and 1 included swelling at the injection site (in the HB-AS04 group).

Fatigue was the most frequent solicited general symptom in both groups (38.9% in the comparator group and 45.5% in the HB-AS04 group). However, the incidence of fatigue with probable or suspected relationship to vaccination was low and similar in both groups (4.0% in the comparator group and 4.9% in the HB-AS04 group). There were 7 instances of severe solicited general symptoms after administration of the comparator HB vaccine (5 cases of fatigue and 2 cases of fever), compared to 3 in the HB-AS04 group (fatigue).

Unsolicited symptoms with a probable or suspected relationship to the study vaccine were reported after administration of 3 doses of HB-AS04 and 6 doses of comparator HB vaccine.

As compared to the incidence of local symptoms (solicited or unsolicited) after the first dose of HB-AS04 vaccine, no increase was seen with subsequent doses.

TABLE 4. Local and General Symptoms After Vaccination (Per Dose Analysis) With HB-AS04 and Comparator HB Vaccine (Total Cohort)

| | | Comparator | |
|-----------------------|---------|------------|----------|
| | | HB vaccine | HB-AS04 |
| Local | | N* = 150 | N* = 122 |
| Pain | Total | 14.7 | 39.3 |
| | Grade 3 | 0.7 | 0.8 |
| Redness [†] | Total | 10.7 | 13.1 |
| | Grade 3 | 0.0 | 0.0 |
| Swelling [†] | Total | 1.3 | 6.6 |
| | Grade 3 | 0.0 | 0.8 |
| General | | N* = 149 | N* = 123 |
| Fatigue | Total | 38.9 | 45.5 |
| | Related | 4.0 | 4.9 |
| | Grade 3 | 3.4 | 2.4 |
| Gastrointestinal | Total | 10.1 | 18.7 |
| | Related | 2.7 | 1.6 |
| | Grade 3 | 0.0 | 0.0 |
| Headache | Total | 12.8 | 13.0 |
| | Related | 5.4 | 5.7 |
| | Grade 3 | 0.0 | 0.0 |
| Fever [‡] | Total | 4.0 | 8.1 |
| | Related | 3.4 | 4.1 |
| | Grade 3 | 1.3 | 0.0 |

NOTE: Grade 3 symptoms prevented daily activity.

*Number of completed symptom sheets (1 per subject after each dose).

[†]Grade 3 redness and swelling >50 mm.

[‡]Grade 3 fever <39°C.

A total of 63 SAEs were reported during the study period. Eleven patients died during the study. The number of fatalities was equally distributed between the HB-AS04 group (n = 5) and the comparator group (n = 6), none of them was determined by the investigator to be related to the vaccine, and all fatalities referred to complications of the subject's underlying liver cirrhosis or to complications experienced posttransplantation. Nineteen subjects with a SAE were removed from the study (10 in the comparator group and 9 in the HB-AS04 group). Two SAEs were considered to be possibly related to vaccination by the investigator. One subject (HB-AS04 group) developed facial dyskinesia and behavioral disorders. A second subject (in the comparator group) developed diabetes mellitus requiring insulin treatment.

DISCUSSION AND CONCLUSIONS

This study involved patients with irreversible liver failure who were eligible for liver transplantation. Ideally, these patients should be protected against HB virus before receiving liver transplantation.

One week after completion of the primary vaccination course (Day 28), the number of subjects achieving seroprotection was low (21.1% after administration of the comparator HB vaccine and 31.7% after HB-AS04 vaccination) and was not significantly different between

the 2 groups. Low seroconversion rates in cirrhotic patients can be attributed to their overall poor medical health and the immune suppression associated with their disease.^{11,12} Our results obtained in the comparator group are in line with the 25-40% seroprotection rate observed after administration of an accelerated primary vaccination with double doses of licensed HB vaccine in liver transplant candidates.⁸⁻¹⁰

At the moment of administration of the booster dose (Month 6-12), significantly more subjects ($P = 0.0337$) were seroprotected in the HB-AS04 group (32.3%) as compared to the comparator group (10.0%), but GMCs were low and comparable in both groups at that time point.

When considering both pre- and post-liver transplant patients, the immune response 1 month after HB-AS04 booster dose was better in terms of seroprotection rate than that obtained after a double booster dose of comparator vaccine. Indeed, the seroprotection rate one month after the HB-AS04 booster dose was twice as high (60.0%) as compared to the seroprotection rate in patients given the comparator HB vaccine (32.0%) ($P = 0.035$). The anti-HBs GMC in the HB-AS04 group tended to be higher (481 mIU/mL) than that elicited in the comparator group (279 mIU/mL) ($P = 0.641$).

In subjects not undergoing liver transplantation before receiving the booster dose, the antibody response following administration of the booster appeared to be better as compared to the response seen in subjects who did undergo a liver transplantation before administration of the booster. These results confirm that, ideally, the booster dose should be given before surgery to avoid the subsequent negative effect of immunosuppressive medication.^{8,10,18}

The relatively low seroprotection rates observed with both vaccines after the primary vaccination course and following a booster dose after liver transplantation are not optimal and clearly a disadvantage in centers where waiting lists are not long. These data therefore support the importance of initiating immunization in all liver disease patients as early as possible in the disease evolution, to improve the protection conferred by vaccination of these individuals.¹⁹

Overall, an improved antibody response was generated with the experimental HB-AS04 vaccine, as compared to the licensed HB vaccine, administered according to the current medical practice for pre-liver transplant patients. This is especially true when considering the vaccination schedule of only 3 doses of 20 μ g HB-AS04 vs. 4 double doses (2 \times 20 μ g) of the comparator vaccine. Moreover, in the present study, 75% of the patients needed liver transplantation because of alcoholic liver cirrhosis or hepatitis C virus infection, and only 18.3% of patients needed liver transplantation for a biliary disease. This is of particular relevance for the interpretation of the seroprotection rates observed in the current study, as it is known that the response to HB vaccination is lower in patients with chronic alcoholism or hepatitis C chronic liver disease, as compared to other causes of liver disease.²⁰ Higher seroprotection rates (73.3%) were also reported in chil-

dren with cholestatic liver disease.²¹ Similarly, in adult patients with cholestatic liver disease, a significantly better response to vaccination was seen as compared to noncholestatic forms of liver disease (43% vs. 7%).²²

The better immunogenicity of the adjuvanted HB-AS04 vaccine observed in this study confirms previous results in healthy subjects^{16,17} as well as in prehemodialysis and hemodialysis patients.²³ Long-term protection after the HB-AS04 booster dose has not been evaluated in this study. However, the superiority of the HB-AS04 vaccine 1 month after completion of the primary vaccination course in another immunodeficient population (hemodialysis patients) was confirmed by the antibody persistence data up to 3 years.²³

Despite a slightly higher reactogenicity, the safety profile of the experimental adjuvanted HB vaccine can be considered as clinically acceptable, with most symptoms being mild to moderate, and transient. One subject reported an SAE that was considered by the investigator to be possibly related to vaccination in the HB-AS04 group. This subject presented facial dyskinesia concomitant with severe hyponatremia and behavioral disorders.

It is likely that in liver transplant patients higher seroprotection rates could also be obtained following additional administration of HB-AS04 vaccine doses. It can be expected that additional booster doses could be safely administered in liver transplant patients, since in this study no increase in reactogenicity was seen with subsequent doses. Also, in hemodialysis patients, booster doses of HB-AS04 vaccine were not associated with an increase in adverse reaction incidence.²³

In conclusion, an improved antibody response was observed in liver transplant candidates with 3 doses of the adjuvanted HB vaccine HB-AS04, as compared to 4 double doses of the comparator HB vaccine, especially when considering the difference in vaccination schedule. Liver transplant candidates could benefit from the use of this experimental adjuvanted HB vaccine to further increase their protection against HB infection, as compared to the licensed HB vaccines that are currently available.

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