Fendrix *vs* Engerix-B for Primo-Vaccination Against Hepatitis B Infection in Patients With Inflammatory Bowel Disease: A Randomized Clinical Trial

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INTRODUCTION: **To compare Engerix-B and Fendrix hepatitis B virus for primo vaccination in inflammatory bowel disease (IBD).**

METHODS: **Patients with IBD were randomized 1:1 to receive Engerix-B double dose or Fendrix single dose at months 0, 1, 2, and 6. Anti-HBs titers were measured 2 months after the third and fourth doses. Response to vaccination was defined as anti-HBs ≥100 UI/L. Anti-HBs titers were measured 2 months after the third and fourth doses and again at 6 and 12 months after the fourth dose.**

RESULTS: **A total of 173 patients were randomized (54% received Engerix-B and 46% Fendrix). Overall, 45% of patients responded (anti-HBs ≥100 IU/L) after 3 doses and 71% after the fourth dose. The response rate after the fourth dose was 75% with Fendrix *vs* 68% with Engerix-B ($P = 0.3$). Older age and treatment with steroids, immunomodulators, or anti–tumor necrosis factor were associated with a lower probability of response. However, the type of vaccine was not associated with the response. Anti-HBs titer negativization occurred in 13% of patients after 6 months and 20% after 12 months. Anti-HBs ≥100 IU/L after vaccination was the only factor associated with maintaining anti-HBs titers during follow-up.**

DISCUSSION: **We could not demonstrate a higher response rate of Fendrix (single dose) over Engerix-B (double dose). A 4-dose schedule is more effective than a 3-dose regimen. Older age and treatment with immunomodulators or anti–tumor necrosis factors impaired the success. A high proportion of IBD patients with protective anti-HBs titers after vaccination loose them over time. The risk of losing protective anti-HBs titers is increased in patients achieving anti-HBs <100 IU/L after the vaccination.**

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INTRODUCTION

Hepatitis B virus (HBV) infection represents a global health problem because it is a recognized etiologic factor of the development of liver cirrhosis and hepatocellular carcinoma, and it causes very important morbidity and mortality (1). For this reason, since 1991, the World Health Organization has recommended the inclusion of the HBV vaccine in the usual vaccination schedule for all children; this strategy has significantly reduced the prevalence of infection and the incidence of medical complications related to chronic infection with HBV (2).

Although it has been demonstrated that patients with inflammatory bowel disease (IBD) have not a higher risk of acquiring HBV infection (3), reactivations of HBV have been reported in up to 7.5% of cases (sometimes with fatal outcomes) in the subgroup of patients with positive markers for HBV infection (4). Practically, all HBV reactivations in patients with IBD have

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occurred in subjects receiving treatment with immunosuppressant or biological drugs (5). At present, the European Crohn's and Colitis Organization (ECCO) recommends the systematic study of the immunological situation of patients with IBD with respect to HBV and vaccination in patients with negative serology (6).

The response rate to the HBV vaccine in patients with IBD is lower than that reported in the general population, which is more than 95% (7–9). The origin of this low response rate in patients with IBD can be due to different factors. On one hand, to the immunological alteration that underlies this disease. On the other hand, a large number of patients with IBD are under treatment with immunosuppressive drugs, which could also condition the failure in the formation of antibodies induced by the vaccine (named anti-HBs).

In addition, in patients who have presented a response to the HBV vaccine, a rapid decrease in anti-HBs titers has been observed in the first year, being undetectable in 17%–50% of cases 10–15 years after vaccination (10,11). The cases of HBV infection described in immunocompetent patients with undetectable anti-HBs, due to a decrease in antibody titers below the initial 10 UI/L, have been mild, and in no case, they have evolved toward chronicity. However, in immunocompromised patients, cases of HBV infections with clinical repercussions have been reported in patients who initially responded to the vaccine and then negativized the anti-HBs titers (12).

ECCO consensus on infections acknowledges that the response to HBV vaccine in patients with IBD is suboptimal and suggests that higher doses of the immunizing antigen may be required to provide protection; however, no recommendation about vaccination strategy is established (6). To try to improve the response rate and the durability of anti-HBs titers, several vaccination schedules have been proposed (double dose, rapid regimen, and booster dose), although the superiority of some over others has not been demonstrated so far.

In this respect, a study performed on patients on hemodialysis compared a vaccine against HBV (Fendrix; GlaxoSmithKline Biologicals) that incorporates a new adjuvant (AS04) with double doses of the previously commercialized vaccine (Engerix-B; GlaxoSmithKline Biologicals) (13). Patients vaccinated with Fendrix presented higher protection rate, and the differences persisted 36 months after vaccination. Fendrix has demonstrated to induce immunogenicity in highly refractory populations, mainly in patients with HIV and renal diseases with failure to standard HBV vaccines (14,15). However, we do not have data on the efficacy of this vaccine in patients with IBD or on what would be the most appropriate vaccination regimen in this group of patients.

In summary, although vaccination against HBV is currently recommended in patients with IBD, the immunological response to the vaccine is low. It is necessary to evaluate new vaccines that may offer greater protection to these patients. In addition, optimal vaccination schedules and long-term immunogenicity of these vaccines remain to be studied. The aim of this study was to compare the response rate to HBV vaccination with 2 types of vaccines—the conventional vaccine (Engerix-B) and a vaccine with adjuvant (Fendrix)—in patients with IBD. In addition, we aimed to identify the factors that predict the response to the HBV vaccine and to analyze the kinetics of the decrease in anti-HBs titers over time in patients who initially responded to this vaccine. We anticipate that the results of this trial will have a relevant impact on the recommendations of the vaccination strategies in patients with IBD.

METHODS

Study design

This is a multicenter, phase 3, prospective, randomized, open-label, and comparative clinical trial to evaluate the efficacy of 2 vaccines against HBV in patients with IBD. Patients were randomized 1:1 to receive either single doses of Fendrix (20-μg HBsAg) or double doses of Engerix-B (2 × 20-μg HBsAg) at months 0, 1, 2, and 6. Both formulations are commercially available and manufactured by GlaxoSmithKline Biologicals.

The titers of anti-HBs used to evaluate the response rate to the vaccine were determined 2 months after the administration of the third dose (at month 4), and 2 months after the administration of the fourth dose (which we considered as a booster), at month 8. The reason was to evaluate the response rate to the vaccination schedule known as "accelerated protocol" (at 0, 1, and 2 months), as well as the increase in the immunogenic response due to the administration of the fourth dose.

Subsequently, patients with positive anti-HBs titers after vaccination (anti-HBs ≥10 IU/L after the fourth dose) were included in a continuation study to analyze the kinetics of anti-HBs titers over time. For this purpose, anti-HBs titers were determined at 6 and 12 months after the last determination of anti-HBs in this study (performed in the eighth month, 2 months after the last dose of vaccine administered at month 6).

Local injection site symptoms (pain, redness, and swelling) and general symptoms (headache, fatigue, and fever) from the day of injection and the 3 subsequent days were queried. Serious adverse events, defined according to the Good Clinical Practice guidelines, that occurred at any time throughout the study period up to at least 30 days after the last vaccine administration were reported.

The study was conducted at 7 IBD hospital units across Spain. Ethics approval for this study was granted by the Clinical Research Ethics Committee of the Hospital Universitario de La Princesa (Madrid). The trial was conducted according to the ethical principles set out in the Declaration of Helsinki and Spanish law regarding clinical trials. It was registered in European Clinical Trial Registry (EudraCT number 2010-023947-14). Written informed consent was obtained from all participating patients.

Patients

Patients were eligible for enrolment in this study if they were older than 18 years, diagnosed with IBD (either Crohn's disease or ulcerative colitis) by the ECCO criteria, were no previously vaccinated against HBV, and had negative HBV serology. Patients with advanced chronic diseases, allergy to components of the vaccine, previous vaccination against HBV, pregnancy or breastfeeding, alcohol abuse, positive serology for HBV, alterations of immunity for causes other than the treatments administered for the control of IBD, prolonged treatment with antibiotics, or refusal to give consent for participation in the study were excluded.

Patients and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination of our research.

Treatment arms

Treatment group 1: Engerix-B injectable suspension of 1 mL containing 20 μg of recombinant HBsAg adsorbed on 0.5-mg

aluminium as aluminium hydroxide. Two monodose vials of the vaccine were mixed and given as a single injection.

Treatment group 2: Fendrix suspension for injection of 0.5 mL containing 20 μg of recombinant HBsAg adjuvanted by AS04C (which contains 2-3-O-desacyl-4′-monophosphoryl lipid A) and adsorbed on 0.5-mg aluminium as aluminium phosphate.

Both vaccines were administered at 0, 1, 2, and 6 months as an intramuscular injection in the deltoid region of the arm, following manufacturers' instructions.

Treatment assignment

The assignment of the treatment was performed through a 1:1 randomization, with a table of random numbers through a computer system. The details of the randomization sequence were unknown to the researchers and the coordinators of each center and were kept in closed and opaque envelopes. Randomization was stratified according to the treatment that patients were receiving for IBD (none, immunosuppressants, or anti–tumor necrosis factor [anti-TNF] agents). Envelopes only contained on their surface the name of the hospital, the number of the envelope, and the treatment that the patient was receiving (none, immunosuppressants, or biologic agents). The envelopes were sent from the coordinating center to each participating site. Once the patient consented to be included in the study and after confirming that the patient met the inclusion criteria and none of the exclusion criteria, the corresponding envelope was opened; the paper inside indicated the vaccine to be administered to the patient.

This was an open study (not blind), so no masking technique was used, except in the analysis of plasma samples for the determination of anti-HBs titers, which was performed blindly: The technician performing the measurement did not know to which vaccine formulation each sample corresponded. The determination of anti-HBs titers was performed locally at each participating center.

Endpoints

The main variable was the response to the vaccine, defined as an anti-HBs titer ≥100 UI/L 2 months after the fourth dose of vaccine. As secondary outcome, the response rate considering anti-HBs ≥10 UI/L was included. To analyze the kinetics of the anti-HBs titers, those patients who had anti-HBs ≥10 IU/L in the postvaccination control after the fourth dose of vaccine were considered. Anti-HBs after the fourth dose of vaccine (at month 8) was considered the basal titers for the study of anti-HBs kinetics. In these patients, the measurement of anti-HBs titers was repeated at 6 and 12 months after the baseline determination (2 months after the fourth dose of vaccine).

Definitions

IBD activity: It was assessed based on the Harvey-Bradshaw index for Crohn's disease and the Partial Mayo Score for ulcerative colitis.

Protective anti-HBs: anti-HBs ≥10 UI/L.

Response to the vaccine: anti-HBs ≥100 UI/L.

Exposure to drugs during vaccination was defined as use of a specific drug—steroids, immunomodulators (thiopurines or methotrexate), or anti-TNF agents—between the first vaccine administration and the anti-HBs measurement 2 months after the fourth dose of vaccine. In the same way, exposure to drugs during follow-up was defined as use of a specific drug—steroids, immunomodulators (thiopurines or methotrexate), or anti-TNF agents—between the anti-HBs measurement 2 months after the fourth dose of vaccine and the end of follow-up.

Initially, 5 separate categories of exposure were created for analysis, as follows:

1. Nonexposed to steroids, immunomodulators, or anti-TNF drugs.
2. Exposed to steroids, but nonexposed to immunomodulators or anti-TNF drugs.
3. Exposed to immunomodulators (with or without steroids) but nonexposed to anti-TNF drugs.
4. Exposed to anti-TNF drugs (with or without steroids) but nonexposed to immunomodulators.
5. Exposed to anti-TNF drugs in combination with immunomodulators (with or without steroids).

Data collection

The demographic characteristics collected were as follows: age, sex, IBD type (Crohn's disease or ulcerative colitis), and immunosuppressive treatment (steroids, azathioprine, mercaptopurine, and methotrexate) or anti-TNF treatment at vaccination or during follow-up. In addition, adverse events occurring during the study period were recorded.

Sample size calculation

In accordance with previous results, if there is a true difference in favor of the experimental treatment—Fendrix—(75% *vs* 65% with double dose of Engerix-B), then 180 patients (90 per group) would be required to be 90% sure (statistic power) that the upper limit of a 1-sided 95% confidence interval (or equivalently a 90% 2-sided confidence interval) will exclude a difference in favor of the standard group of more than 10%.

Statistical analysis

The main variable was the response rate to the vaccine, defined as an anti-HBs titer ≥100 UI/L 2 months after the fourth dose of vaccine. For quantitative variables, the mean and SD or median and interquartile range, depending on whether they were normally distributed or not, were calculated. Comparisons between mean values were performed using the Student *t* test for independent samples. For qualitative variables, percentages and corresponding 95% confidence intervals were calculated. Qualitative variables were compared using the χ^2 test and the Fisher exact test. Statistical significance was considered at $P < 0.05$ for the overall comparison of the groups (Fendrix and Engerix-B).

A binary logistic regression model was used to estimate the effect of the different variables on the response to the vaccine. All the variables, which reached statistical significance in the univariate analysis and those who were considered clinically relevant, including the type of vaccine, were included in the multivariate analysis. Thus, in the multivariate analysis, the dependent variable was the response to the vaccine and the independent variables were age, type of IBD, IBD activity, type of vaccine, and exposure to IBD drugs, among others.

Patients with anti-HBs ≥10 UI/L after completing the vaccination were included in the follow-up study, and the incidence rate for negativization of anti-HBs antibodies was estimated by Kaplan-Meier methods. Differences between curves were evaluated by the log-rank test. The Cox-regression analysis was used to identify predictive factors of anti-HBs negativization.

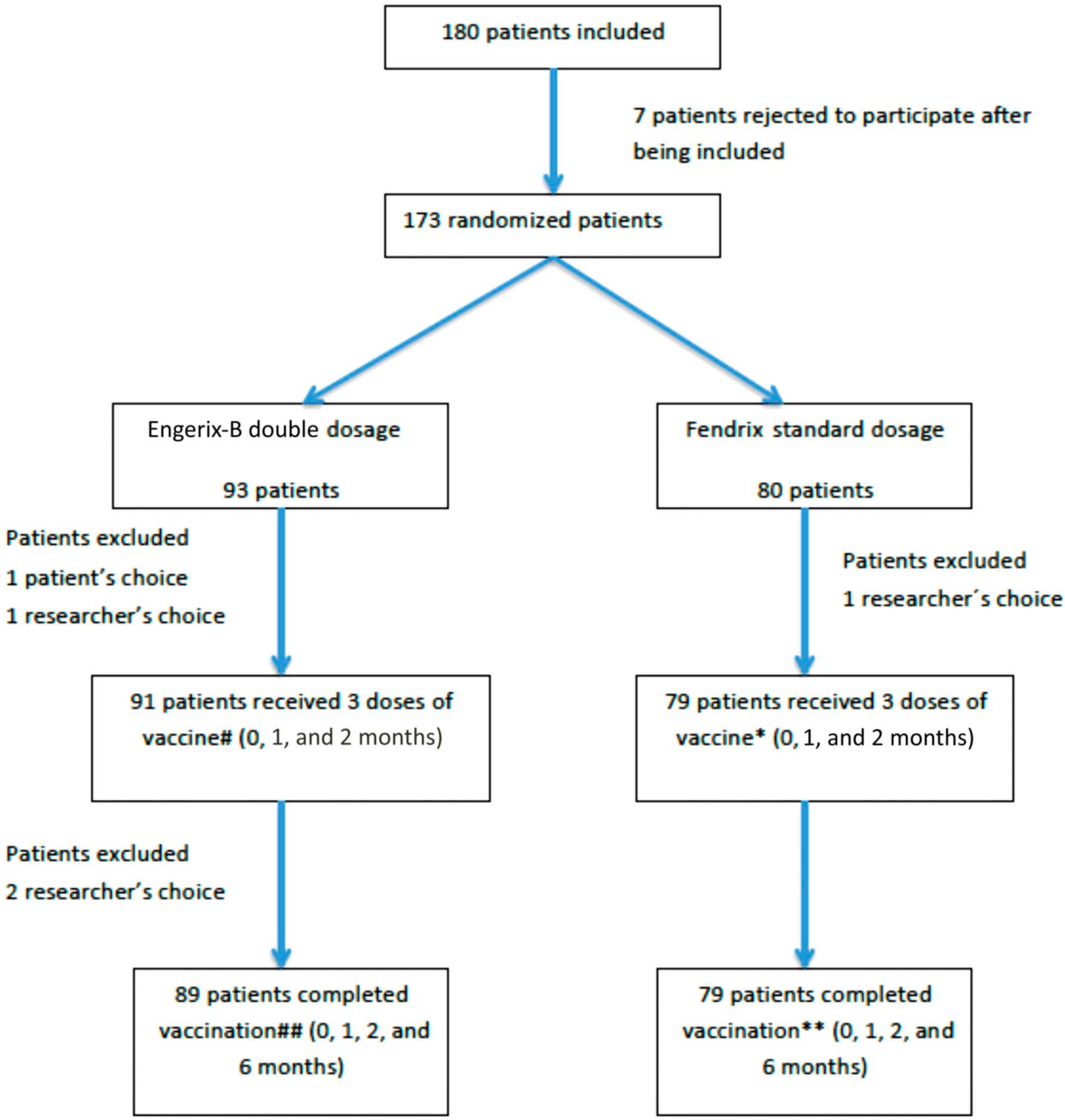

Figure 1. Flowchart of patients included in the study. "#" 90 patients had anti-HBs determination after receiving 3 doses; "##" 84 patients had anti-HBs determination after receiving 4 doses; "*" 74 patients had anti-HBs determination after receiving 3 doses; "**" 75 patients had anti-HBs determination after receiving 3 doses.

RESULTS

A total of 180 patients were included in the study. From them, 173 were randomized (7 patients refused to participate before randomization). Ninety-three patients (54%) were assigned to receive Engerix-B double dose and 80 patients (46%) to Fendrix. The flow chart of patients in the study is represented in Figure 1. From the overall cohort, 24% of the patients were under immunomodulators, 15% under anti-TNF agents, and 24% under combo therapy. The main characteristics of patients are summarized in Table 1. The proportion of patients with active disease during vaccination was significantly higher in the Engerix-B than in the Fendrix group (21 *vs* 10%, $P = 0.02$). However, there were no differences in patients' age, IBD type, disease location, disease behavior, or treatment during vaccination between those assigned to Fendrix and to Engerix-B.

Response to the vaccines

A total of 90 patients from the Engerix-B group and 79 from the Fendrix group received 3 doses of vaccine (at 0, 1, and 2 months). The proportion of patients with anti-HBs ≥100 UI/L or anti-HBs ≥10 UI/L was similar in patients vaccinated with Engerix-B and Fendrix (Table 2).

Eighty-nine patients from the Engerix-B group and 79 from the Fendrix group completed the vaccination (4 doses); 84 and 75

Table 1. Characteristics of the study groups based on vaccine assignment

	Engerix-B (N = 93)	Fendrix (N = 80)	*P*
61 yr or older, n (%)	17 (18)	15 (19)	0.9
Male sex, n (%)	47 (50)	48 (60)	0.2
Crohn's disease, n (%)	49 (53)	39 (49)	0.6
Location			
Ileal, n (%)	23 (47)	16 (42)	0.9
Colonic, n (%)	7 (14)	7 (18)	
Ileocolonic, n (%)	18 (37)	14 (37)	
Behavior			
Inflammatory, n (%)	25 (51)	23 (59)	0.3
Stricturing, n (%)	15 (31)	7 (18)	
Fistulizing, n (%)	9 (18)	9 (23)	
Ulcerative colitis extent			
Extensive, n (%)	21 (48)	19 (46)	0.6
Left-sided, n (%)	15 (34)	15 (37)	
Proctitis, n (%)	8 (18)	7 (17)	
Active disease during vaccination, n (%)	21 (22.6)	8 (10)	0.02
IBD treatment during vaccination			
No immunosuppressants, n (%)	32 (34)	22 (28)	0.8
Steroids, n (%)	5 (5)	3 (4)	
Immunomodulators, n (%)	22 (23)	20 (25)	
Anti-TNF, n (%)	12 (13)	15 (19)	
Anti-TNF plus immunomodulators, n (%)	22 (23)	19 (24)	
Smokers, n (%)	24 (26)	17 (21)	

IBD, inflammatory bowel disease.

patients, respectively, were assessed for vaccine response (Figure 1). The proportion of patients with anti-HBs ≥100 UI/L or anti-HBs ≥10 UI/L after the fourth dose was similar in patients vaccinated with Engerix-B and Fendrix (Table 2). However, there was a trend toward higher response rate in patients vaccinated with Fendrix (considering anti-HBs ≥10 UI/L).

With respect to the vaccination schedule, the response rate (anti-HBs ≥100 UI/L) was significantly higher after the fourth dose of vaccine than after 3 doses of the vaccine both in the Engerix-B and the Fendrix groups. The same finding was observed when considering the response as anti-HBs ≥10 UI/L (Figure 2).

Response to the vaccine according to IBD treatment

Table 3 summarizes the response rate to the vaccine based on vaccine doses and IBD treatment considering both anti-HBs ≥100 UI/L and anti-HBs ≥10 UI/L. Of note, the response rate was lower in patients treated with anti-TNF agents in combination with immunomodulators; the administration of a fourth vaccine dose increased the response to the vaccine in all treatment groups. In patients with no IBD treatment during vaccination, the response rate was 96% after the fourth dose (considering both anti-HBs ≥100 UI/L and anti-HBs ≥10 UI/L).

Response to HBV vaccine was impaired in patients under IBD treatment in comparison with those without immunosuppressive treatment (Table 4). When we analyzed the response rate considering the vaccine group, in the Engerix-B group, the response rate was significantly lower in patients under steroids, immunomodulators, and anti-TNF monotherapy or in combination with immunomodulator than in patients with no treatment. In the Fendrix group, the response rate was lower in patients treated with immunomodulators or anti-TNF in combination with immunomodulators; in addition, patients treated with steroids or anti-TNF had lower response rate in comparison with patients with no treatment, but the difference did not reach statistical significance (the number of patients per group was very low) (Table 4).

In the multivariate analysis, considering success as anti-HBs ≥100 UI/L (as it was defined in the study protocol), older age (older than 60 years) and to receive steroids, immunomodulators, or anti-TNF were associated with a lower probability of response to the vaccine. The type of vaccine was not associated with the response to vaccination (Table 5, a).

However, when we considered success as anti-HBs ≥10 UI/L (standard threshold), to have been vaccinated with Fendrix was associated with higher probability of response. Older age and treatment with anti-TNF monotherapy or in combination with immunomodulators were associated with lower probability of vaccination success (Table 5, b).

Kinetics of anti-HBs antibodies in patients with protective anti-HBs ≥10 UI/L after vaccination

A total of 131 patients had anti-HBs ≥10 UI/L after completing vaccination; from them, 117 patients (90%) accepted to be included in the follow-up study. From those, 55% were male, 54% had ulcerative colitis, and 90% had anti-HBs ≥100 IU/L after vaccination. With respect to IBD treatments, 2.6% received solely steroids during follow-up, 29% immunomodulators in monotherapy, 15% anti-TNF in monotherapy, and 19% combo therapy. There were no differences in the main characteristics (age, anti-HBs titers after complete vaccination, or IBD treatment) between the study groups (Engerix-B or Fendrix), but the proportion of patients exposed to anti-TNFs was superior among

Table 2. Response rate to Fendrix and Engerix-B after 3 and 4 doses of vaccine

a: Response after 3 doses

	Engerix-B (N = 90)	Fendrix (N = 74)	*P*
Anti-HBs ≥100 IU/L (% and 95% CI)	41 (30–52)	50 (38–62)	0.2
Anti-HBs ≥10 IU/L (% and 95% CI)	67 (56–77)	67 (56–79)	0.9

b: Response after 4 doses

	Engerix-B (N = 84)	Fendrix (N = 75)	*P*
Anti-HBs ≥100 IU/L (% and 95% CI)	68 (57–78)	75 (64–85)	0.3
Anti-HBs ≥10 IU/L (% and 95% CI)	77 (68–87)	88 (80–96)	0.07

CI, confidence interval.

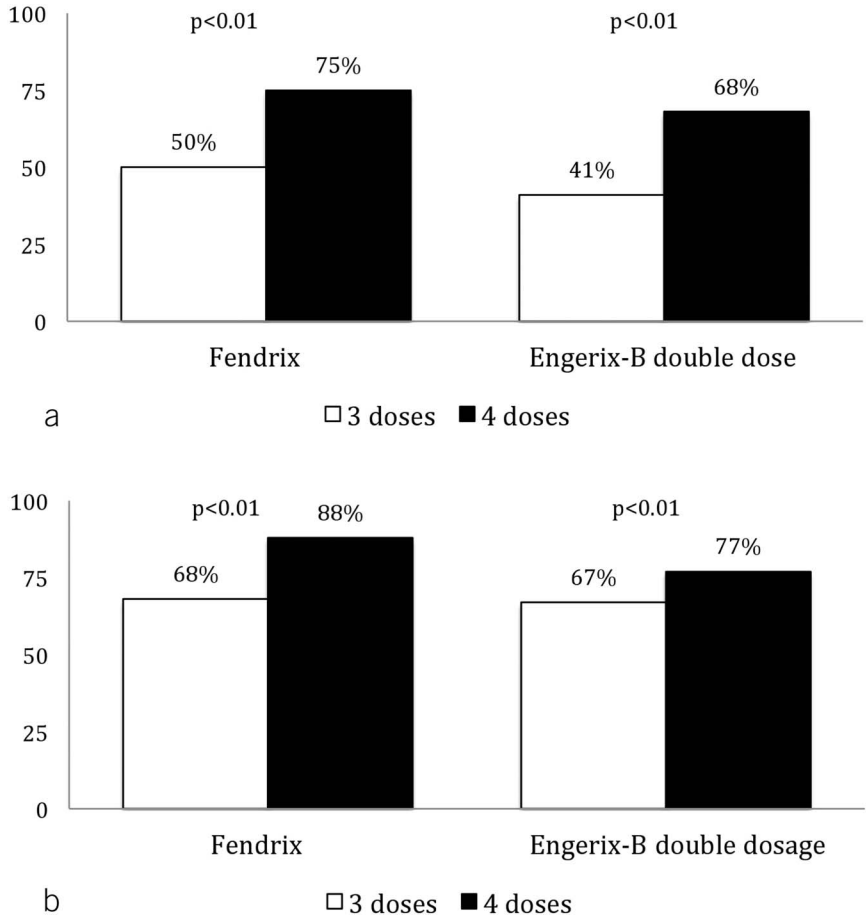

Figure 2. Response rate to the vaccines considering anti-HBs ≥100 IU/L (predefined threshold) and anti-HBs ≥10 IU/L (standard threshold) after 3 and 4 doses. (**a**) Proportion of patients with anti-HBs ≥100 IU/L. (**b**) Proportion of patients with anti-HBs ≥10 IU/L.

patients vaccinated with Fendrix (43 *vs* 25%, $P < 0.04$). A total of 24 patients (20%) lost anti-HBs during follow-up. The cumulative incidence of negativization of anti-HBs titers was 13% after 6 months and 20% after 12 months of follow-up. The proportion of patients who lost anti-HBs titers ≥10 UI/L was significantly higher among patients exposed to anti-TNFs (29% *vs* 18%), but the difference did not reach statistical significance ($P = 0.1$). Table 6 shows the characteristics of patients losing and maintaining anti-HBs ≥10 IU/L during follow-up.

In the multivariate analysis, anti-HBs ≥100 IU/L (*vs* <100 UI/L) after the vaccination was the only factor that was associated with a higher probability of maintaining anti-HBs titers during the follow-up (hazard ratio = 9.8, 95% confidence interval = 4–23, $P < 0.0001$). The type of vaccine administered, patient's age, or immunosuppressive treatment during follow-up was not associated with the risk of negativization of anti-HBs titers.

Safety

A total of 18 patients had adverse events related to the vaccine, all of them were mild. The proportion of patients with adverse events was significantly higher in the Fendrix group (17% vs 4.3%, $P < 0.01$). The most frequent adverse event was pain in the injection site (8 patients in the Fendrix group and 1 in the Engerix-B group). No patient developed HBV infection during the study period.

DISCUSSION

To the best of our knowledge, this is the first clinical trial evaluating the immunogenicity and safety of HB-AS04 vaccine (Fendrix) compared with the commercially available HBV (Engerix-B) in IBD. In addition, we have measured anti-HBs titers at 2 timepoints during vaccination—after the first 3 doses (0, 1, and 2 months), which have been recommended to get a rapid immunization, and after the fourth dose (at month 6)—to evaluate the benefit of the administration of a fourth dose, which can be considered a booster, over the recommended "accelerated protocol."

To date, there is no established recommendation about vaccination against HBV strategy in patients with IBD. Several schedules have been proposed (double dose, booster, etc.); however, the superiority of some protocols over the others has not been demonstrated so far. In our study, we could not demonstrate a superiority of Fendrix over Engerix-B considering success as anti-HBs ≥100 UI/L (predefined threshold)—both after the "accelerated protocol" and after the fourth dose. Nevertheless, considering success as anti-HBs ≥10 UI/L (standard threshold), Fendrix was superior to Engerix-B for inducing vaccine response.

With respect to the dosage, it has been demonstrated that double dose of immunogen is superior to the standard dose. In a previous study from our group, 2 different vaccination protocols were compared: the "standard protocol" (single doses of Engerix-B

Table 3. Response rate to hepatitis B vaccination based on the exposure to inflammatory bowel disease treatments

	Three vaccine doses		Four vaccine doses	
	Anti-HBs ≥100 IU/L	Anti-HBs ≥10 IU/L	Anti-HBs ≥100 IU/L	Anti-HBs ≥10 IU/L
No immunosuppressants, n (%)	31 (62)	45 (90)	44 (96)	44 (96)
Steroids, n (%)	3 (37)	6 (75)	4 (57)	6 (86)
Immunomodulators, n (%)	19 (50)	28 (74)	30 (77)	36 (92)
Anti-TNF agents, n (%)	11 (41)	15 (56)	17 (63)	21 (78)
Anti-TNF plus immunomodulators, n (%)	10 (24)	16 (39)	18 (45)	24 (60)

at 0, 1, and 6 months) and an "accelerated double-dose protocol" (double doses of Engerix-B at 0, 1, and 2 months) (16). The proportion of patients responding—defined as anti-HBs >100 UI/L—to the "accelerated double-dose protocol" was significantly higher than with the standard protocol (55% *vs* 22%, $P < 0.001$). Consistent with these results, Melmed et al. (17) found that only 33% of those who were immunized with the standard dose had detectable anti-HBs antibody titers. In addition, in the study by Vida Perez et al. (18), with the standard administration of 3 doses of vaccine at 0, 1, and 6 months, only 36% had protective titers of antibodies (anti-HBs >10 UI/L). Therefore, the evidence available supports the superiority of double-dose vaccination protocols with Engerix-B; in consequence, we decided not to include a single-dose Engerix-B protocol in our trial. In our study, Fendrix at standard dose was similar or even more immunogenic than double dosage of Engerix-B and could be an alternative choice for patients with IBD.

Regarding the vaccine schedule, although the 3 doses administered over a short period have the theoretical advantage of providing fast immunization for immunosuppressed patients, the administration of a fourth dose with a longer interval with the third one results in higher final antibody titers, acting as a booster. In our trial, the response rate to the "accelerated double-dose protocol" in the Engerix-B group was 41% and increased to 68% after the administration of a fourth dose at month 6 ($P < 0.01$). In the Fendrix group, the response rate to the accelerated schedule was 50% and also increased to 75% after the administration of the fourth dose ($P < 0.01$). Based on our results and on previous observations, the administration of a fourth dose should be added to the "accelerated protocol" both with Engerix-B and Fendrix as an optimized schedule in patients with IBD.

Age (older than 60 years) impaired the response to the vaccine in our cohort; this finding was in accordance with other researchers' results (19–21). In addition, IBD treatment was associated with lower response to the vaccine. The impact of anti-TNF agents on the response to the HBV vaccine has been previously described (9,19,20,22). Furthermore, the results on the impact of immunomodulators on seroconversion are conflicting (9,19,23,24); the sample size was small in most of the studies and might not allow for finding differences based on IBD treatments. In our study, we found that the treatment with steroids, immunomodulators, and anti-TNF agents (alone or in combination with immunomudulators) had a great impact on the vaccination success. In accordance with other studies, patients under anti-TNF treatment alone or in combination with immunomodulators had the lowest probability of responding to the vaccine (19,20).

Other major finding of our study is the high negativization rate of anti-HBs in patients who had responded to the vaccine—20% of patients had anti-HBs <10 UI/L 1 year after vaccination. This observation confirms the results of a previous study of our group, where the incidence rate of loss of protective anti-HBs (≥10 UI/L) in patients with IBD over time was 18% per patient-year (25). It has been established that in the healthy population, subjects reaching anti-HBs ≥10 UI/L after vaccination are protected in the long term, even when they lose protective anti-HBs, because this protection relies on immune memory (26). Clinical infection and chronic infection have not been described in persons with a documented response to previous HBV vaccination; therefore, routine booster injections are not recommended in healthy people. On the contrary, in immunocompromised patients, protection against HBV infection seems to rely on circulating antibodies but not on immune memory (13). In this respect, annual monitoring of anti-HBs is indicated for adults on hemodialysis and for other immunocompromised patients because the risk of having HBV infection is higher when anti-HBs titers are

Table 4. Response rate to the vaccination (anti-HBs ≥100 IU/L) with Fendrix and Engerix-B after 4 doses of vaccine comparing patients exposed to any inflammatory bowel disease treatment with patients not exposed to treatment

	Engerix-B	Fendrix
Steroids *vs* no treatment, n (%)	2 (50) *vs* 26 (96); $P < 0.01$	2 (67) *vs* 18 (95); $P = 0.1$
Immunomodulators *vs* no treatment, n (%)	15 (75) *vs* 26 (96); $P < 0.01$	15 (75) *vs* 18 (95); $P < 0.05$
Anti-TNF agents *vs* no treatment, n (%)	6 (50) *vs* 26 (96); $P < 0.01$	11 (73) *vs* 18 (95); $P = 0.08$
Anti-TNF plus immunomodulators *vs* no treatment, n (%)	8 (38) *vs* 26 (96); $P < 0.01$	10 (53) *vs* 18 (95); $P < 0.01$

Table 5. Multivariate analysis of predictive factors associated with response defined as anti-HBs ≥100 IU/L after 4 doses (a) and response defined as anti-HBs ≥10 IU/L (b) after 4 doses to hepatitis B virus vaccine in patients with inflammatory bowel disease

Variables	Odds ratio	95% confidence interval
a:		
Age (>60 yr *vs* ≤60 yr of age)	0.17	0.06–0.49
Fendrix (single dose) over Engerix-B (double dose)	1.8	0.8–4.1
Inflammatory bowel disease treatments		
Steroids *vs* no treatment	0.03	0.004–0.3
Immunomodulators in monotherapy *vs* no treatment	0.1	0.02–0.58
Anti-TNF in monotherapy *vs* no treatment	0.05	0.01–0.3
Combo therapy *vs* no treatment	0.02	0.004–0.1
b:		
Age (>60 yr *vs* ≤60 yr of age)	0.26	0.08–0.8
Fendrix (single dose) over Engerix-B (double dose)	2.7	1.04–7.1
Inflammatory bowel disease treatments		
Steroids *vs* no treatment	0.2	0.1–2.6
Immunomodulators in monotherapy *vs* no treatment	0.4	0.07–2.9
Anti-TNF in monotherapy *vs* no treatment	0.13	0.02–0.7
Combo therapy *vs* no treatment	0.04	0.008–0.2

Table 6. Characteristics of the study population based on the negativization of anti-HBs in patients with inflammatory bowel disease (IBD) during follow-up

	Negativization (N = 24)	No negativization (N = 89)	*P*
61 yr and older, n (%)	8 (33)	13 (14)	0.02
Male sex, n (%)	14 (58)	48 (60)	0.6
Crohn's disease, n (%)			
Location			
Ileal, n (%)	5 (36)	23 (53)	0.3
Colonic, n (%)	3 (21)	3 (7)	
Ileocolonic, n (%)	6 (43)	16 (37)	
Behavior			
Inflammatory, n (%)	3 (51)	26 (60)	0.03
Stricturing, n (%)	6 (31)	10 (23)	
Fistulizing, n (%)	5 (18)	7 (16)	
Ulcerative colitis location			
Extensive, n (%)	8 (73)	25 (48)	0.2
Left-sided, n (%)	1 (9)	15 (37)	
Proctitis, n (%)	2 (18)	7 (17)	
IBD treatment during vaccination			
No immunosuppressants, n (%)	6 (25)	34 (37)	0.4
Steroids, n (%)	0 (0)	3 (3)	
Immunomodulators, n (%)	7 (29)	27 (29)	
Anti-TNF, n (%)	6 (25)	12 (13)	
Anti-TNF plus immunomodulators, n (%)	5 (21)	17 (18)	
Smokers, n (%)	4 (17)	24 (26)	0.2

below 10 IU/L (10). There are no data on the risk of infection in patients with IBD who lose protective anti-HBs after successful vaccination and what their immune response would be like when exposed to the virus. In consequence, there is no recommendation to monitor the levels of anti-HBs and revaccinate if they are negative, but for those patients on immunosuppressive treatment, it could be recommended. In fact, the treatment with anti-TNF has been associated with the risk of losing protective anti-HBs over time (25). In the present trial, the proportion of patients who lost protective antibodies (anti-HBs ≥10 UI/L) over time was also higher in patients exposed to anti-TNFs than in those not exposed to these agents (29% *vs* 18%); however, this difference did not reach statistical significance. In the present trial, anti-HBs <100 UI/L after vaccination was the only predictive factor for losing protective anti-HBs titers over time (over 9-fold higher than in patients with anti-HBs ≥100 UI/L). This finding underlines the importance of achieving anti-HBs ≥100 UI/L to have long-lasting protection and supports that this threshold should be recommended in patients with IBD (2,27–29).

As previously described, Fendrix was more locally reactogenic than the standard immunization regimen (11), with pain at the injection site occurring in 8 patients vaccinated with Fendrix *vs* in 1 patient in the Engerix-B group. Nevertheless, both vaccines showed a good safety profile, and no patient developed serious adverse events within the trial.

We have to acknowledge some limitations of our study. First of all, a small proportion of patients had active disease during the follow-up and the majority of them had mild disease; therefore, we could not study the association between disease activity and the response to the vaccine. Secondly, only anti-TNF agents were considered in the study because it was the only biologic class approved when the trial was designed; therefore, the impact of other biologics on HBV vaccine response could not be assessed. Finally, the sample size calculation did not take into account concomitant treatment.

Our study has several strengths. Only 1 clinical trial was previously performed comparing different HBV vaccines in patients with IBD. Etzion et al. (30) included 72 patients who were randomized to single0dose Engerix-B *vs* Sci-B-Vac administered at 0, 1, and 6 months. Our study included a higher number of patients and was powered to identify differences in the response rate to the vaccines. In addition, we included double dose of Engerix-B that should be the recommended dosage as

comparator. Finally, we measured anti-HBs titers twice during vaccination to study the benefit of a fourth dose over a 3-dose accelerated protocol.

In conclusion, based on the results of our study, both double-dose Engerix-B or single-dose Fendrix vaccination protocols could be equally recommended in patients with IBD. Patients should be vaccinated early on disease course, when they have the lowest immunosuppressive load. The 4-dose protocol has efficacy advantages with respect to the protocol of 3 doses. It has been observed that approximately 20% of patients lose protective titers 1 year after vaccination. The basal anti-HBs titers (<100 UI/L) are the only predictor of loss of anti-HBs, and therefore, anti-HBs ≥100 UI/L should be the titer required to consider the vaccination successful.

CONFLICTS OF INTEREST

Guarantor of the article: María Chaparro, MD, PhD, and Javier P. Gisbert, MD, PhD.

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Study Highlights

WHAT IS ALREADY KNOWN

- ✓ Vaccination against HBV is currently recommended in patients with IBD; the immunological response to the vaccine is low (30% lower than in healthy population).
- ✓ It is necessary to evaluate new vaccines that may offer greater protection to these patients.
- ✓ In addition, optimal vaccination schedules and long-term immunogenicity of these vaccines remain to be studied.

WHAT IS NEW HERE

- ✓ We could not demonstrate a higher response rate of Fendrix (single dose) over Engerix-B (double dose).
- ✓ A 4-dose schedule is more effective than a 3-dose regimen.
- ✓ Older age and treatment with immunomodulators or anti-TNFs impaired the success.
- ✓ A high proportion of IBD patients with protective anti-HBs titers after vaccination loose them over time.
- ✓ The risk of losing protective anti-HBs titers is increased in patients achieving anti-HBs <100 IU/L after the vaccination; therefore, anti-HBs ≥100 UI/L should be the titer required to consider the vaccination successful.

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