

Factors predicting response to hepatitis B vaccination in patients with inflammatory bowel disease

Laura Sempere^{a,*}, Isabel Almenta^a, Julio Barrenengoa^b, Ana Gutiérrez^a, Cesar O. Villanueva^b, Enrique de-Madaria^a, Vicente García^b, José Sánchez-Payá^b

^a Gastroenterology Department, Hospital General Universitario de Alicante and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain

^b Preventive Medicine Service, Hospital General Universitario de Alicante, Spain

ARTICLE INFO

Article history:

Received 31 December 2012

Received in revised form 26 March 2013

Accepted 24 April 2013

Available online 9 May 2013

Keywords:

Inflammatory bowel disease

Hepatitis B virus

Vaccination

ABSTRACT

Hepatitis-B-seronegative patients with inflammatory bowel disease (IBD) should be vaccinated. However, response to vaccination in this population seems to be poorer than in healthy people. The aim of this study is to assess which clinical, analytical and immunosuppressive therapy parameters affect the response to hepatitis B vaccination in patients with IBD. A follow-up including monitoring of the immunosuppressive therapy of a cohort of 123 patients with IBD was carried out after each round of vaccination against hepatitis B virus. The recombinant HBsAg vaccine (20 µg) was administered using the standard regimen (0, 1 and 6 months). Anti-HBs values >10 IU/L after 1–3 months post-vaccination were considered as a successful response to vaccination. One hundred and five patients (85.5%) completed the programme and response to vaccination was observed in 50 (47.6%) patients. Multivariate analysis showed an independent relationship, with weaker response to vaccination, for IBD duration equal to or longer than 110 months [adjusted OR (95% CI): 0.282 (0.114–0.701)], serum albumin levels below 3.6 mg/dl at the beginning of vaccination [adjusted OR (95% CI): 0.336 (0.112–1.009)], and corticosteroid therapy in more than one vaccination dose [adjusted OR (95% CI): 0.333 (0.135–0.820)]. This study confirms the poor response to hepatitis B vaccination in patients with IBD, being particularly weak in individuals with long-term IBD progression, low serum albumin levels and those on corticosteroid therapy.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

Hepatitis B viral infection is a global health problem [1]. Vaccination schemes for the general population, which started in 1991, have significantly decreased the incidence of hepatitis B infection in developed countries [2]. The serological response after standard vaccination schedules against hepatitis B virus (HBV) is greater than 90% in healthy adult populations [3,4]. Factors associated with a decreased response to HBV vaccine are male gender, advanced age, chronic disease, immunodeficiency, tobacco use and obesity [5,6].

Reactivation of chronic hepatitis B in patients with inflammatory bowel disease (IBD) receiving immunosuppressive therapy can lead to serious liver dysfunction [7]. The success of immunosuppressive therapy in the control of IBD has increased the use of these drugs over the last decade, such that patients with IBD are very likely to need immunosuppressive therapy over the course of their disease. The prevalence of effective seroprotection against HBV is low (12–48.9%) among individuals with IBD, with large differences between countries and vaccination schemes in children [8,9].

Considering this, patients with IBD should be vaccinated against HBV regardless of their treatment [10,11].

Three studies on serological response to HBV vaccine in patients with IBD have been published [12–14]. These studies indicate that the overall response to HBV vaccine in patients with IBD is not as expected in comparison to the general population. Factors associated with reduced response are advanced age, IBD activity and immunosuppressive treatment. Follow-up of immunosuppressive therapy was not performed in any of the three studies during the vaccination period. In clinical practice, immunosuppressive drugs are frequently changed during the vaccination period with potentially crucial effects on vaccination response.

The purpose of this study was to assess the response to an HBV vaccination scheme in a cohort of IBD patients, monitoring the concomitant use of immunosuppressants during the vaccination scheme.

2. Materials and methods

2.1. Study design

This is an observational, retrospective, cohort study carried out at the University General Hospital of Alicante. All patients over

* Corresponding author. Tel.: +34 965126978; fax: +34 965933468.

E-mail address: sempere.lau@gva.es (L. Sempere).

14 years of age with IBD who started vaccination against HBV between January 2004 and February 2011, were included in the study. Vaccination was given in the immunocompromised specialised patient care unit of the Preventive Medicine Service, from which prospectively collected the vaccination data. Patients for which demographic, clinical and/or analytical data were not available were excluded from the study, as well as patients who did not complete the vaccination scheme. Non-compliance with the schedule was defined as missing one or more doses of the vaccine or not undergoing the post-vaccination serological test.

Demographic and clinical data were collected from medical records in the Gastroenterology Unit. Data on concomitant medication were collected from prospective records from the Preventive Medicine Service during the vaccination scheme and from medical records in the Gastroenterology Unit. Vaccination scheme, laboratory and follow-up data were prospectively collected from the Preventive Medicine Service, including pre-vaccination blood tests, three sessions of vaccination and post-vaccination serological tests.

The vaccine was administered to patients who had had no contact with HBV. Non-contact with HBV was defined as seronegativity for antibodies against hepatitis B surface antigen (anti-HBs) and antibodies against hepatitis B core protein (anti-HBc). A recombinant vaccine containing 20 mg of hepatitis B surface antigen (HbsAg) at 0, 1 and 6 months was used, injected intramuscularly in the deltoid region. The response to vaccination was assessed with a follow-up serology study within 1–3 months after administration of the third dose. Anti-HBs values >10 IU/L were considered a successful response to vaccination.

Demographic, clinical and laboratory data were collected at the beginning of the vaccination scheme. The diagnostic criteria used were those described by Lennard-Jones for Crohn's disease (CD) and ulcerative colitis (UC) [15] and IBD was categorised according to the Montreal classification [16]. Clinical remission was defined as 1–3 bowel movements with formed stools with no blood and/or mucus, absence of abdominal pain and/or perianal lesions. Existence of extraintestinal manifestations was determined according to the European Crohn's and Colitis Organisation [17,18]. Comorbidity was determined by the presence of any of the diseases included in the Charlson Comorbidity Index [19]. Regarding weight, individuals with a body mass index (BMI) below 18.5 were defined as having low weight, while a BMI equal or greater than 30 was considered obese.

Concomitant medication information was collected during each vaccination session. Patients on immunosuppressive treatment were those who had received corticosteroids, immunomodulatory drugs (thiopurines, methotrexate or cyclosporine) and/or anti-TNF- α drugs 12 weeks before, or within 4 weeks after each dose of vaccine.

2.2. Ethical considerations

The 1975 Declaration of Helsinki guidelines on good clinical practice (amendments made in 2008) were used for the development and management of the data [20].

2.3. Statistical analysis

In the descriptive analysis of patient characteristics, absolute and relative frequency measurements were employed for qualitative variables. For quantitative variables, mean $\pm$ standard deviation was used with parametric distributions and median and interquartile range with non-parametric distributions.

Assessment of vaccine response among patients receiving immunosuppressive therapy was carried out using the number of doses given to each patient on immunosuppressive treatment; cases in which the drug was present in more than one dose

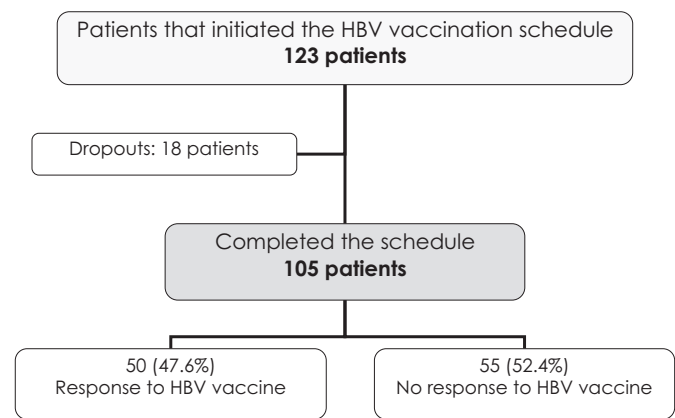


Fig. 1. Study flow chart.

of vaccine were considered representative. Similarly, the various combinations of immunosuppressants were also evaluated. For percentages of response, 95% confidence intervals (CI) were calculated.

The inferential analysis to assess serological response was done by examining the demographic, clinical and treatment variables through univariate statistical tests. Quartiles were used to establish the cut-off points of quantitative variables. The chi-squared test was applied to examine the relationship between categorical variables. The unadjusted odds ratio (OR) and 95% CI were calculated for each variable.

To control for confounding variables and/or variables that modify the effect, as well as to determine which independent variables are associated with negative responses, logistic regression was performed using the variables that provided a statistically significant association with the response to vaccination on the univariate analysis. IBD phenotype was not included in the multivariate analysis because it was different in the two populations studied (CD and UC), nor were the correlated variables due to collinearity problems.

p values of less than 0.05 were considered statistically significant. The data were analysed using SPSS 15.0 for Windows.

3. Results

One hundred and twenty-three patients started the HBV vaccination programme. Eighteen (14.5%) patients did not complete the schedule (Fig. 1). No statistically significant differences were determined for clinical and demographic variables between dropouts and individuals that completed the scheme (data not shown).

Table 1 summarises clinical, demographic, and laboratory variables of the 105 patients eligible for the study. The average age was 41.02 ± 11.12 years, 58 (55.2%) men and 47 (44.8%) women. The mean time of IBD progression was 102.5 ± 84.3 months, from which 80 (76.2%) patients were affected by CD and 25 (23.8%) patients had UC. Fifty patients, 47.6% (95% CI, 37.6–57.6), responded to the vaccine. No serious adverse effects were identified.

The main immunosuppressive drugs that were present in more than one vaccination session were azathioprine in 77 (73.3%) patients and corticosteroids in 50 (47.6%) patients; 25 (23.8%) patients were using anti-TNF- α drugs and only 3 (2.9%) methotrexate (Table 2). Regarding the use of combination therapy, sample size (no. of patients per group) became smaller; the larger groups were those taking immunomodulators as monotherapy (33 patients, 31.4%) and those using a combination of corticosteroids and immunomodulators (32 patients, 30.5%); the remaining groups included less than 10% of the studied population.

Univariate analysis determined that the variables with a statistically significant relationship with a negative response to the

Table 1
Demographic and clinical variables of vaccinated patients (*n* = 105).

Age, years	
Mean $\pm$ SD	41.02 $\pm$ 11.12
Gender, <i>n</i> (%)	
Male	58 (55.2%)
Female	47 (44.8%)
Tobacco use, <i>n</i> (%)	47 (44.8%)
Duration of IBD, months	
Mean $\pm$ SD	102.5 $\pm$ 84.3
Type of IBD, <i>n</i> (%)	
Crohn's disease	80 (76.2%)
Ulcerative colitis	25 (23.8%)
<i>Crohn's disease phenotype</i>	
Age at diagnosis (A), <i>n</i> (%)	
<17 years of age	4 (5%)
17–40 years of age	63 (78.8%)
>40 years of age	13 (16.2%)
Location (L), <i>n</i> (%)	
Ileal	24 (30%)
Colonic	14 (17.5%)
Ileocolonic	29 (36.2%)
With upper GI tract	13 (16.3%)
Behaviour (B), <i>n</i> (%)	
Non-stricturing, non-penetrating	44 (55%)
Stricturing	19 (23.8%)
Penetrating	17 (21.2%)
Perianal disease, <i>n</i> (%)	
Yes	28 (35%)
No	52 (65%)
<i>Ulcerative colitis phenotype, n (%)</i>	
Proctitis	2 (8%)
Left-sided colitis	14 (56%)
Extensive colitis	9 (36%)
Intestinal resections, <i>n</i> (%)	24 (22.9%)
Extraintestinal manifestations, <i>n</i> (%)	29 (27.6%)
IBD activity, <i>n</i> (%)	58 (55.2%)
Comorbidity, <i>n</i> (%)	19 (18.1%)
Low weight, <i>n</i> (%)	16 (15.2%)
Obesity, <i>n</i> (%)	12 (11.4%)
CRP, mg/dl	
Median (p25–p75)	0.41 (0.2–1.02)
Albumin, mg/dl	
Mean $\pm$ SD	3.92 $\pm$ 0.43
Transferrin, mg/dl	
Mean $\pm$ SD	261.37 $\pm$ 48.06

IBD, inflammatory bowel disease; GI, gastrointestinal; CRP, C-reactive protein.

vaccine were ileal CD ($p=0.013$), long-term progression of IBD ($p=0.034$), low serum albumin levels at the beginning of vaccination ($p=0.023$) and the use of corticosteroids in more than one dose of the vaccine ($p=0.023$). These findings were confirmed with unadjusted ORs (Tables 3 and 4). Analysis of drug combinations revealed that the only group associated with a response to the vaccine was the one with five patients for whom anti-TNF- α monotherapy was taken at more than one vaccination dose, showing response to vaccination in 100% of the cases ($p=0.022$); in this case, calculation of the OR was not possible. Short of achieving statistical significance, a poorer response is observed in patients under treatment with a combination of drugs including the use of corticosteroids.

Multivariate-adjusted ORs were calculated using the following variables (Tables 3 and 4): duration of IBD, serum albumin at the beginning of vaccination and corticosteroid therapy. The location of CD was not included in the multivariate analysis (because patients with UC were excluded), nor was the use of anti-TNF- α drugs as monotherapy due to collinearity with the use of corticosteroids and because it was not possible to calculate the OR. The results of the multivariate analysis showed an independent relationship with negative vaccination response for IBD duration equal or longer than 110 months, serum albumin levels below 3.6 mg/dl at the beginning of vaccination and corticosteroid therapy in more than one vaccination dose. Fig. 2 shows the different distribution of IBD duration and serum albumin levels in responders and non-responders to HBV vaccination.

Although not included in the multivariate study, we have observed a much poorer response to HBV vaccination in the subgroup of patients with pure ileal CD. A stratified study was performed (data not shown) with factors associated to the response; the only statistically significant relationship was lower serum albumin values in patients with pure ileal disease.

Of the 55 patients in whom HBV vaccination failed, 44 patients completed a revaccination programme with 3 doses of recombinant vaccine containing 40 mg HBsAg (0, 1, and 6 months). The cumulative efficacy of the vaccination programme was 85.1% (95% CI, 77.4–92.8) 80/94.

4. Discussion

Here we analysed the factors that affect the response to HBV vaccination in patients suffering from IBD, for the first time monitoring

Table 2
Pharmacological therapy received by the patients at the time of vaccination (*n* = 105).

	First dose of the vaccine	Second dose of the vaccine	Third dose of the vaccine	In more than one dose
Class of immunosuppressive drugs				
Corticosteroids	49 (46.7%)	50 (47.6%)	26 (24.8%)	50 (47.6%)
Thiopurines	77 (73.3%)	77 (73.3%)	71 (67.6%)	77 (73.3%)
Methotrexate	3 (2.9%)	4 (3.8%)	6 (5.7%)	3 (2.9%)
Cyclosporine	0	0	0	0
Anti-TNF- α	21 (20%)	25 (23.8%)	35 (33.3%)	25 (23.8%)
Drug combinations				
Per drug group				
Non-immunosuppressants	12 (11.4%)	11 (10.5%)	9 (8.6%)	10 (9.5%)
Corticosteroids as monotherapy	4 (3.8%)	4 (3.8%)	3 (2.9%)	3 (2.9%)
Immunomodulators as monotherapy	33 (31.4%)	33 (31.4%)	48 (45.7%)	33 (31.4%)
Anti-TNF- α as monotherapy	5 (4.8%)	5 (4.8%)	10 (9.5%)	5 (4.8%)
Corticosteroids + immunomodulators	35 (33.3%)	32 (30.5%)	10 (9.5%)	32 (30.5%)
Corticosteroids + anti-TNF- α	4 (3.8%)	5 (4.8%)	6 (5.7%)	5 (4.8%)
Immunomodulators + anti-TNF- α	6 (5.7%)	6 (5.7%)	12 (11.4%)	6 (5.7%)
Corticosteroids + immunomodulators + anti-TNF- α	6 (5.7%)	9 (8.6%)	7 (6.7%)	7 (6.7%)
Other combinations	–	–	–	4 (3.8%)
Per number of immunosuppressants				
No immunosuppressants	12 (11.4%)	11 (10.5%)	9 (8.6%)	10 (9.5%)
1 immunosuppressant	42 (40%)	42 (40%)	61 (58.1%)	42 (40%)
>1 immunosuppressants	51 (48.6%)	52 (49.5%)	35 (33.3%)	52 (49.5%)
Other combinations	–	–	–	1 (0.95%)

Table 3
Correlation between demographic and clinical variables and the response to HBV vaccination ($n = 105$).

Variable	Response to vaccination % (95% CI), n	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age			
≥30 years of age	45.1% (34.3–55.8), 41/91	0.456 (0.142–1.466)	–
<30 years of age	64.3% (35.1–87.2), 9/14	1	
Gender			
Females	46.8% (31.5–62.1), 22/47	0.943 (0.436–2.037)	–
Males	48.3% (34.6–62), 28/58	1	
Tobacco use			
Yes	48.9% (33.6–64.3), 23/47	1.1 (0.509–2.377)	–
No	46.6% (32.9–60.3), 27/58	1	
Duration of IBD			
≥ 110 months	35.6% (20.5–50.7), 16/45	0.422 (0.190–0.935)	0.282 (0.114–0.701)
<110 months	56.7% (43.3–70), 34/60	1	
Type of IBD			
Crohn's disease	47.5% (35.9–59.1), 38/80	0.980 (0.399–2.408)	–
Ulcerative colitis	48% (26.4–69.6), 12/25	1	
<i>Crohn's disease phenotype</i>			
Age at diagnosis (A)			
<17 years of age	25% (0.63–80.6), 1/4	0.323 (0.032–3274)	–
17–40 years of age	50.8% (37.7–63.9), 32/63	1	
>40 years of age	38.5% (13.9–68.4), 5/13	0.605 (0.178–2.054)	–
Location (L)			
Ileal	20.8% (7.1–42.2), 5/24	0.117 (0.025–0.543)	–
Colonic	50% (23–77), 7/14	0.444 (0.92–2.150)	–
Ileocolonic	58.6% (39–78.3), 17/29	0.630 (0.157–2.529)	–
With upper GI tract	69.2% (38.6–90.9), 9/13	1	
Behaviour (B)			
Non-stricturing, non-penetrating	52.3% (36.4–68.2), 23/44	0.974 (0.317–2.987)	–
Stricturing	31.6% (12.6–56.6), 6/19	0.410 (0.106–1.594)	–
Penetrating	52.9% (27.8–77), 9/17	1	–
Perianal disease			
No	46.2% (31.6–60.7), 24/52	0.857 (0.342–2.150)	–
Yes	50% (29.7–70.3), 14/28	1	
<i>Ulcerative colitis phenotype</i>			
Proctitis	50% (1.3–98.7), 1/2	0.800 (0.037–17.196)	–
Left-sided colitis	42.9% (17.7–71.1), 6/14	0.600 (0.111–3.245)	–
Extensive colitis	55.6% (21.2–86.3), 5/9	1	
Intestinal resections			
Yes	45.8% (23.8–67.9), 11/24	0.911 (0.365–2.272)	–
No	48.1% (36.7–59.6), 39/81	1	
Extraintestinal manifestations			
Yes	44.8% (25–64.7), 13/29	0.856 (0.363–2.022)	–
No	48.7% (36.8–60.6), 37/76	1	
IBD activity			
Yes	39.7% (26.2–53.1), 23/58	0.487 (0.223–1.064)	–
No	57.4% (42.2–72.6), 27/47	1	
Comorbidity			
Yes	42.1% (20.3–66.5), 8/19	0.762 (0.279–2.08)	–
No	48.8% (37.7–60), 42/86	1	
Low weight			
Yes	37.5% (15.2–64.6), 6/16	0.614 (0.205–1.833)	–
No	49.4% (38.5–60.4), 44/89	1	
Obesity			
Yes	58.3% (27.7–84.8), 7/12	1.628 (0.482–5.502)	–
No	46.2% (35.6–56.9), 43/93	1	
CRP (mg/dl)			
<0.5	42.1% (28.4–55.8), 24/57	0.615 (0.284–1.334)	–
≥0.5	54.2% (39–69.3), 26/48	1	
Albumin (mg/dl)			
<3.6	26.1% (10.2–48.4), 6/23	0.305 (0.109–0.851)	0.336 (0.112–1.009)
≥3.6	53.7% (42.3–65.1), 44/82	1	
Transferrin (mg/dl)			
<220	45.5% (22.4–68.5), 10/22	0.896 (0.349–2.301)	–
≥220	48.2% (36.8–59.5), 40/83	1	

IBD, inflammatory bowel disease; GI, gastrointestinal; CRP, C-reactive protein; OR, odds ratio; CI, confidence interval.

immunosuppressive therapy at the three vaccination sessions, assessing laboratory variables such as C-reactive protein, albumin and transferrin. Furthermore, we also evaluated for the first time variables associated with negative response to HBV vaccine in the general population, such as comorbidity, obesity and tobacco use, in patients with IBD. Results show a clear relationship between the course of IBD, serum albumin levels and corticosteroid use with

the response to HBV vaccination. Compared to studies carried out in the general population, no relationship was determined between response to vaccination and other factors such as male gender, advanced age, comorbidity, obesity and tobacco use in this study [5,6].

To date only three studies on the response to HBV vaccination in individuals with IBD have been published [12–14]. The response in

Table 4
Correlation between pharmacological therapy and the response to HBV vaccination ($n = 105$).

	Response to vaccination % (95% CI), <i>n</i>	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Class of immunosuppressive drugs			
Corticosteroids			
More than one dose	36% (21.7–50.3), 18/50	0.404 (0.184–0.889)	0.333 (0.135–0.820)
None or one dose	58.2% (44.2–72.1), 32/55	1	
Thiopurines			
More than one dose	44.2% (32.4–55.9), 34/77	0.593 (0.248–1.420)	–
None or one dose	57.1% (37–77.3), 16/28	1	
Methotrexate			
More than one dose	66.7% (9.4–99.2), 2/3	2.25 (0.198–25.6)	–
None or one dose	47.1% (36.9–57.2), 48/102	1	
Anti-TNF-α			
More than one dose	52% (30.4–73.6), 13/25	1.25 (0.512–3.095)	–
None or one dose	46.3% (34.7–57.8), 37/80	1	
Immunosuppressive drug combinations			
Corticosteroids as monotherapy			
More than one dose	33.3% (0.8–90.6), 1/3	0.541 (0.48–6.153)	–
None or one dose	48% (37.8–58.2), 49/102	1	
Immunomodulators as monotherapy			
More than one dose	54.5% (36–73), 18/33	1.5 (0.655–3.433)	–
None or one dose	44.4% (32.2–56.6), 32/72	1	
Anti-TNF-α as monotherapy			
More than one dose	100% (47.8–100), 5/5	Not calculable	–
None or one dose	45% (34.7–55.3), 45/100	1	
Corticosteroids + immunomodulators			
More than one dose	34.4% (16.4–52.4), 11/32	0.457 (0.193–1.082)	–
None or one dose	53.4% (41.3–65.6), 39/73	1	
Corticosteroids + anti-TNF-α			
More than one dose	20% (0.5–71.6), 1/5	0.26 (0.28–2.41)	–
None or one dose	49% (38.7–59.3), 49/100	1	
Immunomodulators + anti-TNF-α			
More than one dose	50% (11.8–88.2), 3/6	1.106 (0.213–5.751)	–
None or one dose	47.5% (37.1–57.8), 47/99	1	
Corticosteroids + immunomodulators + anti-TNF-α			
More than one dose	28.6% (3.7–71), 2/7	0.417 (0.077–2.251)	–
None or one dose	49% (38.6–59.4), 48/98	1	

OR, odds ratio; CI, confidence interval.

IBD was much lower in comparison to the general population. Here the response was 47.6%. This is slightly better than the response observed in the study carried out by Vida et al. (34.1%) and much lower than the study by Altunoz et al. (77%), both of which used standard HBV vaccination schemes. In a study by Gisbert et al., in which an accelerated and double-dose schedule was used, response from 59% of the participants was obtained. A recent Spanish study with IBD patients compared the standard 3-dose schedule (20 μ g of HBsAg at 0, 1, and 6 months) in two hospitals with the accelerated and double-dose schedule (40 μ g of HBsAg at 0, 1, and 2 months) in a different hospital [21]. Results showed a significantly higher response rate in patients who received a double dose in the accelerated schedule compared to those who received the standard schedule, 75% and 41% response to vaccination, respectively.

Regarding factors associated with a poorer vaccination response, Vida et al. showed a significantly lower response in patients with advanced age [12]. Gisbert et al. showed a significantly lower response in patients with advanced age and in patients on anti-TNF- α therapy [14]. In the study by Altunoz et al. a poor response was observed in patients with active IBD and those taking immunosuppressants, but a multivariate analysis was not performed to confirm this finding [13].

Contrary to the results reported by Vida et al. and Gisbert et al., here we show a poorer response in patients with long-term progression of IBD, independent of age. Recent evidence has shown that the immune response in patients varies during the course of the disease [22–24]. It has been observed that the polarisation of the T-helper response varies in early and late IBD. The response to HBV vaccination requires coordinated secretion of T-helper cytokines [25]. Maybe a different T-helper function in late IBD could explain

the poor response to HBV vaccination in patients with late IBD, but this hypothesis should be studied in future studies. On the other hand, although age could be assumed to follow in parallel to time of IBD progression, age in our study population loses significance, probably because most patients (90.5% representing 95 patients) were aged between 20 and 59 years. In studies carried out in the general population, the greatest response differences are observed in individuals younger than 20 years of age, for whom maximum response occurs, and in individuals older than 59, for whom the response decreases below 70% [4,5,26].

A second factor associated with a poor response to vaccination was serum albumin levels at the beginning of the vaccination schedule. Theoretically, a poorer response in a patient with low serum albumin levels could be associated with either damaging effects of malnutrition on the immune system or impairments in transport and cellular interaction with HBsAg [27,28]. A significant relationship has been shown between malnutrition, assessed by low serum albumin concentrations, in patients with chronic kidney failure and a poorer response to HBV vaccination [29]. Contrary to what was expected, no relationship was found between response and other nutritional parameters such as transferrin and low weight.

The use of corticosteroids in more than one vaccination session was also associated with a poorer response to HBV vaccination. The damaging effects of corticosteroids on the immune system (on T-lymphocyte function and the production of immunoglobulins) are wellknown [30–32]. There is a lack of evidence in the literature regarding the effects of corticosteroids on response to vaccination. Only Vida et al. analysed the use of corticosteroids during vaccination in patients with IBD, although in conjunction

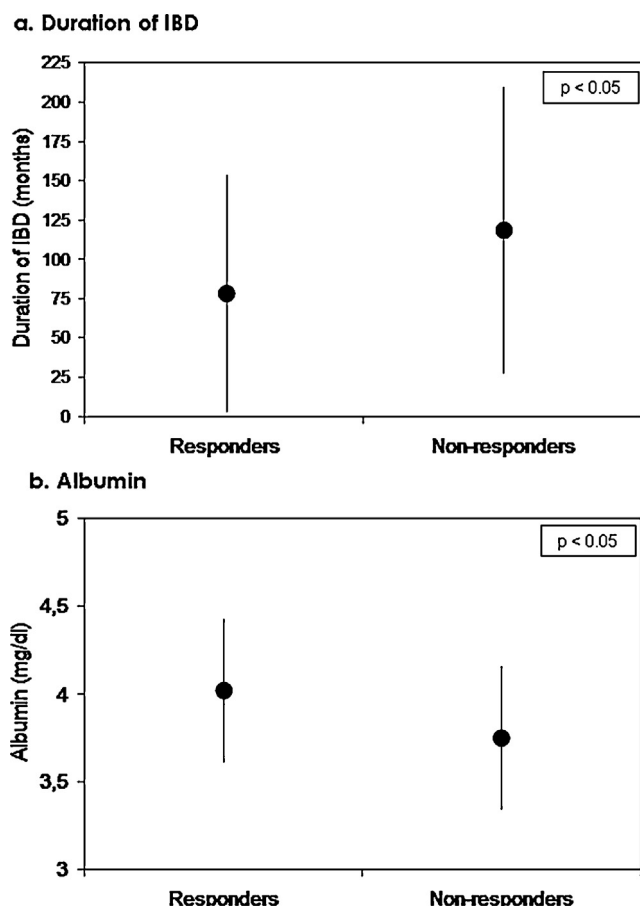


Fig. 2. Duration of IBD and serum albumin in patients with response and non-response to hepatitis B vaccination (mean $\pm$ SD).

with immunomodulatory and biological drugs [12]. Other studies in which corticosteroid therapy was used included patients with autoimmune diseases or asthma who were vaccinated against influenza or the pneumococcal vaccine. The influenza vaccine was effective in these patients, although showing reduced immunogenicity, while the immunogenicity of the pneumococcal vaccine was similar to that found in patients who were not treated with corticosteroids [33–35].

Here, response to vaccination was not affected by thiopurines which is in agreement with another study on IBD patients [36]. With regard to methotrexate, response data are not very valuable given the low number of patients receiving that treatment. It is worth noting that there was response from all five patients using anti-TNF- α drugs as monotherapy in more than one dose of vaccination. This result has also been published in patients with rheumatoid arthritis who were vaccinated against pneumococcal infection [37]. Further prospective studies should be designed to confirm this. These results could be explained with recent evidence indicating a beneficial effect of anti-TNF- α therapy on humoral immunity [38,39]. This is in disagreement with the study by Gisbert et al. in which a poorer vaccination response is observed in patients on anti-TNF- α therapy [14]. This difference between studies could be explained by the fact that Gisbert et al. did not perform a sub-analysis of the patients on monotherapy and did not assess concomitant corticosteroid therapy. Here, analysis of each of the combination immunosuppression therapies clearly showed, short of achieving statistical significance, a poorer response in patients with combinations that included corticosteroids. The lack of statistical significance might be due to the small number of patients in each group. This was not observed for combination therapies

that do not include corticosteroids. It seems that the use of corticosteroids in combination therapy has more relevance than the deleterious effects of the other immunosuppressants.

Regarding the poor response to HBV vaccination in patients with ileal CD, this could be explained by reduced protein absorption in the small bowel being responsible for the decrease in serum albumin. Further prospective studies should be conducted on CD regarding this topic, including a detailed evaluation of disease extension.

Although our study is a retrospective cohort study, the lack of information associated with this type of study did not occur because we had appropriate prospective registries regarding vaccination scheme follow-up, concomitant treatment and laboratory tests. On the other hand, the clinical and demographic data were collected from medical records, so they did not necessarily include tests to assess the exact extension of the disease and mucosal activity at the time of vaccination. Another limitation is the small number of patients younger than 20 years of age, due to the universal newborn and adolescent immunisation schedule established in our health system in 1992.

In summary, this study reinforces current evidence regarding a poor response to HBV vaccination in IBD and the need to carry out new studies to assess other vaccination schedules in primary immunisation as well as catch-up schedules in unresponsive subjects. We believe there is strong evidence on the adverse effects of long-term progression of IBD, low levels of serum albumin and corticosteroids treatment on response to HBV vaccination. All IBD patients who are seronegative for HBV should be vaccinated at diagnosis when their nutritional status is good and the corticosteroid washout period has concluded.

Acknowledgements

The authors thank the nursing staff at the Preventive Medicine Service and the Gastroenterology Unit for their assistance in the preparation of this manuscript.

CIBERehd is funded by the Instituto de Salud Carlos III.

References

- [1] Maynard JE. Hepatitis B: global importance and need for control. *Vaccine* 1990;8(Suppl.):S18–20, discussion S1–3.
- [2] Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004;11:97–107.
- [3] Szmuness W, Stevens CE, Harley EJ, Zang EA, Oleszko WR, William DC, et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. *N Engl J Med* 1980;303:833–41.
- [4] Coates T, Wilson R, Patrick G, Andre F, Watson V. Hepatitis B vaccines: assessment of the seroprotective efficacy of two recombinant DNA vaccines. *Clin Ther* 2001;23:392–403.
- [5] Hadler SC, Margolis HS. Hepatitis B immunization: vaccine types, efficacy, and indications for immunization. *Curr Clin Top Infect Dis* 1992;12:282–308.
- [6] Averhoff F, Mahoney F, Coleman P, Schatz G, Hurwitz E, Margolis H. Immunogenicity of hepatitis B vaccines. Implications for persons at occupational risk of hepatitis B virus infection. *Am J Prev Med* 1998;15:1–8.
- [7] Loras C, Gisbert JP, Minguez M, Merino O, Bujanda L, Saro C, et al. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. *Gut* 2010;59:1340–6.
- [8] Loras C, Saro C, Gonzalez-Huix F, Minguez M, Merino O, Gisbert JP, et al. Prevalence and factors related to hepatitis B and C in inflammatory bowel disease patients in Spain: a nationwide, multicenter study. *Am J Gastroenterol* 2009;104:57–63.
- [9] Chevaux JB, Nani A, Oussalah A, Venard V, Bensenane M, Belle A, et al. Prevalence of hepatitis B and C and risk factors for nonvaccination in inflammatory bowel disease patients in Northeast France. *Inflamm Bowel Dis* 2010;16:916–24.
- [10] Rahier JF, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, et al. European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;3:47–91.
- [11] Gisbert JP, Chaparro M, Esteve M. Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011;33:619–33.

- [12] Vida Perez L, Gomez Camacho F, Garcia Sanchez V, Iglesias Flores EM, Castillo Molina L, Cerezo Ruiz A, et al. Adequate rate of response to hepatitis B virus vaccination in patients with inflammatory bowel disease. *Med Clin (Barc)* 2009;132:331–5.
- [13] Altunoz ME, Senates E, Yesil A, Calhan T, Ovunc AO. Patients with inflammatory bowel disease have a lower response rate to HBV vaccination compared to controls. *Dig Dis Sci* 2012;57:1039–44.
- [14] Gisbert JP, Villagrasa JR, Rodriguez-Nogueiras A, Chaparro M. Efficacy of hepatitis B vaccination and revaccination and factors impacting on response in patients with inflammatory bowel disease. *Am J Gastroenterol* 2012;107:1460–6.
- [15] Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1989;170:2–6, discussion 16–9.
- [16] Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;19(Suppl. A):5–36.
- [17] Biancone L, Michetti P, Travis S, Escher JC, Moser G, Forbes A, et al. European evidence-based consensus on the management of ulcerative colitis: special situations. *J Crohns Colitis* 2008;2:63–92.
- [18] Van Assche G, Dignass A, Reinisch W, van der Woude CJ, Sturm A, De Vos M, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: special situations. *J Crohns Colitis* 2010;4:63–101.
- [19] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
- [20] Declaration of Helsinki. World Medical Association. *World Med J* 2008;54:120–4. Available from: <http://www.wma.net>
- [21] Gisbert JP, Menchen L, Garcia-Sanchez V, Marin I, Villagrasa JR, Chaparro M. Comparison of the effectiveness of two protocols for vaccination (standard and double dosage) against hepatitis B virus in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2012;35:1379–85.
- [22] Kugathasan S, Saubermann LJ, Smith L, Kou D, Itoh J, Binion DG, et al. Mucosal T-cell immunoregulation varies in early and late inflammatory bowel disease. *Gut* 2007;56:1696–705.
- [23] Fiocchi C. Early versus late immune mediated inflammatory diseases. *Acta Gastroenterol Belg* 2011;74:548–52.
- [24] Veny M, Esteller M, Ricart E, Pique JM, Panes J, Salas A. Late Crohn's disease patients present an increase in peripheral Th17 cells and cytokine production compared with early patients. *Aliment Pharmacol Ther* 2010;31:561–72.
- [25] Kardar GA, Jeddi-Tehrani M, Shokri F. Diminished Th1 and Th2 cytokine production in healthy adult nonresponders to recombinant hepatitis B vaccine. *Scand J Immunol* 2002;55:311–4.
- [26] de Rave S, Heijtkink RA, Bakker-Bendik M, Boot J, Schalm SW. Immunogenicity of standard and low dose vaccination using yeast-derived recombinant hepatitis B surface antigen in elderly volunteers. *Vaccine* 1994;12:532–4.
- [27] Faulk WP, Edsall G. Vaccines and vaccination programs – special emphasis in malnutrition. *Am J Clin Nutr* 1978;31:2237–47.
- [28] Thung SN, Gerber MA. Specificities of albumin receptors and albumin antibodies. *Infect Immun* 1981;32:1292–4.
- [29] Fabrizi F, Dixit V, Martin P, Jadoul M, Messa P. Meta-analysis. The impact of nutritional status on the immune response to hepatitis B virus vaccine in chronic kidney disease. *Dig Dis Sci* 2012;57:1366–72.
- [30] Ashwell JD, Lu FW, Vacchio MS. Glucocorticoids in T cell development and function. *Annu Rev Immunol* 2000;18:309–45.
- [31] Posey WC, Nelson HS, Branch B, Pearlman DS. The effects of acute corticosteroid therapy for asthma on serum immunoglobulin levels. *J Allergy Clin Immunol* 1978;62:340–8.
- [32] Fedor ME, Rubinstein A. Effects of long-term low-dose corticosteroid therapy on humoral immunity. *Ann Allergy Asthma Immunol* 2006;97:113–6.
- [33] Herron A, Dettliff G, Hixon B, Brandwin L, Ortbals D, Hornick R, et al. Influenza vaccination in patients with rheumatic diseases. Safety and efficacy. *JAMA* 1979;242:53–6.
- [34] Aikawa NE, Campos LM, Silva CA, Carvalho JF, Saad CG, Trudes G, et al. Glucocorticoid: major factor for reduced immunogenicity of 2009 influenza A (H1N1) vaccine in patients with juvenile autoimmune rheumatic disease. *J Rheumatol* 2012;39:167–73.
- [35] Lahood N, Emerson SS, Kumar P, Sorensen RU. Antibody levels and response to pneumococcal vaccine in steroid-dependent asthma. *Ann Allergy* 1993;70:289–94.
- [36] Dotan I, Werner L, Vigodman S, Agarwal S, Pfeffer J, Horowitz N, et al. Normal response to vaccines in inflammatory bowel disease patients treated with thiopurines. *Inflamm Bowel Dis* 2012;18:261–8.
- [37] Kapetanovic MC, Saxne T, Sjöholm A, Truedsson L, Jonsson G, Geborek P. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2006;45:106–11.
- [38] Via CS, Shustov A, Rus V, Lang T, Nguyen P, Finkelman FD. In vivo neutralization of TNF-alpha promotes humoral autoimmunity by preventing the induction of CTL. *J Immunol* 2001;167:6821–6.
- [39] Souto-Carneiro MM, Mahadevan V, Takada K, Fritsch-Stork R, Nanki T, Brown M, et al. Alterations in peripheral blood memory B cells in patients with active rheumatoid arthritis are dependent on the action of tumour necrosis factor. *Arthritis Res Ther* 2009;11:R84.