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Impact of surveillance of hepatitis b and hepatitis c in patients with inflammatory bowel disease under anti-TNF therapies: Multicenter prospective observational study (REPENTINA 3)☆

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KEYWORDS
Hepatitis B;
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Abstract

Aims: Assess IBD patients starting anti-TNF for the impact of preventive measures in HBV and/or HCV, and the predictive response factors to HBV vaccination.

Abbreviations: (HBV), hepatitis B virus; (HCV), hepatitis C virus; (IBD), inflammatory bowel disease; (IFX), infliximab; (ADA), adalimumab.

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disease;
Hepatitis B vaccination;
Anti-TNF treatment;

Methods: Multicenter prospective study including 389 IBD patients. Four interventions were established: I-1) anti-HBs <100 IU/L: HBV vaccination with double doses at 0-1-2 months, and revaccination if titres <100 IU/L (seroprotection defined as anti-HBs10-100 IU/L and effective vaccination anti-HBs >100 IU/L); I-2) anti-HBs >100 IU/L (previous effective vaccination): monitoring levels; I-3) anti-HBc and/or HCV+: analysis every two months; I-4) HBsAg+: start anti-virals.
Results: I-1 and I-2) For first vaccination, effective vaccination and seroprotection were obtained in 26.4% and 43.5%, and for revaccination 31.3% and 44.4%, respectively. Predictive factors of effective vaccination were age ≤ 30 years (OR = 2.2) and being vaccinated simultaneously with anti-TNF (OR = 5.2) instead of late vaccination, whereas age ≤ 30 years (OR = 2.6) and anti-TNF monotherapy (OR = 2.4) were predictive for seroprotection. 80.8% of patients previously vaccinated maintained titres at 29 months follow-up. The only factor related to maintaining titres was previous vaccination versus achieving effective vaccination during anti-TNF (HR = 2.49); I-3 and I-4) HBV-DNA + without reactivation was detected in 7% of 29 anti-HBc. No reactivation was found in the remaining HCV (n = 5) or HBsAg (n = 4) patients.
Conclusions: 1) Response to vaccination/revaccination is low in patients with anti-TNF. Young patients vaccinated at the beginning of anti-TNF and receiving it as a monotheraphy showed better response. 2) Long-lasting effective vaccination is greatest in patients previously vaccinated. 3) Following-up the established surveillance and/or preventive anti-viral therapy seems to be safe in HBV and HCV patients.

1. Introduction

The hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are important worldwide diseases, with 400 and 170 million carriers, respectively.[1,2] The prevalence of these infections in inflammatory bowel disease (IBD) patients is similar to that found in the general population.[3,4] However, HBV reactivation related to immunosuppressant therapy in IBD patients may be life-threatening. In fact, in the previous REPENTINA 2 study,[5] we demonstrated that in patients with hepatitis B surface antigen (HBsAg) up to 36% had liver dysfunction, with 67% liver failure. In the same clinical setting, patients with HCV showed a lower frequency and less severity of liver dysfunction than patients with HBV. Active preventive measures with anti-viral treatment or vaccination for HBV and surveillance for HCV are clearly necessary. It has to be taken into account that a low HBV vaccination response has been reported in IBD patients. As recently demonstrated,[6] patients with IBD had a low response to single doses of HBV vaccination in comparison with double doses. It has also been suggested that anti-TNF treatment in these patients has a negative impact on response to vaccination.[7] There is little information regarding factors related to HBV vaccination response and maintenance of protective titres over time in IBD patients. In addition, little information is available regarding the effect of anti-TNF treatment in the evolution of HBV and HCV infections.[8]

For the above reasons, the aims of our study were to assess IBD patients under anti-TNF treatment for the impact of preventive measures and/or treatment in HBV and/or HCV infection and the predictive factors of response to HBV vaccination.

2. Patients and methods

2.1. Design and inclusion criteria

This is a multicenter, prospective observational study carried out in 9 Spanish hospitals. We included IBD patients who started anti-TNF treatment and four sets of interventions were established depending on the patients' markers at the time of inclusion. These interventions were based on the 'real life' patients that may be found in clinical practice setting:

- *Intervention 1 (vaccination): patients with levels of antibodies to hepatitis B surface antigen (anti-HBs) <100 IU/L*: HBV vaccination was administered with double doses and rapid schedule (0–1–2 months), and revaccination with same schedule if titres were lower than 100 IU/L after 2 months following the last dose of HBV vaccination. The established protocol for vaccination schedule consisted of double doses of Engerix-B (GlaxoSmithKline) (20 μg of HBsAg, two 1.0 mL monodose vials of the vaccine) at the beginning of anti-TNF treatment (from 15 days before to 15 days after the first anti-TNF dose). However some patients that were vaccinated later (from months to several years after the beginning of anti-TNF treatment), and thus not following the established protocol rules, were also included. This type of vaccination was defined as late vaccination schedule; this was taken into account for the statistical analysis. Levels of anti-HBs were monitored during the follow-up.

We defined *seroprotection* as anti-HBs between 10 and 100 IU/L and *effective vaccination* as anti-HBs over 100 IU/L.

- *Intervention 2 (anti-HBs monitoring): patients with previous effective vaccination [anti-HBs >100 IU/L without positive antibodies to hepatitis B core protein (anti-HBc)]*: monitoring of anti-HB levels at 4 months after starting anti-TNF treatment and at the end of follow-up.
- *Intervention 3 (liver dysfunction monitoring): patients with positive anti-HBc (with or without anti-HBs), showing past HBV infection and HBsAg clearance) and/or positive HCV*: analytical laboratory variables and viral

markers were measured every two months for 2 years during anti-TNF maintenance treatment. In case of anti-TNF removal before the end of the 2-year follow-up, blood tests were performed every two months for 6 additional months after finishing anti-TNF. If circulating HBV DNA was detected anti-viral treatment was started and/or anti-TNF treatment was removed.

- *Intervention 4 (anti-viral treatment): immune active or inactive HBsAg carriers*: anti-viral treatment was administered to reduce HBV DNA <2000 IU/mL in immune active carriers before starting anti-TNF. In inactive HBsAg carriers the anti-viral was started simultaneously with anti-TNF. In both cases anti-viral treatment was maintained during all the anti-TNF treatment or at least 1 year after its removal. The same follow-up as the previous intervention was carried out. The anti-viral treatment followed the established recommendations at the time. Lamivudine was the recommended anti-viral treatment at the beginning of the registry,[9] whereas third-generation nucleoside/nucleotide anti-virals such as entecavir and tenofovir were recommended later due to their high potency and genetic barrier.[1]

An electronic database for the REPENTINA study (REGISTRO HEPATITIS ENFERMEDAD INFLAMATORIA INTESTINAL) was created to record all the information via the internet (www.repentina.com). The database remained open from March 2006 to December 2012. The number of patients included per hospital ranged from 3 to 90 and the number of IBD patient files among participating centres ranged from 354 to 1983.

The study protocol was approved by the Ethics Committee of the leading hospital (Hospital Universitari Mútua de Terrassa).

2.2. Factors related to hepatic disease

The following analytical laboratory variables assessing liver function were recorded: aminotransferase levels (ALT, AST), alkaline phosphatase (AP), gamma glutamyltranspeptidase (GGT), total bilirubin, albumin, hemogram, and prothrombin time, all measured with standard laboratory techniques. Clinical data related to hepatic function such as presence of hepatic encephalopathy or ascites were recorded, in order to establish the existence of acute hepatic failure.

2.3. HBV and HCV infection markers

The following markers were recorded: HBsAg, anti-HBs, anti-HBc, hepatitis B e antigen (HBeAg), antibodies to hepatitis B e antigen (anti-HBe), and antibodies to hepatitis C virus (anti-HCV), HCV RNA and/or HBV DNA.

2.4. Statistical analysis

Results are expressed as mean ± standard error of the mean (SEM), median and range, and percentages and their 95% confidence interval (CI) when appropriate. In univariate analysis, χ^2 test and Fisher exact test were used to compare proportions, and Student's t test was used to compare quantitative variables. Multivariate analysis was performed using binary logistic regression analysis. The cut-off to assess the relation of age on HBV vaccination was chosen based on the calculated mean age — 30 and 35 years — for analysis of first vaccination and revaccination respectively. Logistic regression analysis was made to evaluate predictive factors of effective vaccination and seroprotection. A survival analysis was made to evaluate predictive factors in maintaining anti-HB titres over time. Cox proportional-hazards regression was used to analyse the independent predictive factors related to maintenance of effective vaccination and seroprotection over time. All the factors with a $p < 0.1$ in the univariate analysis were included in the multivariate analysis. The odds ratio (OR), hazard ratio (HR), and the 95% confidence interval (CI) were calculated to assess the strength of each significant association.

3. Results

3.1. Demographics of the IBD population

A total of 389 patients were included (307 Crohn's disease, 82 ulcerative colitis, 205 males, mean age: 40 ± 0.7 years) under anti-TNF treatment (248 receiving infliximab, 138 receiving adalimumab, 3 receiving certolizumab). Two hundred and eighty-seven patients (74%) were taking other immunosuppressive drugs in combination with anti-TNF (66.5% thiopurines, 4.6% metrotexate, 0.3% thiopurines + corticosteroids, and 1.5% corticosteroids only). The remaining patients (26%) were taking anti-TNF in monotherapy.

The median time from IBD diagnosis at inclusion was 61 months (range from 0 to 643). The maximum disease activity during disease evolution was moderate in 66.5% of the patients and severe in 30.3%, and the majority of them had an episodic evolution (63.2%). Table 1 shows the clinical characteristics of the IBD population according to the Montreal classification.

3.2. Results according to interventions 1 and 2

A total of 254 patients were included in intervention 1 (vaccination in patients with anti-HBs <100 IU/L; n = 235 for <10 IU/L and n = 19 for 10–100 IU/L). For the first vaccination, effective vaccination and seroprotection were obtained in 26.4% (67/254) and in 43.5% (110/254) of the patients, and for revaccination 31.3% (45/144) and 44.4% (64/144), respectively (Fig. 1). In forty-three patients that did not achieve effective vaccination (anti-HBs >100 IU/L) at the first vaccination, the protocol was not applied correctly and these patients were not revaccinated. Of these, 30% achieved seroprotection (anti-HBs 10–100 IU/L). At the end of the vaccination, a total of 56.7% (144/254) (95% CI, 50–62%) of the patients achieved some level of protection (ant-HBs > 10 IU/L) against HBV.

In Table 2, the univariate analysis of factors related to seroprotection and effective vaccination in the first vaccination is shown. In multivariate analysis, age equal to or less than 30 years (OR 2.23; 95% CI 1.18–4.47; p = 0.023) and following the established vaccination schedule protocol (starting the vaccination schedule simultaneously with the anti-TNF instead of late vaccination) (OR, 5.22; 95% CI 1.53–17.77; p = 0.008) were the only predictive factors for effective vaccination. Age equal to or less than 30 years (OR, 2.61; 95% CI 1.33–5.13; p = 0.005) and the use of anti-TNF in

Table 1 Clinical characteristics of IBD population according to the Montreal classification.

Crohn's disease (n = 307)			
Age at diagnosis (A)	%		
A1 (≤16 years)	11.2		
A2 (17–40 years)	67.4		
A3 (>40 years)	21.4		
Location (L)	%	Upper GI modifier (L4)	%
L1 (Terminal ileum)	30.8	L1 + L4	8.4
L2 (Colon)	13.8	L2 + L4	0.3
L3 (Ileocolon)	42.8	L3 + L4	2.6
L4 (Upper GI)	1.3		
Behaviour (B)	%	Perianal disease modifier (p)	%
B1 (Non-stricturing, non-penetrating)	38.7	B1p	15.8
B2 (Stricturing)	15.2	B2p	4.5
B3 (Penetrating)	15.8	B3p	10
Ulcerative colitis (n = 82) %			
Ulcerative proctitis (E1)		8.5	
Left-sided ulcerative colitis (E2)		47.6	
Extensive ulcerative colitis (E3)		43.9	

monotherapy (OR, 2.43; 95% CI 1.35–4.37; p = 0.003) were the only predictive factors for seroprotection.

We carried out the same statistical analysis to assess the factors related to effective vaccination and seroprotection after revaccination (Table 3). In this case, age equal to or less than 35 years (OR, 4.4; 95% CI 2.01–9.51; p = 0.000) and achieving seroprotection in the first vaccination (OR 3.41; 95% CI 1.39–8.41; p = 0.007) were the only independent predictive factors of effective vaccination. Taking into account these two factors, only 25.3% of the patients older than 35 without any response to the first vaccination achieved some response to HBV revaccination (anti-HBs > 10 IU/L) (Table 4).

Regarding intervention 2 (patients with previous vaccination, anti-HBs >100 IU/L), 99 patients were included. Median period of time elapsed from vaccination was 24 months (range, 6–156), with the mean age of patients at that moment of 31.3 ± 1.7 years. Of these patients, 89.9% maintained titres 4 months after the beginning of anti-TNF treatment, and 80.8% (95% CI, 72–87%) of patients maintained the anti-HB titres after a mean follow-up of 29 months (range, 4–108). Of note, patients achieving effective vaccination following intervention 1 maintained titres >100 IU/L in only 40.7% of cases (95% CI, 30–52%), after a mean follow-up of 33 months (range, 6–72) (p = 0.000). We analysed the factors related to the maintenance of anti-HB titres over time including both those patients from intervention 1 achieving anti-HB titres >100 IU/L and those from intervention 2. In Table 5, variables included for univariate analysis are shown.

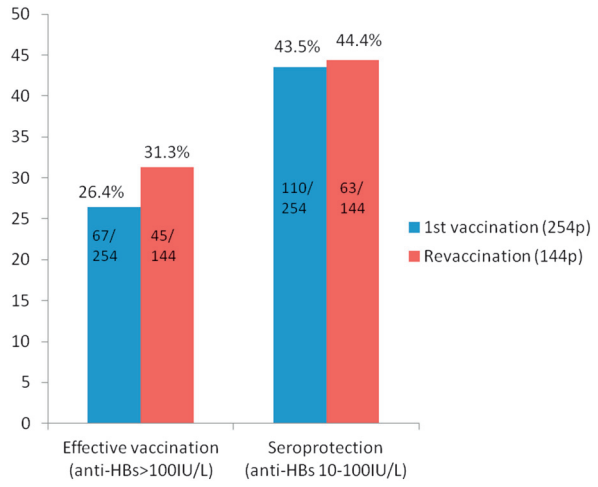

Figure 1 Percentage of effective vaccination and seroprotection after first vaccination and revaccination in patients with anti-HBs <100 IU/L. Intervention 1.

In the multivariate Cox regression analysis, the only factor related to maintaining titres over time was previous vaccination (intervention 2) as compared to achieve effective vaccination during the anti-TNF treatment (intervention 1) [HR, 2.49 (95% CI 1.4–4.3), p = 0.001 for anti-HBs >100 IU/L; and HR, 2.68 (95% CI 1.1–6.3), p = 0.024 for anti-HBs >10 IU/L], as reflected in the survival graphs (Figs. 2 and 3). Moreover, patients with anti-HB titres >100 IU/L after completing interventions 1 and 2 significantly maintained some type of seroprotection (anti-HBs > 10 IU/L) compared to those with anti-HB titres between 10 and 100 IU/l (82.5% vs 66.7%; p = 0.04).

We also analysed the factors related to the maintenance of anti-HB titres over time including only the patients vaccinated during the study period (from intervention 1). There were no significant associations with the variables assessed in univariate survival analysis (data not shown). This analysis was repeated including only the patients previously vaccinated (from intervention 2); in this analysis the age at vaccination (≤20 vs >20 years) and the time elapsed from vaccination (≤24 vs >24 months) were included as variables. We found that a time period from previous vaccination longer than 24 months was the only factor independently associated with maintaining anti-HB

Table 2 Factors related to achieve seroprotection (n = 110) and effective vaccination (n = 67) in the first vaccination in patients included in intervention 1 (n = 254 patients). Univariate analysis.

	% Seroprotection		% Effective vaccination	
Previous vaccine markers	39%	P 0.000	25%	P 0.033
<10 (n = 235)	100%		47.4%	
10–100 (n = 19)				
Previous vaccine	55.6%	P 0.120	33.3%	P 0.322
Yes (n = 37)	41.7%		25.5%	
No (n = 217)				
Type of treatment *	38%	P 0.012	24%	P 0.198
IFX (n = 159)	54.3%		31.5%	
ADA (n = 95)				
Established vaccination	45.8%	P 0.103	30%	P 0.005
Schedule **	31.6%		7.9%	
Yes (n = 216)				
No (n = 38)				
Immunosuppressant	38.3%	P 0.003	24.6%	P 0.170
Yes (n = 187)	59%		33.3%	
No (n = 67)				
Diagnosis	46.7%	P 0.056	28.6%	P 0.152
Crohn's disease (n = 200)	32%		18.9%	
Ucerative colitis (n = 54)				
Disease duration	47.3%	P 0.540	30.9%	P 0.412
≤1 year (n = 55)	42.6%		25.4%	
>1 year (n = 199)				
Age	63%	P 0.003	39.1%	P 0.030
≤30 years (n = 46)	38.9%		23.5%	
>30 years (n = 208)				
Sex	40.8%	P 0.341	24%	P 0.465
♂ (n = 131)	46.7%		28.7%	
♀ (n = 123)				

IFX: infliximab, ADA: adalimumab.
* IFX and ADA included both patients treated in monotherapy and combo regimens (81% and 62% combo therapy in IFX and ADA respectively).
** Beginning the vaccination simultaneously with the anti-TNF vs late vaccination.

titres >100 IU/L (93.3% vs 66%; HR, 4.42; 95% CI, 1–20.1, p = 0.05).

3.3. Results of interventions 3 and 4 (patients with positive markers)

A total of 29 patients had positive markers to anti-HBc (7.5%) and of these 21 had also anti-HBs; four patients were positive for HBsAg (1%) and 5 were anti-HCV positive (1.3%). During the follow-up, 7% (2/29) of the anti-HBc positive patients (one of them with positive anti-HBs) presented circulating DNA without reactivation. In one case the level of HBV DNA was 700 IU/mL and in the other case was 2000 IU/mL, with liver test in the normal range (including AST/ALT). Infliximab was removed in the first case and in the other anti-viral treatment was added. Reactivation was not detected in the remaining patients with HBsAg, all of them with negative DNA (n = 4; all of them undergoing anti-viral treatment, 2 under lamivudine and 2 under entecavir).

In the case of HCV (n = 5), only one patient had positive RNA, and 2 of them also had positive anti-HBc. None of them received anti-viral treatment and none presented worsening of the underlying liver disease.

4. Discussion

The REPENTINA III study is the first study evaluating a long-term prospective surveillance programme of HBV and HCV infections and the largest study assessing the efficacy of HBV vaccination in patients with IBD under anti-TNF treatment. IBD patients should be vaccinated against HBV as soon as possible, ideally before the start of immunosuppressive treatments since recent studies have demonstrated a better response to HBV vaccination in patients not treated with immunosuppressants and/or anti-TNF.[6,7] However, IBD specialists frequently receive patients to be treated with anti-TNF that have not previously been immunised against HBV. Thus, our aim was to go deeper in achieving successful vaccination and to identify factors related to successful vaccination in those patients who were more difficult to protect; those being patients treated with anti-TNFs,[7] mainly under combo therapy.

The efficacy of the standard HBV vaccination regimen has been found to be very low in non-selected IBD patients.[6,10,11] We used a double-dose and rapid vaccination schedule that proved to be better than to the standard as used in a previous study.[6]

Table 3 Factors related to achieve seroprotection (n = 63) and effective vaccination (n = 45) in the revaccination in patients included in intervention 1 (n = 144 patients). Univariate analysis.

	% Seroprotection		% Effective vaccination	
Previous vaccine markers	43%	P 0.038	31.4%	P 0.592
<10 (n = 140)	100%		50%	
10–100 (n = 4)				
Previous vaccine	37.5%	P 0.539	18.8%	P 0.270
Yes (n = 17)	45.6%		33.6%	
No (n = 127)				
Type of treatment*	40.7%	P 0.159	28.6%	P 0.218
IFX (n = 93)	53%		38.8%	
ADA (n = 51)				
Established vaccination	46.2%	P 0.437	33.3%	P 0.425
Schedule**	37.5%		25%	
Yes (n = 120)				
No (n = 24)				
Immunosuppressant	40.6%	P 0.043	28.3%	P 0.066
Yes (n = 110)	60.6%		45.5%	
No (n = 34)				
Diagnosis	49%	P 0.069	34%	P 0.366
Crohn's disease (n = 109)	31.4%		25.7%	
Ucerative colitis (n = 35)				
Disease duration	46.7%	P 0.805	30%	P 0.800
≤1 year (n = 31)	44%		32.4%	
>1 year (n = 113)				
Age	62.9%	P 0.001	51.8%	P 0.000
≤35 years (n = 55)	33.3%		18.8%	
>35 years (n = 89)				
Seroprotection in first vaccination	79.3%	P 0.000	55.2%	P 0.003
Yes (n = 30)	35.7%		25.9%	
No (n = 114)				
Sex	40%	P 0.233	28%	P 0.288
♂ (n = 76)	50%		36.4%	
♀ (n = 68)				

IFX: infliximab, ADA: adalimumab.
* IFX and ADA included both patients treated in monotherapy and combo regimens (86% and 61.5% combo therapy in IFX and ADA respectively).
** Beginning the vaccination simultaneously with the anti-TNF vs late vaccination.

Using the same double-dose and rapid vaccination schedule, with revaccination if necessary, we found a percentage of response to HBV vaccination (anti-HBs > 10 IU/L) of 57% in a selected anti-TNF treated IBD population. This response rate is lower than that recently described by Gisbert et al.[7] who found a 79% response using the same vaccination schedule in non-selected IBD patients. The differences are probably due to the type of IBD populations included. In fact, if we look at the patients under anti-TNF in the study of Gisbert et al.,[7] 29% of effective vaccination and 46% of seroprotection for the first vaccination was obtained, which is a similar figure to ours (26% and 43%, respectively).

Herein we provide additional information showing that those patients receiving vaccination at the beginning of the

Table 4 Probability of achieving response to HBV revaccination depending on age and having obtained seroprotection (anti-HBs 10–100 IU/L) in the first vaccination (n = 144 patients).

	Seroprotection at first vaccination (anti-HBs 10–100 IU/L)			
	Yes (n = 29)		No (n = 115)	
	Anti-HBs >10 IU/L	Anti-HBs >100 IU/L	Anti-HBs >10 IU/L	Anti-HBs >100 IU/L
Age ≤ 35 years (n = 54)	85.7% (12/14)	64.3% (9/14)	55% (22/40)	47.5% (19/40)
Age > 35 years (n = 90)	73.3% (11/15)	46.7% (6/15)	25.3% (19/75)	13.3% (10/75)

Table 5 Factors related to the maintenance of anti-HBs titres over time. Univariate survival analysis. (n = 180 patients).

	% anti-HBs >100 IU/L (n = 113)		% anti-HBs >10 IU/L (n = 149)	
Intervention	40.7%	P 0.000	71.6%	P 0.009
I-1 (n = 81)	80.8%		91.9%	
I-2 (n = 99)				
Revaccination	35.5%	P 0.007	74.2%	P 0.333
Yes (n = 32)	68.2%		84.5%	
No (n = 148)				
Treatment*	58.8%	P 0.654	82.4%	P 0.207
1 (n = 18)	57.4%		77%	
2 (n = 62)	68.7%		88.9%	
3 (n = 100)				
Diagnosis	62.7%	P 0.332	86%	P 0.081
Crohn's disease (n = 150)	62.1%		65.5%	
Ucerative colitis (n = 30)				
Disease duration	63.9%	P 0.684	86.1%	P 0.476
≤1 year (n = 36)	62.5%		81.9%	
>1 year (n = 144)				
Age	80%	P 0.006	94.3%	P 0.011
≤30 years (n = 70)	51.8%		75.5%	
>30 years (n = 110)				
Sex	65.9%	P 0.559	86.4%	P 0.335
♂ (n = 88)	62.8%		79.3%	
♀ (n = 92)				

* 1 = monotherapy with immunosuppressant, 2 = monotherapy with anti-TNF, 3 = combination therapy (immunosuppressant + anti-TNF).

anti-TNF treatment had a five times better response than those for whom the vaccination was administered during anti-TNF maintenance treatment (OR, 5.22). We also found that those patients treated with anti-TNF in monotherapy had a better response than those treated with combo therapy (59% vs 38% seroprotection rate), suggesting an additional negative effect of immunosuppressants. This is in contrast to what was previously reported in the other above-mentioned study,[7] in which no immunosuppressant effect (mainly thiopurine drugs) was found. Therefore prolonged deep immunosuppression is probably an important factor in worsened response to HBV vaccination.

The most important factor related to effective vaccination and seroprotection, both for the first vaccination and revaccination, was young age at administration. In fact, in previous studies,[7,10,11] the youngest patients had the highest percentages of response (anti-HBs > 10 IU/L) to HBV vaccination with both double dose schedule[6] and the standard regime.[10,11] Moreover, we provide additional data demonstrating that young age is a predictive factor for effective vaccination (anti-HBs > 100 IU/L) both at initial vaccination and revaccination. Obtaining seroprotection (anti-HBs 10–100 IU/L) at first vaccination was another independent predictive factor for effective vaccination (anti-HBs > 100 IU/L) after revaccination. This result confirms a similar finding of a previous study in which the data were analysed in a univariate manner.[7] Thus revaccination should not generally be recommended to older patients (>35 years) who have not presented any response to the first vaccination (anti-HBs < 10 IU/L), since the response rate in these patients was only 25%.

Another important question is the level of anti-HBs considered protective after HBV vaccination. The present study has the longest evolution follow-up of anti-HB titres over time, with a mean follow-up of 33 months for patients included in intervention 1 and 29 months for patients included in intervention 2. As previously noted,[12] we also found that a high proportion of patients lose protective titres over time after successful vaccination, most frequently patients with the lowest anti-HB titres. The decrease in anti-HB levels over time has also been observed in healthy immunocompetent individuals. However, even at risk of HBV exposure they develop only a subclinical infection.[13,14] In this sense, a recent meta-analysis demonstrated that though transient HBsAg seroconversion may occur sparsely among the previously vaccinated individuals, chronic carrier state may not occur in immunocompetent patients. These results, however, are known to be not applicable to immunocompromised individuals for which there are insufficient information to know which is the best attitude to follow.[15] In contrast, though rarely reported, clinically relevant HBV infection may occur in immunosuppressed vaccinated responders who have lost anti-HB levels.[16] So, it is advisable to achieve levels of anti-HBs >100 IU/L so as to be adequately protected against HBV, as recommended by a number of scientific societies and the World Health Organization (WHO).[17,18] Moreover, in patients showing a decline of anti-HBs over time, a booster dose is recommended in order to achieve an anamnestic response.

The only independent predictive factor related to maintaining titres over time was previous vaccination (intervention 2) as compared to achieving effective vaccination during the anti-TNF treatment (intervention 1) (anti-HBs > 100 IU/L: HR, 2.49; and anti-HBs > 10 IU/L: HR, 2.68). For patients from intervention 2, the only independent factor associated with

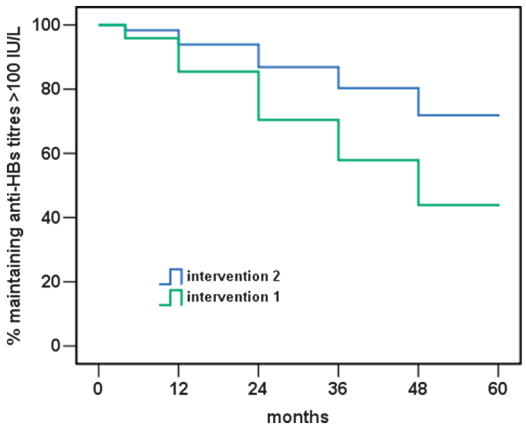

Figure 2 Survival graphs of maintaining anti-HB titres >100 IU/L over time in patients with previous vaccination (intervention 2) vs those who achieve effective vaccination during anti-TNF treatment (intervention 1).

maintaining anti-HBs titres >100 IU/L after starting anti-TNF was a period of time from vaccination longer than 24 months, which argues for the benefit of universal vaccination early in life. In fact, the WHO recently recommended administration of HBV as soon as possible after birth irrespective of the degree of endemicity.[18] In contrast, some countries with low endemicity, recommend HBV vaccination for high-risk groups only.[19] However, population migration from countries of high to low endemicity may affect HBV prevalence at a local level. Additionally, IBD travellers from low to high risk areas, are particularly exposed.

The management of immunosuppression in IBD patients having HBV markers of a theoretically past infection (anti-HBc-positive patients with or without anti-HBs, after HBsAg clearance) is a challenging situation, and one about which there is only limited information.[20–22] In the present study with a prospective bimonthly follow-up (clinical and analytical), we did not find any HBV reactivation. Circulating HBV DNA was detected in 7% of anti-HBc-positive patients without clinical or biochemical reactivation. This tight monitoring prompts early intervention, in advance of HBV reactivation, which highlights the safety benefit of this form of control. Moreover, this argues against the systematic use of anti-viral prophylactic treatment in all anti-HBc-positive patients and in favour of restricting its use to those with circulating HBV DNA detection. All of these data confirm the results of the most extensive information emerging from the previous retrospective cohort (REPENTINA II study) including 63 anti-HBc IBD patients.[5] Similar results have recently been reported in rheumatic patients with anti-HBc under anti-TNF treatment.[23]

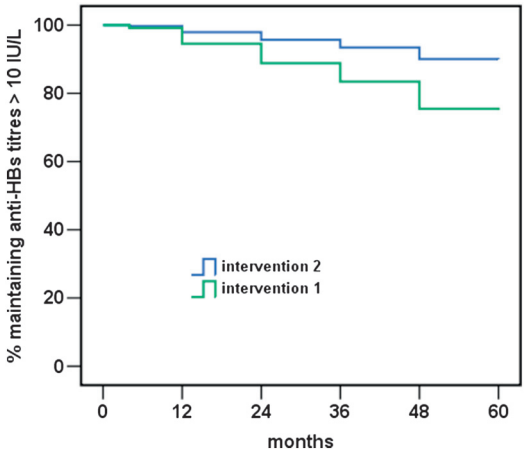

Figure 3 Survival graphs of maintaining anti-HB titres >10 IU/L over time in patients with previous vaccination (intervention 2) vs those who achieve effective vaccination during anti-TNF treatment (intervention 1).

One of the limitations of the study is the small number of patients included with HBsAg and anti-HCV. However it is the largest series of HBV and HCV infections followed prospectively. Despite of that, this study using very strict monitoring confirms the safety of anti-TNF treatment in both HBsAg-positive patients concomitantly treated with anti-viral prophylactic therapy and HCV-positive patients.[20–22,24] Neither clinical nor subclinical (analytical) reactivation was detected after long-term follow-up. Another limitation is the lack of an age-matched healthy control group to assess the efficacy of HBV vaccination. This would allow knowing if the IBD itself is responsible of a low response to HBV vaccination or if the low response is due to older age at vaccination in IBD patients compared to healthy controls. In this sense, even in paediatric population, the older age at vaccination was related with the absence of protective antibodies.[25]

In conclusion, the response to HBV vaccination and revaccination is low in IBD patients treated with anti-TNF even when a double dose and revaccination are used. The best prevention against HBV is likely obtained by universal vaccination early in life. In non-vaccinated patients, vaccination is advised as early as possible, ideally after the diagnosis of IBD as has been recently recommended in updated ECCO guidelines on opportunistic infections.[26] In anti-TNF treated patients, young people vaccinated at the beginning of the treatment administered as monotheraphy will have the better response. In addition, revaccination in older patients not achieving seroprotection at first vaccination should probably be restricted to those at high risk of exposure. Following the established interventions of surveillance and preventive anti-viral therapy for HBV and surveillance for HCV patients under anti-TNF treatment is safe.

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Declaration of conflicts of interest

None for all authors.

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