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Prevalence and natural history of hepatitis B and C infections in a large population of IBD patients treated with anti-tumor necrosis factor-α agents☆

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Abstract

Background: The prevalence rates of hepatitis B virus (HBV) and hepatitis C virus (HCV) in patients with inflammatory bowel disease (IBD) have been reported to be higher than rates of infection among the general population. Although several cases of HBV infection reactivation in IBD patients treated with anti-TNF-α agents have been described, no evidence exists that anti-TNF-α therapy exacerbates the course of HCV. The aims of this study were to assess the prevalence of HBV and HCV and the rate of HBV vaccination in a population of IBD patients; and to investigate the long-term effects of anti-TNF-α therapy in the subgroup with HBV or HCV infections.

Methods: 301 patients were studied. Prior to the initiation of anti-TNF-α therapy, serum samples were tested for HBsAg and anti-HBc, anti-HBs and anti-HCV antibodies. During the follow-up, HBsAg and anti-HBc positive patients underwent periodic blood testing for viral markers, HBV-DNA and liver function; anti-HCV positive patients were assessed for liver function and HCV-RNA.

☆ Statement of authorship: AP planned the study and drafted the manuscript; CF, MM, AA, GA, GM, DP, IDV collected data; MC interpreted data and statistical analysis; AG, GR edited the manuscript; LG helped to draft the manuscript. All authors read and approved the final draft submitted.

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Results: One patient was HBsAg positive (0.3%), and 22 (7.3%) tested positive for anti-HBc. Seventy-two patients (23.9%) had been vaccinated for HBV. Four patients tested positive for anti-HCV (1.3%). During anti-TNF-α therapy, none of the patients experienced HBV or HCV reactivation.
Conclusions: HBV and HCV infection rates were similar to infection rates among the general population. Less than one quarter of the patients had been vaccinated against HBV. Anti-TNF-α agents appear to be safe for patients with HBV infection; more data are needed for patients with HCV infection.

1. Introduction

Patients affected by inflammatory bowel disease (IBD) are considered to be at increased risk for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections.[1,2] Indeed, two studies conducted more than a decade ago in Italy and France showed a higher prevalence of HBV and HCV infections in IBD patients compared to the general population.[1,2] However, more recent studies performed in France, Spain and Greece failed to confirm these previous results; instead, these studies reported that HBV and HCV infection rates in IBD patients were similar to or lower than those found in the general population.[3–5] Data concerning the serologic evidence of HBV vaccination in IBD patients are limited. Only two studies have reported vaccination rates in IBD patients, which ranged from 12% to 49%.[3,4] These data are of interest due to the increasingly widespread use of biological agents in IBD treatment, particularly the anti-tumor necrosis factor alpha (TNF)-α agents infliximab (IFX) and adalimumab (ADA).[6] Several cases of HBV infection reactivation have been reported in patients treated with anti-TNF-α agents.[7–13] In several of these instances, patients exhibited particularly severe or even lethal disease.[7–10] Thus, a number of reports and clinical guidelines have recently recommended to test all IBD patients for HBV infection, preferably at the time of diagnosis, and to vaccinate seronegative patients.[14–18]

Anti-TNF-α therapy does not appear to worsen the course of HCV infection, even though the long-term consequences of this therapy on disease progression are not yet well known.[14–17,19] The aims of the present study were first to assess the prevalence of HBV and HCV infections and the HBV vaccination rate in a population of IBD patients with either Crohn's disease (CD) or ulcerative colitis (UC). Second, this study aimed to evaluate the safety of anti-TNF-α agents in IBD patients infected with either HBV or HCV.

2. Patients and methods

2.1. Patients

Between January 2005 and September 2010, consecutive inpatients and outpatients affected by IBD seen in the Department of Internal Medicine and Gastroenterology, Catholic University of Rome, Italy were enrolled in the study prior to the initiation of anti-TNF-α therapy. All patients gave informed consent to participate in the study. The study was approved by the Ethical Committee of our hospital. At the time of enrollment, the following demographic and disease-related features were recorded: type of diagnosis (CD or UC), sex, age at diagnosis, age at study enrollment, disease duration, previous surgeries (IBD and non-IBD related), Montreal classification and concomitant immunosuppressive and/or steroidal therapies.

2.2. HBV and HCV testing at time of study enrollment

Serum samples from all patients were tested for hepatitis B surface antigen (HBsAg) and antibodies against hepatitis B core antigen (anti-HBc), HBsAg (anti-HBs) and HCV (anti-HCV).

The patients who tested positive for HBsAg were further tested for hepatitis B e-antigen (HBeAg), antibodies against HBeAg (anti-HBe) and HBV-DNA; patients who tested positive for anti-HBc antibodies were tested for HBV-DNA. Anti-HCV positive patients were tested for HCV-RNA. HBV and HCV markers were assessed by chemiluminescent microparticle immunoassays (CMIAs) (Architect i2000sr System, Abbott Laboratories, Abbott Park, Illinois, U.S.A.). HBV-DNA and HCV-RNA were assessed by real time (RT)-PCR (Abbott RealTime HBV and HCV assays, Abbott Laboratories, Abbott Park, Illinois, U.S.A.). The threshold value was 10 UI/mL for HBV-DNA and 12 UI/mL for HCV-RNA.

2.3. Follow-up of patients with HBV and HCV positive markers

HBsAg positive and anti-HBc positive patients underwent periodic liver function tests (LFTs), including examination of alanine-aminotransferase (ALT), aspartate-aminotransferase (AST), γ-glutamyl-transferase (γ-GT), alkaline phosphatases (ALK) and total bilirubin levels every three months. These patients were also tested for viral markers and HBV-DNA every six months or if alterations in LFTs values occurred; HBV-DNA levels were also examined in changes in viral markers were observed. Anti-HCV positive patients underwent LFTs every three months, and HCV-RNA levels were assessed every six months or if alterations in LFTs results were observed.

2.4. Definitions of HBV infection and HBV vaccination

Patients with positive HBV serological markers were classified as having either a) current HBV infection, including

patients with chronic HBV infection or patients in an inactive HBsAg carrier state, or b) past or resolved HBV infection, including carriers of "occult" HBV infection (patients who were anti-HBc+with or without anti-HBs antibodies). Patients with effective vaccinations were defined as individuals with anti-HBs antibody levels of >10 mIU/ml that did not have anti-HBc antibodies.

2.5. Definitions of HCV infection

Patients who were anti-HCV positive with negative HCV-RNA were considered to have an inactive HCV infection; patients who were HCV-RNA positive were defined as having a chronic HCV infection. In these patients, the HCV genotype was also assessed.

2.6. Statistical analysis

Quantitative variables are expressed as the mean ± standard deviation (SD). Statistical comparisons between two groups were performed using the chi-square ($\chi 2$) test for categorical variables comparison and the Student's *t*-test for unpaired data comparison. Comparisons among multiple groups were analyzed by one-way analysis of variance (ANOVA). The *post-hoc* effect was assessed by Bonferroni *t*-test. We also looked for risk factors for not being vaccinated for HBV infection among the baseline characteristics by comparing vaccinated and nonvaccinated patients. When considering continuous variables for dichotomous analysis, cutoff values were determined by receiver operating characteristic (ROC) analysis, using vaccination status as classification variable. Then, we performed a multivariate analysis to identify independent variables predictive of HBV vaccination by using logistic regression analysis. A P-value of ≤0.05 was considered significant. All statistical analyses were performed using the SPSS™ 13.0 statistical software package (SPSS, Chicago, Illinois, U.S.A.).

3. Results

3.1. Patient features

Overall, 301 IBD patients were included in the study; of these, 184 had CD and 117 had UC (Table 1). The mean patient age at the time of enrollment was 41.9 ± 13.2 years; the mean patient age was not significantly different between CD and UC patients (P=0.474). However, CD patients were significantly younger at diagnosis compared to UC patients (30.1 ± 11.7 years vs. 35 ± 13.9 years, P=0.026); disease duration was also longer in CD compared to UC patients (10.5 ± 8.4 years vs. 8.9 ± 6.5 years, P=0.009). In terms of surgical interventions, 65.2% of the CD patients had previously undergone surgical procedures, while only 34.2% of the UC patients were treated surgically (P<0.001). Patients were also subdivided according to the Montreal classification (Table 2).

Table 1 Patient baseline characteristics.

	IBD (n=301)	CD (n=184)	UC (n=117)	P-value (CD vs. UC)
Sex M/F (ratio)	142/159	92/92 (1)	50/67	P=0.218
Age at IBD diagnosis (mean ± SD)	32 ± 12.8	30.1 ± 11.7	35 ± 13.9	P=0.026
Age at inclusion (mean ± SD)	41.9 ± 13.2	40.6 ± 12.9	44 ± 13.6	P=0.474
Disease duration (mean ± SD)	9.9 ± 7.7	10.5 ± 8.4	8.9 ± 6.5	P=0.009
Previous surgery (%)	160 (53.2)	120 (65.2)	40 (34.2)	P<0.001

3.2. IBD patient treatments (Table 3)

During the study, approximately 80% of the patients were treated with IFX, 30% with ADA and 1.7% with certolizumab pegol (CER). Because some patients were consecutively treated with two or three anti-TNF-α agents, the total percentage of therapies received by the patients is greater than 100% (Table 3). The mean duration of IFX therapy was more than two years (25.5 ± 22.3 months), while the mean duration of ADA therapy was 15 ± 10.8 months. At the time of study enrollment, approximately two-thirds of the patients were receiving treatment with an immunosuppressive agent (azathioprine/6-mercaptopurine or methotrexate); treatment rates with these agents were not significantly different between CD and UC patients. More than 50% of the patients were receiving steroids, and steroid treatment was significantly higher in UC patients compared to CD patients (84.6% vs. 34.2%, P<0.001).

3.3. HBV and HCV prevalence and HBV vaccination rate (Fig. 1)

In our population, only one patient was HBsAg positive (0.3%); this individual tested negative for HBV-DNA and exhibited normal LFTs results and thus was classified as an

Table 2 Distribution of the patients according to the Montreal classification.

CD (n=184)		UC (n=117)	
Age at diagnosis	*%*	*Extension*	*%*
A1 (≤16 years)	8.2	E1 (Ulcerative proctitis)	1.7
A2 (17–40 years)	72.3	E2 (Left-sided UC)	20.5
A3 (>40 years)	19.6	E3 (Extensive UC)	77.8
Location			
Location	*%*		
L1 (Terminal ileum)	27.7		
L2 (Colon)	15.7		
L3 (Ileocolon)	55.9		
L4 (Upper GI)	3.1		
Location			
Behavior	*%*		
B1 (Nonstricturing, nonpenetrating)	29.9		
B2 (Stricturing)	35.3		
B3 (Penetrating)	34.8		
P (Perianal disease)	27.7		

Table 3 IBD patient treatments.

	IBD (n=301)	CD (n=184)	UC (n=117)	P-value (CD vs. UC)
Anti-TNF-α[a]				
IFX (%)	239 (79.4)	123 (66.8)	116 (99.1)	P<0.001
IFX infusions (mean n. ± SD)	14.3 ±10.9	15.5 ±11.3	13.1 ±10.4	P=0.170
Duration of IFX therapy (months)	25.5 ±22.3	28.4 ±24.2	22.4 ±21.3	P=0.062
ADA (%)	91 (30.2)	84 (45.7)	7 (6)	P<0.001
ADA injections (mean n. ± SD)	33.7 ±21.1	34±21	30 ±23.2	P=0.838
Duration of ADA therapy (months)	15 ±10.8	15.2 ±10.7	12.7 ±11.7	P=0.864
CTZ (%)	5 (1.7)	5 (2.7)	–	–
CTZ injections (mean n. ± SD)	32 ±16.7	32 ±16.7	–	–
Duration of CTZ therapy (months)	32 ±16.9	32 ±16.9	–	–
Immunosuppressive therapies				
Azathioprine/6-MP (%)	172 (57.2)	104 (56.6)	68 (58.1)	P=0.943
Methotrexate (%)	24 (8)	13 (7.1)	11 (9.4)	P=0.466
Steroids (%)	162 (53.8)	63 (34.2)	99 (84.6)	P<0.001

[a]Some patients were consecutively treated with 2 or 3 anti-TNF-α agents.

inactive HBV carrier. Overall, 22 patients (7.3%) tested positive for anti-HBc antibodies. Seventy-two patients (23.9%) were effectively vaccinated for HBV. Only four patients were anti-HCV positive (1.3%); of these, only 1 had detectable levels of HCV-RNA. There were no statistically significant differences in the prevalence of HBV and HCV viral markers or in HBV vaccination rates between CD and UC patients (Fig. 2).

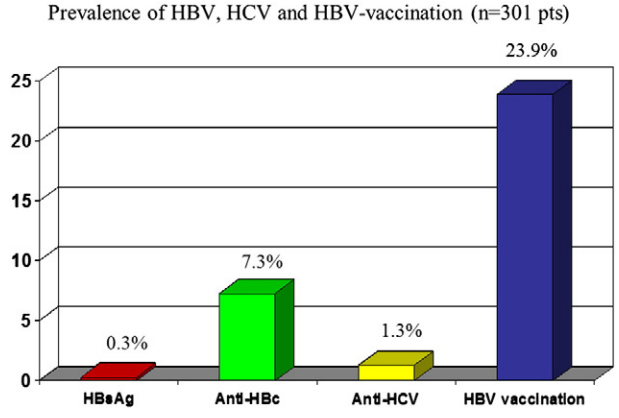

Figure 1 Prevalence of HBV markers (HBsAg and anti-HBc antibodies), anti-HCV antibodies and HBV vaccination in our cohort of patients (n=301).

3.4. Risk factors for HBV and HCV infections (Table 4)

For further analysis, the population was subdivided into three groups: a) patients with effective HBV vaccination (n=72), b) patients that exhibited positive HBV markers (n=23) and c) patients that were negative for HBV markers (n=206). We compared these three groups analyzing several variables: age at enrollment, age at diagnosis, disease duration, sex, previous surgery, immunosuppressant use and steroid treatment. We found that age at study enrollment, age at diagnosis and disease duration were significantly different among the three groups (P<0.001, P<0.001, and P=0.001, respectively). The three groups differ also for the prevalence rates of surgical interventions (P=0.012). Then, we evaluated whether baseline characteristics were possible risk factors for viral hepatitis, dividing our population into patients with or without serological evidence of HBV or HCV infections. We found that age at study enrollment (P<0.001) and at diagnosis (P=0.001) and disease duration (P=0.0018) were significantly associated with HBV or HCV infections. Sex (P=0.934), kind of IBD (CD or UC, P=0.962) and a previous surgical intervention (P=0.215) were not significantly associated with HBV or HCV infections.

3.5. Risk factors for nonvaccination for HBV

In univariate analysis the mean ages at diagnosis and at study enrollment of IBD patients with effective vaccination were significantly lower than in not vaccinated patients: 21.3±7 versus 35.4±12.4 years (P<0.001) and 28.2±7.5 versus 46.2±11.7 years (P<0.001), respectively. Disease duration was

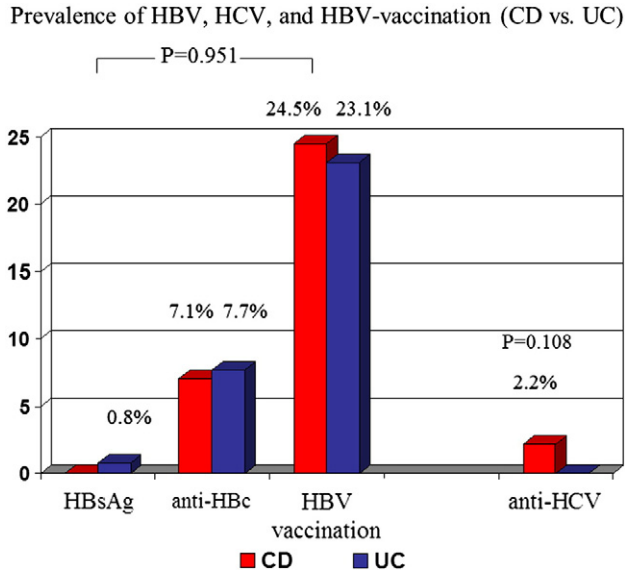

Figure 2 Comparison of the prevalence of HBV markers (HBsAg and anti-HBc antibodies), anti-HCV antibodies and HBV vaccination between Crohn's disease (CD) and ulcerative colitis (UC) patients.

Table 4 Factors associated with HBV vaccination or HBV infection.

	HBV Vaccination (n=72)	Positive HBV markers (n=23)	Negative HBV markers (n=206)	P value*
Age at inclusion (years)	28.2±7.5	54.4±12	45.3±11.3	P<0.001
Age at diagnosis (years)	21.3±7	42.2±14.6	34.6±11.9	P<0.001
Disease duration (years)	7±4.5	12.2±9.3	10.7±8.2	P=0.001
M (%)	35 (48.6)	9 (39.1)	98 (47.6)	P=0.815
Previous surgery (%)	28 (38.9)	15 (65.2)	116 (56.3)	P=0.012
Immunosuppressants (%)	43 (59.7)	13 (56.2)	128 (62.1)	P=0.931
Steroids (%)	41 (56.9)	14 (60.9)	107 (51.9)	P=0.469

*Comparisons among multiple groups were performed by one-way analysis of variance (ANOVA).

shorter in vaccinated than in not vaccinated patients: 7±4.5 versus 10.8±8.3 years (P<0.001). Also a previous surgical intervention was significantly less frequent in vaccinated patients (P<0.005). Sex (P=0.780) and kind of IBD (P=0.784) did not differ statistically between the two groups of patients. ROC analysis identified the following thresholds for continuous variables: age at diagnosis ≤24 years (likelihood ratio positive [LR+]=4.54, P<0.001), age at inclusion ≤31 years (LR+=13.86, P<0.001) and disease duration ≤10 years (LR+=1.43, P=0.001). In multivariate analysis age at inclusion >31 years (OR 0.029; 95% CI: 0.009–0.93, P<0.001) and age at diagnosis >24 years (OR 0.220; 95% CI: 0.079–0.615, P<0.004) were the only independent risk factors for not being vaccinated for HBV.

3.6. Safety of anti-TNF-α therapy in IBD patients with positive viral markers

During anti-TNF-α therapy, patients with positive HBV and HCV markers (23 with positive HBV markers and four HCV carriers) (Table 5) did not show any viral reactivation, which was defined as HBsAg detection in patients previously negative for HBsAg or HBV-DNA or HCV-RNA detection in patients with previously undetectable levels. Moreover, all patients with positive viral markers maintained normal LFTs results throughout the follow-up period. Only a 45-year-old woman with UC who tested HBsAg positive at study enrollment received prophylactic treatment for HBV. She started chemoprophylaxis with lamivudine (100 mg/day) a week prior to starting IFX treatment and continued on lamivudine until six months after stopping IFX therapy. This patient underwent a total coloproctectomy with ileo-anal pouch anastomosis for loss of responsiveness to IFX after 8 infusions. The only patient who was anti-HCV positive with detectable levels of HCV-RNA had HCV genotype 2b. He was affected by ileocolonic CD and had been on ADA for two years. He was previously treated with PEG-interferon plus ribavirin; however, this treatment was suspended after two months due to behavioral disorders. During ADA therapy, his serum levels of HCV-RNA were stable but consistently detectable; he also exhibited normal LFTs results.

4. Discussion

Patients with IBD have been considered to be at increased risk for nosocomial transmission of HBV and HCV infections. This hypothesis was confirmed by French and Italian studies that reported that IBD patients exhibited HBV and HCV infection rates greater than those of the general population.[1,2] Indeed, Biancone et al. reported that 10.9% of CD patients and 11.5% of UC patients tested positive for anti-HBc antibodies compared to 5.1% of controls (P=0.016 and P=0.02, respectively).[2] In the same study, the prevalence of anti-HCV antibody positive individuals was 7.4% in CD patients, 0.6% in UC patients and 5.1% in the controls.[2] A study conducted in 1998 in the south of France reported a prevalence rate of 5.98% for HCV infection in IBD patients.[1] In contrast with these older studies, our results show that both HBV and HCV infection rates are lower than those first reported in IBD patients; instead, HBV and HCV infection rates in IBD patients were comparable to or even lower than rates among the general Italian population. In fact, in our study, only one patient out of 301 (0.3%) was an HBsAg carrier, 22 (7.3%) were anti-HBc positive and only 4 were (1.4%) anti-HCV positive. These rates are similar to the findings of two epidemiological studies recently performed in Italy

Table 5 Features of patients with positive HBV and HCV markers and anti-TNF-α therapy.

	HBV-positive (n=23)[a]	HCV-positive (n=4)
Anti-TNF-α therapy		
IFX (%)	65.2	75
IFX infusions (mean n.±SD)	13.9±10	9.3±11.8
Duration of IFX therapy (months)	24.2±21.6	15±23.4
ADA (%)	30.4	50
ADA injections (mean n.±SD)	51.5±39.1	83.5±60
Duration of ADA therapy (months)	23.5±19.2	39±29.6
CTZ (%)	4.3	–
CTZ injections (mean n.±SD)	28	–
Duration of CTZ therapy (months)	35	–
Concomitant immunosuppressive therapy (%)	59.1	50
Concomitant steroids (%)	63.6	25

[a]One patient was both HCV and anti-HBc positive.

regarding the prevalence of HBV and HCV infections.[20,21] In the first study, carried out in a cohort of 965 subjects who were all residents of northern Italy, the HBsAg prevalence was 1%, and the overall prevalence of anti-HBc positive individuals (isolated or together with anti-HBs) was 12.6%; the prevalence of HCV was 2.6%.[20] In another survey that was conducted with 2195 residents of a southern Italian town, 2.6% of the population tested positive for anti-HCV antibodies. The overall prevalence rates for HBsAg and anti-HBc antibodies were 0.5% and 12%, respectively.[21] The lower prevalence rates of HBV and HCV infections found in our study compared to the earlier data[2] are likely due to recently introduced public health measures that include refinements in blood screening for transfusions, the use of universal precautions in medical settings and the effective implementation of a universal anti-HBV vaccination. In Italy, mandatory universal vaccination for HBV of neonates and 12-year-olds (for this latter group restricted to the first 12 years of application of the law) was introduced in 1991.[22] As a result of this policy, a generation of children and young adults (29-year age cohorts at present) is emerging that have almost no HBV infection markers.[23]

Similar findings were also reported in a recent (2006–2007) multi-institutional Spanish epidemiologic study of 2,076 IBD patients.[4] This study found that 0.8%, 8% and 1, 3% of UC patients tested positive for HBsAg, anti-HBc antibodies and anti-HCV antibodies, respectively. In CD patients, the investigators observed prevalence rates of 0.6%, 7.1% and 2.3%, for HBsAg, anti-HBc antibodies and anti-HCV antibodies, respectively.[4] Further confirmation of the changing epidemiology of HBV and HCV infections in IBD patients in Europe comes from two other studies conducted recently in France and Greece, where the prevalence of HBV and HCV infections was low and comparable to that of the general population.[3,5] However, epidemiological data on the prevalence of HBV and HCV infections in IBD patients from countries where preventive measures to reduce the incidence of viral hepatitis are not yet adequate differ radically from the data from European countries. In a recent study performed in Brazil on a population of 176 patients with IBD, 30 patients (17%) were anti-HBc positive, and four of these (2.6% of the sample) were HBsAg positive.[24] Another important issue addressed in this study concerns the rate of vaccination for HBV in patients with IBD. In recent years, leading scientific societies have published a number of recommendations and guidelines that propose routine screening for HBV infection at the time of IBD diagnosis followed by the subsequent vaccination of seronegative patients.[14–18] However, in our study population, the prevalence of HBV vaccination was only 23.9%, a result identical to the findings in the aforementioned epidemiological study performed in 2009 on a population from Northern Italy.[20] It is interesting to note that the average age of patients in this survey was similar to that of our cohort of patients (42.1 and 41.9 years, respectively). These results clearly indicate that in our population of IBD patients, the majority of the patients were vaccinated through mass vaccination campaigns introduced in Italy in 1991, rather than through intervention by gastroenterologists. Similar data are presented in a study by Loras et al., which showed that only 12% of IBD patients were effectively vaccinated against HBV.[4] The only other data currently available concerning HBV vaccination rates in IBD patients comes from a study by Cheavaux et al.[3] that reported a vaccination prevalence of approximately 49% in a population whose mean age was significantly lower compared to our population or the population examined in the Spanish study. HBV vaccination in patients with IBD is important because of the potential risk of infection reactivation during immunosuppressive therapy; in particular, therapy with biological agents such as anti-TNF-α antibodies poses a risk for infection reactivation.[7–11] For HBsAg carriers, recent guidelines from the European Crohn's and Colitis Organization (ECCO) recommend the prophylactic use of anti-viral drugs such as lamivudine during treatment with anti-TNF-α agents and for at least 6 months after treatment cessation.[14] For the so-called "occult" HBV carriers (anti-HBc+), active monitoring of LFTs results and serological markers during anti-TNF-α therapy is recommended to detect early signs of viral reactivation indicated by the reappearance of HBsAg and/or HBV-DNA.[14] The effectiveness of prophylaxis with lamivudine in preventing HBV reactivation in HBsAg carriers was confirmed by a recent meta-analysis of 21 studies that included patients who underwent chemotherapy for solid and blood tumors or for bone marrow and kidney transplant.[25]

The data from our study, although limited by the small number of HCV-positive patients, confirm the long-term safety of therapy with anti-TNF-α agents. In fact, we identified in our IBD population 23 patients positive for HBV markers and four positive for HCV markers (one patients was either anti-HBc and anti-HCV antibodies positive). They had been treated with anti-TNF-α agents for a mean period of approximately 24 months without developing any viral reactivation.

Finally, we would like to address the potential limitations of this study. The patients included represent a select population of IBD patients comprising only patients treated with biological therapy. However, this population is worth studying to accomplish the intended objectives of this study. Patients receiving biologic therapies represent a cohort of patients with a more aggressive disease course. Therefore, we can hypothesize that this population of patients would also be characterized by a greater number of hospitalizations, surgeries, blood transfusions and endoscopic examinations. Thus, epidemiological data on the prevalence of HBV and HCV in this cohort may be of interest. In conclusion, the results of this study demonstrate that the prevalence of HBV and HCV infections in a cohort of Italian patients with IBD does not differ from that of the general population. Rates of HBV and HCV infection were lower than those previously reported in an IBD population of the same origin. However, HBV vaccination rates were identical to that of the general population. These data suggest that more effort is needed to increase vaccination rates among IBD patients, which is recommended by international guidelines. In addition, the data obtained from this study confirm that treatment with anti-TNF-α agents is safe for patients that test positive for HBV markers provided that there is active surveillance for viral reactivation and that prophylactic anti-viral drugs are used when indicated. More data are needed regarding the long-term safety of anti-TNF-α agents in patients with HCV infection because of the low number of patients with HCV infection included in this study.

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Conflict of interest

None.

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