

Viral Hepatitis B during Chronic Inflammatory Bowel Diseases at Fez University Hospital: Prevalence and Risk Factors

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Abstract

Patients with chronic inflammatory bowel diseases (IBD) have long been considered at risk for viral hepatitis B. However, recent epidemiological studies have found similar prevalence, or even lower than in the general population. The objective of this work is to determine the prevalence of viral hepatitis B (HVB) during IBD, to determine the risk factors in the service of Hepato-gastroenterology of university hospital Hassan II-Fez, and of evaluate the impact on therapeutic management. **PATIENTS AND METHODS:** This is a retrospective study, spread over a period of 17 years and a half (January 2001-June 2017). All patients treated for IBD who are tested for Hbs Ag and anti Hbc were included. The HVB DNA levels were tested in case of positivity of HbsAg or anti Hbc. Results: Over the study period, 755 patients were included. The average age of our patients was 35 years [14 - 87] with a sex-ratio H/F of 0.67. We had 391 cases (51.8%) of Crohn's disease (CD) and 364 cases (48.2%) of ulcerative colitis (UC). Anti HBc test was positive in 1.98% of cases (N = 15). In these patients, HBsAg was positive in 1.19% of cases (N = 9). The prevalence of HVB was 2.55% in CD (N = 10) versus 1.37% in UC (N = 5). In our work, no history of surgery, digestive endoscopy or transfusion has been shown to be a risk factor for viral transmission. **CONCLUSION:** The prevalence of HVB in IBD is similar to that of the general population. The safety of blood transfusions and the improvement of asepsis probably explain these results. However, the risk of viral reactivation during HVB, sometimes fatal under immunosuppressive treatment, requires systematic screening.

Keywords

IBD, UC, CD, Hbs Ag, Ab Hbc, HVB DNA Levels, Prevalence, Viral Hepatitis

1. Introduction

Viral hepatitis B is a real public health problem. Each year, about 10 to 30 million new infections are reported. An estimated two billion people have been exposed to the hepatitis B virus (HBV), and 350 million is the number of chronic HBV carriers in the world [1] [2]. Each year, 1.2 million deaths are due to chronic viral hepatitis (HVB), cirrhosis and hepato-cellular carcinoma [2]. The global geographical distribution is very variable; it delimits three geographical categories according to the prevalence of the presence of the surface antigen of hepatitis B (Ag HBs). The disease is endemic in Africa, south of the Sahara, in the Amazon Basin, in Haiti and in the Dominican Republic [3]. Few studies have been done to estimate the prevalence of HVB in Morocco, a recent study conducted in the general population allowed to place Morocco among the low endemicity countries with a prevalence of carriage of HBs Ag estimated currently at 1.66% in active population [4]. Patients followed for IBD have long been considered at high risk of infection with hepatitis B virus [5], given the transfusion requirements and the frequent use of surgical treatment and to endoscopic procedures during the course of the disease [6] [7] [8]. During the past decade, the indications for immunosuppressive drugs (mainly azathioprine/mercaptopurine and methotrexate) and immunomodulators have continued to increase due to their clinical benefits. Their prescriptions are earlier and often prolonged. As a result, concerns about the safety of prescribing immunosuppressive drugs are becoming more and more important for professionals involved in the management of these patients. Among these concerns is the risk of reactivation of viral hepatitis B. Several cases of viral reactivation have been described under immunosuppressive treatment for IBD, sometimes complicated by severe or even fatal hepatitis [9] [10]. The carrier rate of HBV is not exactly specified in this group of patients in Morocco. The main objective of this study is to evaluate the prevalence of chronic HVB in patients treated for IBD in the Fez University Hospital, and to determine risk factors involved in the transmission of HBV infection.

2. Materials and Methods

This is a retrospective, analytical and descriptive study, spread over a period of 17 years and a half from January 2001 to June 2017 on the study of exploitable clinical records. All included patients had clinical, endoscopic, histological and/or radiological criteria for the diagnosis of IBD. All of these patients tested for HBsAg, anti HBc. The search and quantification of HBV DNA by PCR was only required in case of positivity of HbsAg or anti Hbc. Other serologies have been systematically requested: Syphilitic serology, HIV and the serology of viral hepatitis c (anti-HCV antibodies).

To identify possible risk factors for transmission of HBV infection in this population, we proceeded to the collection of clinical data and a history of blood transfusion, surgical and endoscopic interventions, acupuncture, tattoos, or dialysis from patients' medical records.

The statistical analysis of the data was done using Excel software and Epi Info 2007 for Windows. Descriptive analysis was performed using proportions calculations for qualitative variables (frequency, percentage), means, and standard deviations for quantitative variables. The different frequency comparisons were made using the Chi-square test (X²).

3. Results

During the study period, 755 patients followed for IBD were included. The average age of our patients was 35 years old with extremes ranging from 14 to 87 years old. A clear predominance of women was noted with a sex ratio H/F of 0, 67. We had 391 cases (51.8%) of Crohn's disease (CD) and 364 cases (48.2%) of ulcerative colitis (UC).

A history of surgery was noted in 19.75% of cases (N = 149), and 22.26% (N = 168) of our patients received a transfusion during the evolution of the disease. Of the patients included, 730 underwent endoscopic exploration (96.64%). The history of tattooing, dialysis or acupuncture has not been noted in any of our patients (**Table 1**).

Anti HBc test was positive in 1.98% of cases (N = 15) among them 67% (N = 10) cases of CD and 33% (N = 5) cases of UC. HBs Ag was positive in 1.19% (N = 9). The prevalence of HVB was 2.55% in CD (N = 10) versus 1.37% in UC (N = 5). The search and quantification of HBV DNA by PCR was tested in case of positivity of Ag Hbs or anti-Hbc Ab. It was undetectable in 67% of patients (N = 10) (**Table 2**).

In patients with positive HBsAg, HVB DNA level was undetectable in 07 patients. Immunosuppressive therapy was initiated in 04 patients with preemptive treatment with Tenofovir in one patient with Crohn's disease and Lamivudine switched after to Tenofovir in another patient with Crohn's disease. Virologic

Table 1. Risk factors for transmission of HVB.

Risk factors (N = 755)	N (%)
Blood transfusion	168 (22.26%)
surgery	149 (19.75%)
Digestive Endoscopy	730 (96.64%).
Dialysis	0
acupuncture	0
Tattoo	0

Table 2. Distribution of anti HBc, HBsAg and HVB DNA level by type of IBD.

IBD	AC HBc + n (%)	Ag Hbs + n (%)	PCR détectablen (%)
RCH (N = 364)	5 (1.37%)	4 (1.09%)	3 (0.8%)
MC (N = 391)	10 (2.55%)	7 (1.79%)	1 (0.2%)

markers were monitored without reactivation. Two other patients were placed on Telbuvudine and Lamivudine but they were lost of follow-up after 2 months of treatment. The other 03 patients were in remission under Mesalamine alone.

In the other four patients, HVB DNA level was > 2000 IU/ml. Two patients were put on the background treatment: the first on azathioprine and the second on anti-TNF after initiating respectively treatment with Lamivudine and Entecavir (**Figure 1**). The other 2 patients were in remission under Mesalamine alone and could not afford antiviral treatment. Viral reactivation was not noted during immunosuppressive therapy.

In patients with positive anti HBc and negative HBsAg, the HVB DNA level was undetectable in all our patients (n = 4). One patient of them was lost to follow-up. No patient received antiviral treatment. Immunosuppressive therapy (Azathioprine) was initiated in one patient and immunomodulator in one other with surveillance of virologic markers. The others patients were on remission under mesalamine. No case of HBV reactivation was noted after an average follow-up of 18 months.

In our work, it has been observed that the type of the disease, age, sex, history of surgery, transfusion or digestive endoscopies are not considered as risk factors for transmission of HBV infection (**Table 3**).

4. Discussion

In Morocco, some studies are interested in estimating the prevalence of HVB; they have been performed in blood donors, Healthcare workers, or at-risk patients with prevalence ranging from 1% to 15% [12] [13] [14] [15]. A recent

Table 3. Risk factors for HBV infection.

Risk factors		Anti-HBC				<i>p</i>
		Positive		Négative		
		n	%	n	%	
Age	<50 ans	11	85.7	648	85.9%	0.8008
	>50 ans	4	14.3	107	14.1%	
Sex	Masculin	6	42.85	304	40.26%	0.7773
	Féminin	9	57.15	451	59.74%	
IBD	MC	10	57.15	391	51.8%	0.4259
	RCH	5	42.85	364	48.2%	
surgery	Oui	1	14.3	150	19.9%	0.8459
	NON	14	85.7	605	80.1%	
Transfusion	Oui	4	28.57	167	22.07%	0.2618
	NON	11	71.43	588	77.93%	
Digestive endoscopy	OUI	15	100	729	96.54%	0.9704
	NON	0	0	26	3.46%	

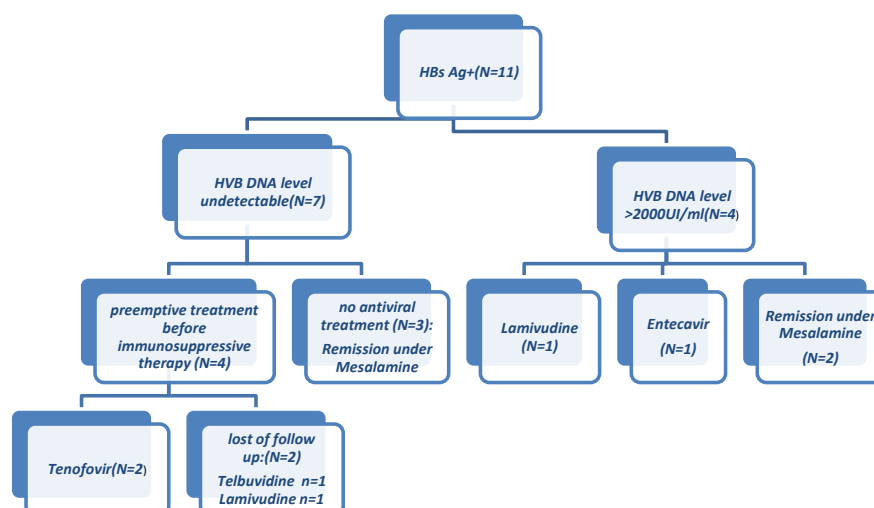


Figure 1. Strategy of care of our patients with Ag Hbs+.

study in the general population made it possible to place Morocco among the low endemicity countries with a prevalence of carriage of HBsAg estimated at 1.66% in the active population [4].

In our study, the prevalence of HVB in patients followed for IBD was similar to that observed in the general population, or 1.98% joining recent data from the literature. In a multicenter Spanish study including 2076 patients with IBD, the prevalence of hepatitis B biomarkers was similar to the general Spanish population: less than 1% of IBD patients had HBsAg and less than 10% had anti HBc positive. Similar results have also been published in a recent study in France [16] [17]. Contrary to the results observed in our work, no difference in the prevalence of HVB was noted between the patients presenting with UC and those followed for MC. Several previous studies reported in the literature, have shown a prevalence of HBV infection relatively higher than that of the general population, thus considering patients followed for IBD at high risk of HVB infection [18] [19]. Biancone *et al.* [19] reported a higher prevalence of anti- HBc in Italian patients with MC (10.9%, $p = 0.016$) and UC (11.5%, $p = 0.02$) compared to the control group (5.1%). The risk of viral hepatitis in patients followed for IBD has been associated with blood transfusions and surgery, suggesting nosocomial transmission of the virus [19] [20]. In our work, neither the history of transfusion nor surgery has been shown to be a risk factor for infection. During these last few years, studies, verifying the possibility of transmission of HVB or HVC mainly following therapeutic endoscopic procedures, have shown the presence of HBV DNA in the channels of endoscopes that have not been submitted to appropriate disinfection procedures [21]. Among our patients, 96.64% ($N = 730$) had at least one gastrointestinal endoscopy without being shown to be a risk factor for infection ($p = 0.9704$).

A clear predominance of women was noted in our work corresponding to 60% of patients. Statistical analysis did not show a statistically significant difference

between the two sexes regarding the positivity of anti-HBc ($p = 0.7773$). In contrast to results reported by Biancone *et al.*, who found that females were a risk factor for HBV infection [19].

Some studies have shown that corticosteroids, immunosuppressive therapy and immunomodulatory therapies may influence the course of liver disease in patients treated for IBD and who are HBV-infected, especially inactive carriers [22] [23] [24]. Fatal viral reactivations have been described in patients with IBD or other autoimmune diseases treated with immunosuppressive therapy [9] [10]-[25].

For patients with resolved HBV infection, a viral reactivation, occurring up to 40% of cases, has been reported after chemotherapy [26] [27] [28] [29]. Although the risk during IBD appears to be much lower, a case of reactivation after infliximab therapy in a patient followed for MC and having occult HBV infection has been reported [26]. Indeed, immunosuppression induced by these drugs can cause viral replication and spread of infection within hepatocytes. When these drugs were suspended and the immunological reaction was reestablished, the infected hepatocytes rapidly destroyed with an increase in transaminase levels ("flare") and a reduction in viremia [30] [31]. Given the risk of viral reactivation, and the availability of drugs effective against HBV, screening measures are necessary. The American Association for the Study of Liver Diseases (AASLD) recommends screening for HBV for patients requiring immunosuppression, including patients with IBD [32]. HBV testing should be done at the time of diagnosis [32].

The AASLD [32] and the European Association for the Study of the Liver (EASL) [33] recommend the early introduction of nucleoside or nucleotide analogues for any HBsAg positive patient. Prophylaxis for HBV should be initiated at least 7 days before therapy and should be maintained for 6 months to 1 year after completion of therapy. The European Crohn's and Colitis Organization (ECCO) [34] also recommend early introduction of analogues in patients with IBD and HBsAg positive requiring immunosuppression, regardless of the number and type of immunosuppressive therapy. However, it must be started between one and three weeks before the introduction of immunosuppressive therapy and maintained for 6 months after stopping [33] [34].

In patients with resolved hepatitis B (Hbc positive, HBs Ag negative), routine use of antiviral prophylaxis in IBD patients is not recommended [35] [36] [37]. This approach differs from the recommendations for chemotherapy patients and in particular for Rituximab, where antiviral prophylaxis is recommended [36] [37] [38]. Nevertheless, careful and constant monitoring of virologic markers, including HBV DNA, is required in these patients during treatment for the early recognition of viral reactivation and early stage analogue therapy [38].

In sero-negative patients, vaccination must be mandatory. Because HBV vaccine is inactivated, immunosuppressive drugs are not a contraindication. On the other hand, the effectiveness of this vaccination under immunosuppressive

therapy is uncertain. The serological response should therefore be measured to give a booster dose if needed [34].

5. Conclusion

In our study, the prevalence of HVB in IBD is similar to that of the general population. The statistical study did not demonstrate specific risk factors. The safety of blood transfusions and the improvement of asepsis probably explain these results. However, the risk of viral reactivation during HVB, sometimes fatal under immunosuppressive therapy, requires systematic screening. Therefore, antiviral prophylaxis is recommended in all positive HBsAg patients. Patients with resolved viral infection require virologic marker monitoring. Vaccination of seronegative patients is mandatory, given the risk of HBV contamination and its potential consequences.

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