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Effect of immunosuppressive therapy on patients with inflammatory bowel diseases and hepatitis B or C virus infection

F. Morisco,[1] F. Castiglione,[1] A. Rispo,[1] T. Stroffolini,[2] S. Sansone,[1] R. Vitale,[1] M. Guarino,[1] L. Biancone,[3] A. Caruso,[4] R. D'Inca,[4] R. Marmo,[5] A. Orlando,[6] G. Riegler,[7] L. Donnarumma,[1] S. Camera,[1] F. Zorzi,[3] S. Renna,[6] V. Bove,[7] G. Tontini,[8] M. Vecchi[8] and N. Caporaso[1] [1]*Clinical and Experimental Medicine, Gastroenterology Unit, University of Naples 'Federico II', Naples, Italy;* [2]*Department of Infectious and Tropical Diseases, University 'La Sapienza', Rome, Italy;* [3]*Gastroenterology Unit, University of Rome 'Tor Vergata', Rome, Italy;* [4]*Gastroenterology Unit, University of Padova, Padova, Italy;* [5]*Gastroenterology Unit, Polla Hospital, Polla, Italy;* [6]*Palermo Hospital 'V. Cervello', Palermo, Italy;* [7]*Gastroenterology Unit, Second University of Naples, Naples, Italy; and* [8]*Gastroenterology and Gastrointestinal Endoscopy Unit, IRCCS Policlinico San Donato & University of Milan, Milan, Italy*

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SUMMARY. Viral hepatitis reactivation has been widely reported in patients undergoing immunosuppressive therapy; however, few data are available about the risk of HBV and HCV reactivation in patients with inflammatory bowel disease, receiving immunosuppressive drugs. The aim of our study was to assess the prevalence of HBV and HCV infection in a consecutive series of patients with inflammatory bowel disease and to value the effects of immunosuppressive therapy during the course of the infection. Retrospective observational multicenter study included all consecutive patients with inflammatory bowel disease who have attended seven Italian tertiary referral hospitals in the last decade. A total of 5096 patients were consecutively included: 2485 Crohn's disease and 2611 Ulcerative Colitis. 30.5% and 29.7% of the patients were investigated for HBV and HCV infection. A total of 30 HBsAg positive, 17 isolated anti-HBc and 60 anti-HCV-positive patients were identified. In all, 20 patients with HBV or HCV infection received immunosuppressive therapy (six HBsAg+; four isolated anti-HBc+ and 10 anti-HCV+). One of six patients showed HBsAg+ and one of four isolated anti-HBc+ experienced reactivation of hepatitis. Two of six HBsAg patients received prophylactic therapy with lamivudine. Only one of 10 anti-HCV+ patients showed mild increase in viral load and ALT elevation. Screening procedures for HBV and HCV infection at diagnosis have been underused in patients with inflammatory bowel disease. We confirm the role of immunosuppressive therapy in HBV reactivation, but the impact on clinical course seems to be less relevant than previous reported.

Keywords: antivirals, biological agents, HBV reactivation, HCV reactivation, prophylaxis.

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic immune-mediated inflammatory bowel diseases (IBD) of an unknown aetiology. Traditional immunosuppressors, mainly azathioprine/6-MP, methotrexate and ciclosporin, represent an important therapeutic option for patients affected by steroid-dependent or steroid-refractory IBD, with an overall efficacy of about 50% [1–3].

Abbreviations: IBD, inflammatory bowel disease; IT, immunosuppressive therapy; CD, Crohn's disease; UC, Ulcerative Colitis; HBV, hepatitis virus B; HCV, hepatitis virus C; TNF-a, tumour necrosis factor alpha; UNL, upper normal limit.

Correspondence: Filomena Morisco, Department of Food Science, Parco Gussone Ed 84, 80055 Portici (Na), Italy.
E-mail: filomena.morisco@unina.it

It is now well known that (immunosuppresive therapy) IT can be associated with a number of severe adverse events, such as the development of particular malignancies (i.e. EBV-related lymphoma) [4], severe opportunistic infections, and reactivation of chronic viral hepatitis infection, therefore, the need for a careful follow-up is mandatory in these patients [5,6].

In the last decade, this topic has been gaining much scientific interest after the widespread therapeutic use of the tumour necrosis factor alpha (TNF-α) inhibitors. These biological drugs, characterized by strong immunosuppressive properties, have shown a significant clinical benefit in the management of severe IBD. In particular, infliximab and adalimumab demonstrated high efficacy in patients with IBD by not responding to steroids and/or to conventional immunosuppressors [7–9].

The use of anti-TNFα has been associated with a high risk of developing HBV reactivation. To date, literature

data have reported nine patients with IBD infected with HBV (eight HBsAg+ inactive carriers and one occult infection with isolated positivity for anti-HBc) who have experienced reactivation during and after treatment with anti-TNFα [10–17]. In this context, HBV reactivation has ranged from self-limiting anicteric relapse to severe hepatitis, up to liver failure and death. In addition, Loras *et al.* [18] observed six cases of hepatic failure in a series of 25 HBsAg patients, undergoing various types of immunosuppressants.

On the other hand, the effect of conventional immunosuppressive drugs does not appear to be associated with high risk of HBV reactivation even if it has been less largely investigated. In fact only three cases of reactivation, which resulted in hepatic failure in two of them during conventional immunosuppressive therapy, such as prednisolone and/or azathioprine, are reported in literature [19,20].

The data regarding the effects of IT in patients with HCV infection differ from those observed in patients with HBV. In fact in immunocompromized patients, the frequency and severity of hepatitis C (HCV) reactivation also appears to be much lower in an onco-ematological setting that uses high levels of immunosuppression [21]. In addition, anti-TNF therapies have been successfully used as adjuvant therapy in patients undergoing specific antiviral treatment for HCV infection with ribavirin and interferon [22]. Thus far, even if a large amount of information concerning the relationship between IT for IBD and the behaviour of HBV/HCV infections are becoming more available, the impact of different immunosuppressants on the risk of reactivation remains poorly investigated.

The aims of this multicenter study were as follows: to estimate the prevalence of HBV and HCV infection in a consecutive series of patients with IBD who have been observed in the last decade in Italy; to evaluate the effect of conventional and biological IT on the course of HBV and HCV infection in this series of patients; and to identify the risk factors for viral reactivation.

MATERIALS AND METHODS

Study design and target population

This is a retrospective, observational, multicenter, nationwide study carried out in seven Italian tertiary referral centres specialized in the diagnosis and treatment for IBD selected on the basis of voluntary participation. The geographical distribution of the centres was representative of the whole Country (two in Northern Italy, one in Central Italy, three in Southern Italy and one in Sicily).

The target population consisted of all adult (>18 years) consecutive patients with IBD observed in the seven referral centres from 1 January 2000 to 31 December 2008. Among these, all patients with HBV or HCV infection were selected for the inclusion in the study.

Definition of HBV and HCV infection

Hepatitis virus B infection was defined according to the National Institute Health Conference on Management of hepatitis B [23] as subjects positive for HBsAg, independently from the e-/anti-e positivity and the levels of HBV-DNA.

Subjects with positivity for anti-HBc and concomitant HBsAg and anti-HBs negativity were considered as a potential occult infective category and analysed for the same parameters as the HBsAg-positive patients [24].

Hepatitis virus C infection was defined as subjects positive for anti-HCV with or without positivity for HCV-RNA.

Definition of HBV and HCV reactivation

In HBV-positive patients, the following virological events were considered significant: (i) in HBsAg-positive patients (active or inactive carriers), the increase of at least one logarithm of HBV-DNA with or without the concomitant increase of transaminases; (ii) in isolated anti-HBc positive, the re-emergence of HBsAg or appearance or increase at least one logarithm of HBV-DNA. In viremic patients, reactivation of HCV was defined as a significant increase of HCV-RNA (at least one logarithm) with or without a concomitant increase of transaminases.

In anti-HCV-positive but HCV-RNA-negative patients, the appearance of HCV-RNA has been considered as a relevant event.

Definition of liver disease

The diagnosis of HBV inactive carrier was based on normal serum ALT and HBV-DNA <2000 UI/ml.

The diagnosis of chronic hepatitis was based on ALT levels (over the UNL) and HBV-DNA >2000 UI/mL.

The diagnosis of cirrhosis was established by histology (Ishak score of 6, Knodell score of 4 and METAVIR score of 4) or by unequivocal clinical picture and imaging technique results.

Categorical data

Demographical, clinical, biochemical, histological, virological and therapeutic data were collected from medical records by case report form. Results were expressed as means (SD), medians and percentages, as appropriate.

Ethical consideration

This study was independently designed by the authors, conducted in compliance with the 1975 Declaration of Helsinki and approved by the Ethic Committee of each participating centre.

RESULTS

Patients population

A total of 5096 patients with IBD were consecutively included in the study: 2485 CD and 2611 UC. The number of patients included for each centre ranged from 268 to 1750.

In total, 1556 (30.5%) and 1513 (29.7%) patients among the overall IBD population were investigated for HBV and HCV markers, respectively. The percentage of patients tested for HBV or HCV for each hospital ranged from 10.7% to 49.2%. The percentage of patients investigated for HBV and HCV, respectively, in CD and UC group is reported in Table 1. A positive serology for both HCV and HBV infection was found in 107/3069 (3.48%) of the cases. A total of 30 HBsAg-positive, 17 isolated anti-HBc and 60 anti-HCV-positive patients were identified.

HBV infection

In total, 30/1556 patients (1.92%) had a positive serology for HBsAg and 17/1556 (1.09%) for isolated anti-HBc. The main features of the 30 subjects with HBsAg positivity are reported in Table 2. Thirteen patients were affected by CD (nine men and four women, mean age 40.8 years) and 17 by UC (12 men and five women, mean age 39.7 years). Three patients were HBeAg positive and 27 showed 'e minus' infection. Twenty-two were inactive carriers, while eight had chronic hepatitis. None of them showed signs of cirrhosis. No coinfection HBV/HDV was observed.

Seventeen patients were positive for isolated anti-HBc (nine men and eight women, mean age 40.6 years). Two patients with isolated anti-HBc positivity showed concomitant anti-HCV positivity. All patients had normal aminotransferase levels and no data on basal HBV-DNA levels were available.

Among patients with HBV, overall, 10 underwent IT (six HBsAg+ and four with isolated anti-HBc). The principal characteristics of the six HBsAg-positive patients undergoing IT are reported in Table 3. Two of six HBsAg-positive patients were previously treated with Lamivudine prophylaxis. Among the four, the ones who were HBsAg positive were treated with immunosuppressive therapy without prophylaxis, one received azathioprine (2 mg/kg/day) together with infliximab (5 mg/kg i.v. at 0, 2, and 6 weeks), 2 received methotrexate (15 mg/week i.m) and one was given chronic therapy with cyclosporine (100 mg/day) for concomitant kidney transplantation. One inactive HBsAg carrier experienced reactivation of HBV hepatitis, with increase in ALT levels of 2.5-fold the upper normal limit and of HBV-DNA from negative to 10^5 UI/mL (see Table 3). The episode of reactivation occurred after only 2 weeks of immunosuppressive treatment in the only HBsAg-positive patient receiving two simultaneous drugs (infliximab and azathioprine), without antiviral prophylaxis.

Four isolated anti-HBc-positive patients received IT and none of these were preventively treated with lamivudine prophylaxis. The schedules of treatment and the main characteristics of the episode of reactivation are reported in Table 4. One patient showed a severe episode of reactivation with flare of ALT (10-fold the UNL) and reappearance of HBsAg [12]. In this case, the episode of reactivation was observed very early after the start of two concomitant immunosuppressive drugs (infliximab and steroids). Given the low rate of reactivation, no additional analysis for risk factors was performed.

Table 1 Numbers and percentage of patients investigated for HBV and HCV infection in study population. The data are shown in relation to type of inflammatory bowel disease

	Observed	Tested for HBV (%)	Tested for HCV (%)
CD	2.485	910 (36.6)	875 (35.2)
UC	2.611	646 (24.7)	638 (24.4)
Total	5.096	1.556 (30.5)	1.513 (29.7)

CD, Crohn's disease; UC, Ulcerative Colitis; HBV, hepatitis B virus; HCV, hepatitis C virus.

HCV infection

In total, 60/1513 patients (3.96%) had a positive serology for anti-HCV.

The principal characteristics of the 60 subjects with anti-HCV positivity are illustrated in Table 5. Thirty-one patients were affected by CD (19 men and 12 women, mean age 38.9 years) and 29 by UC (19 men and 10 women, mean age 41.4 years).

Among these, 60 anti-HCV patients, 10 underwent IT (all with CD). The primary characteristics of the 10 patients treated with IT are reported in Table 6. Seven received azathioprine (2-mg/kg/day), four in monotherapy, one combined with infliximab (5mg/kg i.v. at 0, 2, and 6 weeks), one associated with adalimumab and one with methotrexate and infliximab. The last patient was also subsequently treated with adalimumab.

Of the three remaining patients, one received infliximab (5 mg/kg i.v. at 0, 2, and 6 weeks), one received an endoscopic injection of infliximab on pre-anastomotic ileal recurrence and one received adalimumab (induction regimen 160/80 mg/s/every other week, maintenance regimen 40 mg/s/every other week).

Only 1/10 patient showed 2.6-fold increase in HCV-RNA levels, with elevation of ALT (2.5 times the upper normal limit), see Table 6.

Table 2 Principal characteristics of the 30 HBsAg-positive patients

	Sex	Age at diagnosis	IBD type	HBeAg+ status	HBV-DNA (UI/mL)	Status of HBV disease	Immunosuppressive therapy
1	F	38	CD	Neg	$<10^3$	IC	No
2	M	47	CD	Neg	$<10^3$	IC	Ciclosporin*
3	M	54	CD	Neg	$<10^3$	IC	No
4	M	60	CD	Neg	10^5	CH	No
5	M	45	CD	Neg	Pos	CH	No
6	F	56	CD	Neg	NDA	IC	No
7	M	26	CD	Neg	Neg	IC	AZT + IFX
8	M	24	CD	Pos	Pos	CH	No
9	M	45	CD	NDA	NDA	IC	No
10	F	52	CD	Neg	NDA	IC	Mtx
11	F	26	CD	Neg	NDA	IC	IFX
12	M	18	CD	Neg	Pos	IC	No
13	M	40	CD	Neg	NDA	IC	No
14	M	43	UC	Pos	Pos	CH	No
15	F	41	UC	Neg	Pos	CH	No
16	M	40	UC	Neg	Pos	IC	No
17	M	52	UC	Neg	270.140	CH	Mtx + IFX
18	M	33	UC	Neg	Neg	IC	No
19	M	26	UC	Pos	10^5	CH	No
20	F	36	UC	Neg	3.5×10^3	CH	No
21	M	24	UC	Neg	Neg	IC	No
22	F	44	UC	Neg	Neg	IC	No
23	M	60	UC	Neg	NDA	IC	No
24	M	38	UC	Neg	<103	IC	No
25	F	73	UC	Neg	Neg	IC	No
26	M	24	UC	Neg	Neg	IC	Mtx
27	M	27	UC	Neg	Neg	IC	No
28	M	53	UC	Neg	Neg	IC	No
29	M	15	UC	Neg	Neg	IC	No
30	F	46	UC	Neg	Neg	IC	No

Legend: -NDA, no data available; Neg, negative; Pos, positive.
IBD type: CD, Crohn's disease; UC, Ulcerative Colitis.
Status of HBV disease: IC, inactive carrier; CH, chronic hepatitis.
Azt, Azathioprine; Mtx, Methotrexate; Ifx, Infliximab.
*kidney transplanted patient.

In this last case, the reactivation was observed in a patient with single immunosuppressive drug (azathioprine). No biochemical reactivation or significant increase in HCV-RNA was observed in the remainder of the cases.

It is worth noting that no case of HCV-RNA appearance or ALT increase occurred in anti-HCV+/HCV-RNA-negative patients.

Given the low rate of reactivation, no additional analysis for risk factor was performed.

DISCUSSION

The reactivation of viral hepatitis, in particular HBV disease, has been widely reported in patients undergoing IT in different clinical conditions with particular frequency and severity in onco-haematological and transplant settings [25–27].

Differently, few data are available on the risk of HBV and HCV reactivation in patients with IBD receiving IT [18,28]. Nevertheless, the questions regarding the optimal management (screening, prevention, monitoring and therapy) of immunosuppressed patients with IBD with HBV infection remain to be addressed.

Our study analyses the clinical course of HBV and HCV infection in a large series of consecutive patients with IBD observed in the last decade in seven referral centres in Italy, even if the retrospective design of the study could limit the accuracy of some findings.

Patients with IBD are considered at risk of viral infections because of the frequent need of invasive proce-

Table 3 Clinical behaviour of the six HBsAg-positive patients undergoing immunosuppressive therapy

No.	IBD	Immunosuppressive drugs	Duration therapy (weeks)	Prophylaxis	Episode of reactivation	Reactivation			Therapy
						Time	ALT (× UNL)	HBV-DNA (UI/mL)	
1	CD	Ciclosporin	52	No	No	–	–	–	–
2	CD	Azt Ifx	2	No	Yes	4 weeks	2.5	2×10^5	None
3	CD	Mtx	NDA	No	No	–	–	–	–
4	CD	Ifx	400	Yes	No	–	–	–	–
5	UC	Mtx	136	No	No	–	–	–	–
6	UC	Mtx Ifx	35	Yes	No	–	–	–	–

CD, Crohn's disease; UC, ulcerative Colitis; Azt, azathioprine; Mtx, methotrexate; Ifx, infliximab; NDA, no data available.

dures; nonetheless, the prevalence of HBV and HCV infection in patients with IBD has been recently reported to be similar to the prevalence of the general population of Western European Countries (Spain and France) [29,30]. In Italy, the prevalence reported by a single study performed in patients observed between 1997 and 1999 was relatively higher and specifically 2.1% for HBV and 7.4% for HCV [31]. No thorough information is available in literature and the true prevalence is unknown at present in Italy. Recently, in a cohort of patients treated with anti-TNF-alfa agents, the prevalence of HBsAg (0.3%) and anti-HCV (1.3%) was similar to the general population [32]. Unfortunately, our study does not resolve the question because only 30% of the study population has been investigated for HBV/HCV infection. The result appears to be in contrast with the emerging consensus regarding the universal screening procedure at least for HBV infection [24] and must be evaluated in the context of recent knowledge, concerning the risks related to intensive IT. In fact, the risk of viral reactivation in immunosuppressed patients has been well established only in recent years (half of the 2000') compared to the total period of observation analysed in our study (2000–2008). In our series, we found an infection rate of 1.92% for HBV and of 3.96% for HCV, even though the low screening-percentage limits the possibility of an adequate estimate of the prevalence.

In this perspective, the recent guidelines of EASL (European Association of the Study of the Liver), of the ECCO (European Crohn's and Colitis Organization) and of the IG-IBD (Italian Group for the Study of Inflammatory Bowel Disease) recommend that all patients with IBD should be investigated for HBsAg, HBcAb and HBsAb to assess the infection or vaccination status [6,33]. Moreover, HBV vaccination is recommended in all sero-negative patients. This approach seems to be appropriate considering the wide range of HBV infection in Europe (from <1% in Western countries to >5% in Eastern Europe) and the persistent low implementation of HBV vaccination in the population of Western Europe as reported in recent papers [29,30,32]. The need of a universal screening procedure and vaccination at time of diagnosis is supported by the consideration that severe hepatitis B reactivation seems to be frequent when IT is carried out.

Hepatitis virus B reactivation during IBD immunosuppression has been reported in literature as case reports [10–16], and only one prospective case series study of patients with HBV/HCV infection is available [18].

Differently, our study population, with retrospective but consecutive enrolment of all patients with CD and UC referred to the participating centres, represents the Italian IBD population observed in referral centres in the last decade.

We observed 1/4 (25%) episodes of reactivation in HBsAg patients undergoing biological IT when prophylaxis therapy was not used. Although this percentage is lower than that observed in inactive HBV carriers (50%) using chemotherapy for solid tumours (50%) [25,34], the rate observed remained decisively high.

From a pathogenetic point of view, the risk of HBV reactivation is closely related to the levels and type of immunosuppression, and in general, the levels of immunosuppression required for the control of IBD are less relevant than that used in onco-haematological and transplant settings.

In our series of HBV-positive cases, the reactivation occurred when anti-TNFα agents were combined with other immunosuppressants. In particular, the only episode of reactivation observed was associated with the contemporary use of infliximab and azathioprine. This observation agrees with the results of Loras *et al.* [18] who reported an increased risk of reactivation in patients with IBD treated with combined IT [10–12,14–16].

We did not observe episodes of reactivation in patients receiving only one immunosuppressant or treated by

Table 4 Clinical behaviour of the four isolated anti-HBc-positive patients undergoing immunosuppressive therapy

No.	IBD	Immunosuppressive drugs	Duration therapy (weeks)	Prophylaxis	Reactivation	Reactivation			
						Time	ALT (× UNL)	HBV-DNA (UI/mL)	Therapy
1	CD	Azt Ifx Adb	1 (2005) 2 (2008) 2009->to now	No	No	–	–	–	–
2	CD	Azt Ciclosporin Ifx	12 (2003) 104 (1997) 46 (2003)	No	No	–	–	–	–
3	CD[12]	Azt (intolerance) Ifx Mtx (Sd) Ifx + Steroids (25 mg/days)	4 (2001) 28 (2001) 8 (2004) 4 (2004)	No	Yes	Within 1 month from starting Ifx+ Steroids	10	+	Lamivudine
4	UC	Ifx	32 (2008)	No	No	–	–	–	–

CD, Crohn's disease; UC, ulcerative Colitis; Azt, azathioprine; Mtx, methotrexate; Ifx, infliximab; Adb, adalimumab; NDA, no data available; Sd, standard dose.

conventional IT. Furthermore, to date, no episodes of reactivation have been reported in literature in patients using adalimumab as monotherapy in IBD.

The conventional/non-biological immunosuppressive drugs (azathioprine, methotrexate, ciclosporin) determine lower levels of immunosuppression in comparison with TNF-α inhibitors, but scarce information is available on their effects in the IBD setting and on their risk to induce HBV reactivation. Three recent case reports of HBV reactivation (two with virological flare and liver dysfunction and one with fulminant hepatic failure) have been reported in literature [19,20], during a conventional therapeutic schedule (combined therapy with prednisone and azathioprine in two of three cases). Therefore, with the lack of specific studies on this topic, it is very difficult to make an assessment of the risk of reactivation during conventional immunosuppression.

We observed one episode of reactivation in the four patients with isolated HBcAb+. The episode of reactivation occurred early after the start of therapy (4 weeks), again during combined therapy (infliximab and steroids) and with the increase in aminotransferases together with the HBsAg and HBV-DNA emergence. This is the case already described in literature [12] and, to our knowledge, remains the only case of reactivation reported in HBsAg-negative/HBcAb-positive patients in IBD setting.

The risk of reactivation for the category of isolated HBcAb+ is controversial and seems to be related to the clinical setting and type of immunosuppression. There are several reported cases of HBV reactivation in HBcAb+ subjects with and without concomitant HBsAb positivity in patients who have undergone bone marrow transplantation or cytotoxic chemotherapy for lymphoma [26], with reactivation ranging from 12% to 50% [24]. In these patients, the use of intense immunosuppression, monoclonal antibodies anti-lynfphocyte B and T (anti-CD20) are particularly considered as risk factors. Conversely, in other clinical settings (reumathology, dermatology ect.), the anti-HBc+ isolated subjects seem to be at low risk of reactivation [35–37].

Unfortunately, in our retrospective analysis, the anti-HBs measurement was available in only a few patients. This limit, even if not very significant in this series, did not allow us to come up with an adequate evaluation for the risk of reactivation in this subset of patients.

Although the majority of reported episodes of HBV reactivation occur at the time of immune reconstitution (when immunosuppression is stopped), in our series, the two events occurred after only 1 month of therapy, showing mild severity and absence of liver failure. The early HBV reactivation is usually a severe clinical condition related to a massive viral replication with frequent fatal consequences. However, the episodes observed in our series seem to be light and rapidly well controlled by the antiviral therapy. It is possible that the different

Table 5 Principal characteristics of 60 anti HCV-positive patients in relation to type of inflammatory bowel disease

	anti-HCV+ No. 60	
	CD	UC
No. of patients	31	29
Gender M/F	19/12	19/10
Mean age at diagnosis (years) (range)	38.9 (12–60)	41.4 (16–66)
HCV-RNA (UI/mL)	41.000–3.540.000	37.700–2.780.000
Genotype 1, 2, 3, 4 (%)	60, 30, 5, 5	57, 32, 7, 4
ALT × UNL (range)	0.4–2.0	0.3–6.0

CD, Crohn's disease; UC, ulcerative Colitis.

Table 6 Clinical behaviour of the 10 anti-HCV-positive patients undergoing immunosuppressive therapy

No.	IBD	Immunosuppressive drugs	Duration (weeks)	Reactivation	Time	ALT (× UNL)	HCV-RNA (UI/mL)
1	CD	Local IFX	NDA	No	–	–	–
2	CD	AZT	288	No	–	–	–
3	CD	AZT + IFX	56	No	–	–	–
4	CD	IFX	18	No	–	–	–
5	CD	AZT	155	Yes	2007	4	2.25×10^6 *
6	CD	AZT	184	No	–	–	–
7	CD	AZT	52	No	–	–	–
		MTX	104				
		IFX	156				
		ADA	2				
8	CD	AZT	260	No	–	–	–
9	CD	AZT	NDA	No	–	–	–
		ADA	125				
10	CD	ADA	132	No	–	–	–

CD, Crohn's disease; UC, ulcerative Colitis; Azt, azathioprine; Mtx, methotrexate; Ifx, infliximab; NDA, no data available; IBD, inflammatory bowel disease.
*Basal HCV-RNA 850.000 UI/mL

magnitude of immunosuppression and a different grade of underlying liver damage have determined a different clinical course [18].

It is possible to hypothesize that the flares observed after IT suspension may have a more unfavorable clinical outcome because of the progressively increased viral replication during immunosuppression. As consequence, an higher number of hepatocytes dies when the restoration of immunological response occurs.

Overall, in patients with HCV infection, the use of IT appears to determine lower frequency and severity of viral reactivation than in HBV [18,38]. This finding is confirmed in this study.

In our series of 10 anti-HCV+/HCV-RNA+ patients undergoing IT, we observed only one patient with significant increase in viral load, but not reaching the criteria for reactivation (≥ 1 log elevation). This event was associated with very mild liver dysfunction (ALT 2.5-fold the UNL). The episode was observed after a long period of treatment (about 36 months) with azathioprine alone.

In conclusion:

1. To date, the real HBV and HCV infection rate in the population of IBD Italian patients is still unknown, and the screening procedures at diagnosis have been underused.
2. Based largely on this retrospective study, IT plays an important role in HBV reactivation; however, the magnitude (frequency and severity) of the phenomenon seems to be less relevant than that previously reported in literature.
3. The contemporary use of more than one immunosuppressive drug is confirmed as a risk factor for reactivation, but this risk does not seem to be related to a specific type of immunosuppressant.

4. Hepatitis C infection does not appear to be associated with a significant risk of reactivation in the course of IT, and the rare episode observed was characterized by mild severity.
5. Even if the results of our study do not confirm the frequency and severity of the episode of reactivation already described, patients with IBD with HBV or HCV infection have to be closely monitored. HBV-positive patients have to be treated with prophylactic or therapeutic antiviral strategies when they start IT. Interestingly enough, this precautious procedure seems to be adequate with the prevision regarding the implementation of new drugs characterized by strong immunosuppressive properties.

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