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Inflammatory bowel disease and hepatitis B and C in Western Balkans: A referral centre study and review of the literature

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Abstract

Background and aims: There is limited data on IBD patients diagnosed with viral hepatitis B and C. The aim of the study was to assess the prevalence of chronic HBV or HCV infection in IBD patients followed by our centre and to describe and review the course of bowel and liver disease during therapy.
Methods: Single centre retrospective study on 482 consecutive IBD patients. Laboratory investigation for HBV and HCV was performed with routine methods. Treatment protocols for HBV included IFNa and nucleot(s)ide administration and for HCV combined IFNa and ribavirin.
Results: We diagnosed 15 patients (15/482, 3.1%) with HBV or HCV. Of these, 11 were HBV (11/482, 2.3%) and 4 were HCV (4/482, 0.8%). Nine of eleven HBV patients received antiviral therapy (8 lamivudine, 1 IFNa). Five lamivudine patients were switched to tenofovir and in another one adefovir dipivoxil were added. Bowel disease was in remission in ten of the eleven HBV patients. One patient was diagnosed with carcinoid tumor. Two HCV patients received IFNa that was well tolerated. One HCV patient denied therapy and one died from hepatocellular cancer. Of the seven patients on azathioprine only one achieved sustained response. Four patients on Infliximab achieved bowel disease remission but experienced biochemical or virological flare.
Conclusions: This study demonstrates that prevalence of HBV and HCV infection in a large IBD cohort from Western Balkans is compared to that of the background population. IBD patients under immunosuppressants may apparently be treated with safety if preventive antiviral treatment is administered.

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1. Introduction

Patients with longstanding inflammatory bowel disease (IBD) seem to be at higher risk for hepatitis B (HBV) and hepatitis C virus (HCV) infection compared with the general population because of the need for high-risk procedures such as endoscopy and surgery as well as blood transfusions.[1,2]

According to epidemiological and treatment group studies the cumulative prevalence of either HCV or HBV seem to present a large variance. According to studies from Spain and Italy, the prevalence of HBsAg(+) has been reported to range from 2.7% to 7.5%[3,4] while the prevalence of HCV(+) has been reported to range from 1.2% to 17.1%.[3,5]

Furthermore, according to a study from south France the prevalence of HCV was higher in Crohn's disease (CD) patients undergoing surgery compared to ulcerative colitis (UC) patients.[6] In addition, according to studies from Italy[4] and Rio de Janeiro[7] anti-HBcore(+) prevalence was higher in IBD patients compared to the control group individuals.

It is remarkable that there is not always agreement among studies. In two recent studies from Spain[8] and France[9] the cumulative prevalence of HBV and HCV infection in IBD patients was similar to that of the general population of reference and was lower compared to previously published series.

HBV or HCV virus in IBD seems to increase patients' morbidity. In an IBD cohort from Stockholm, infections with hepatitis B and C transmitted by blood transfusions accounted for various abnormalities in liver function.[10] In addition, co-existence of HCV and primary sclerosing cholangitis (PSC) and the development of de novo IBD after liver transplantation for acute severe flare of HBV have been also described.[11,12]

Several case studies have reported worsening[2,5,13,14] or onset of IBD[1] while patients are being treated for HCV. On the other hand, the chronic use of immunomodulators to treat IBD could potentially make the HCV worse. It has been suggested that the spectrum and frequency of IFNa toxicity is similar in HCV infected patients with and without IBD[15] and, of interest, IFNa has been proposed as an option for the treatment of steroid-resistant UC but no significant advantage was observed.[16]

There is scarce information about the effect of immunomodulatory drugs on the clinical course of liver disease in IBD patients with concomitant HBV or HCV virus infection[17] and several cases of reactivation of HBV infection in IBD patients receiving Infliximab have been reported.[2,18]

The aim of this study was to assess the prevalence of chronic HBV or HCV infection in IBD patients followed by our centre and to describe our experience during therapy and follow up of these patients. In addition, the present article reviews all currently available literature on the topic.

2. Patients and methods

2.1. Referral single centre study

Our department is a national referral centre for IBD with one of the largest outpatient IBD and hepatology clinics in the country and in western Balkans. This department is the only referral centre for IBD therapeutics in Northwest Greece and is currently coordinating clinical observational studies and epidemiological surveys in more than 1000 IBD patients.

For this study we retrospectively analysed the electronic database of our outpatient clinic that is including 482 consecutive patients from the same geographical area (Table 1). Of these patients 308 were diagnosed with UC (male/female: 173(56%)/135(44%), median age 41.3 years, range 14–79 years), 145 with CD (m/f: 82(56%)/63(44%), median age 38.7 years, range 14–73 years) and 29 with indeterminate colitis (m/f: 18(62%)/11(38%), median age 33.4 years, range 22–43 years). We analysed 453 patients as patients with indeterminate colitis are showing most likely minor risk factors (i.e. surgery).

2.2. Prevalence of hepatitis B and C in the area

Northwest Greece has a population of approximately 800,000 inhabitants and represents an area of low hepatitis B prevalence, never exceeding the 3% of the native population. In Greece HBV vaccination in neonates was started on in the early 90s in parallel with screening of all pregnant women, while vaccination in 11 year adolescents started in 1998 with a 90% estimated coverage. HCV prevalence in our area is less that 0.5%.[19]

2.3. Hepatological follow up in IBD patients

All IBD patients undergo regular follow up in the out-patient clinic including 6-monthly liver function tests and biannual abdominal ultrasonography in order to better assess IBD behaviour and potential complications. A liver biopsy was suggested to all patients with unexplained transaminase elevations for at least 6-month duration. All HBsAg(+) or HCV(+) patients are followed every three months with liver function tests and every six months with liver ultrasound, a-fetoprotein and HBV-DNA or HCV-RNA respectively.

Table 1 Clinical characteristics of the IBD patient cohort.

Parameter	CD (n=145)	UC (n=308)
Age in years (median, range)	38.7 (14–73)	41.3 (14–79)
Sex (male/female)	82 / 63	173 / 135
Follow up time in years (median, range)	6.2 (1–22)	8.3 (1–29)
Patients operated for bowel disease	19	16
Cumulative number of surgeries	33	22
Number of patients receiving blood transfusions	24	31
Number of colonoscopies	385	965
Disease location for CD		
Ileitis	92	
Colitis	15	
Ileocolitis	38	
Disease location for UC		
Pancolitis		34
Left-sided colitis		219
Proctitis		55

Table 2 Overview of clinical parameters in IBD patients followed for hepatitis B or C.

Parameter	HBV ($n=11$)	HCV ($n=4$)
Age (median, range)	49.5 (37–65)	65.5. (53–85)
Sex (M/F)	9/2	4/0
UC/CD	9/2	4/0
UC location (left sided/pancolitis)	5/4	2/2
CD location (ileocolitis)	2	–
Follow up for IBD (median, range in years)	11 (2–24)	15 (2–24)
Follow up for hepatitis (median, range in years)	13.2 (2–30)	11.2 (2–24)
Patients operated for bowel disease	0	1 (*ileostomy*)
Cumulative number of surgeries	0	1
No of patients receiving blood transfusions	0	1
Number of colonoscopies	19	11
IBD main maintenance therapy		
Infliximab (IFX)	3	1
Azathioprine	6 (3 switched to IFX)	1
5-ASA	5	1
None	–	1
Hepatitis therapy		
Lamivudine (switched to tenofovir)	7 (5)	–
Lamivudine + adefovir dipivoxil	1	–
Interferon-a	1	2
None	2	2
IBD outcome	10 remission	3 remission
	1 carcinoid	1 ileostomy (*prior to IFNa*)
Hepatitis outcome	6 sustained response	1 sustained response
	3 virological flare	1 hepatocellular cancer
	2 biochemical flare	2 biochemical flare

2.4. Laboratory investigation for HBV and HCV

Aminotransferase levels, alkaline phosphatase, gamma glutamyl transferase and total bilirubin were measured by standard laboratory methods. Coded serum samples were tested in the laboratory of Immunology of our department for HBV and HCV.

Every sample was examined for HBV using routine methods. HBsAg and anti-HBcore IgM and IgG were tested by enzyme-linked immunosorbent assay. Antibodies to HBsAg

Table 3 Clinical and laboratory parameters of IBD patients diagnosed with chronic viral hepatitis B or C. [Abbreviations: IBD = inflammatory bowel disease, CD = Crohn's disease, UC = Ulcerative colitis, M = male, F = Female, ASA = aminosalicylates, IFX = Infliximab, COR = corticosteroids, AZA = azathioprine (–) = no therapy AD = adefovir dipivoxil, LAM = lamivudine, IFN = interferon, UNL = upper normal limit. * = Concomitant diagnosis of IBD and hepatitis. ** = Biochemical and virological remission. [+]Switched to tenofovir].

No	Sex	IBD diagnosis	Hepatitis diagnosis (genotype)	Hepatitis duration (years)	IBD therapy	Hepatitis therapy [years]	Hepatitis outcome
1	M	UC	HBV	27	5-ASA	(–)	Quiescent**
2	F	UC	HBV	15	IFX, (AZA)	LAM [9]	HBV-DNA >400c/μl[+]
3	M	CD	HBV	2*	AZA, COR	LAM [2]	Sustained response
4	M	UC	HBV	3*	5-ASA	LAM [3]	Sustained response
5	M	UC	HBV	4	5-ASA, AZA	LAM/AD [4]	Sustained response
6	M	UC	HBV	30	5-ASA, AZA	LAM [6]	HBV-DNA >400c/μl[+]
7	M	UC	HBV	17	5-ASA	LAM [8]	HBV-DNA >400c/μl[+]
8	F	UC	HBV	18	5-ASA	IFNa [1.5]	Sustained response
9	M	UC	HBV	13*	5-ASA	(–)	Quiescent**
10	M	UC	HBV	14	IFX, (AZA)	LAM [4]	ALT>x2UNL[+]
11	M	CD	HBV	3	IFX, (AZA)	LAM [3]	ALT>x2UNL[+]
12	M	UC	HCV (3)	2*	IFX	(–)	ALT>X1.5UNL
13	M	UC	HCV (3)	12	AZA, COR	(–)	Hepatocellular cancer
14	M	UC	HCV (1a)	17	–	IFNa [1.5]	Sustained response
15	M	UC	HCV (1a)	24	5-ASA	IFNa [1.5]	ALT>X1.5UNL

Table 4 Prevalence of hepatitis B and/or hepatitis C markers in patients with inflammatory bowel disease. [Abbreviations: IBD = inflammatory bowel disease, CD = Crohn's disease, UC = Ulcerative colitis, IC = indeterminate colitis, M = males, F = Females, C = controls].

Author	Journal	Year of publication	Study area	Type of study	Patients/ Controls	Sex (M/F)	% HBsAg+	% Anti-HBs+	% HBcore+	% HCV(+)	Comments
Chevaux et al. [9]	IBD journal [in press]	2009	Northeast France	Hospital based	315 IBD			48.9% IBD			–HBV and HCV similar to background population
					252 CD		0.79% CD		2.78% CD	0.79% CD	–Low percentage of effective HBV vaccination
					63 UC		1.59% UC		1.59% UC	1.59% UC	–Identified nonvaccination risk factors
Loras et al.[8]	Am J Gastro	2009	Spain	Multicenter Hospital based	2076 IBD	1043 M/ 1033F					–HBV and HCV similar to background population and lower than previously reported
					1128 CD		0.6% CD	17% CD	7.1% CD	2.3% CD	–Low percentage of effective HBV vaccination
					928 UC		0.8% UC	14.9% UC	8% UC	1.3% UC	
					20 IC		0 % IC	17.6 % IC	5.3% IC	0% IC	
Tolentino et al. [7]	World J Gastro	2008	Rio de Janeiro	Hospital based	102 CD	68 M/ 108F	0% CD	Not investigated	43.3% CD	Not investigated	–Surgery does not increase HBV risk
					74 UC		2.3% UC		56.7% UC		–Prevalence 17% of HBcore(+) while 7.9% in the Brazilian population and 2.5% in the Rio de Janeiro population
Bargiggia et al. [5]	APT	2005	Italy	Hospital based	513 IBD 302 CD 211 UC		Not investigated	Not investigated	Not investigated	19 CD (6.2%) 23 UC(10.9%)	–21 (10 CD/11UC) treated with IFNa
Esteve et al. [3]	Gut	2004	Spain	Multicenter Hospital based	80 CD		7.5%	Not investigated	Not investigated	1.2%	–Patients screened and then treated with IFX
Biancone et al. [4]	IBD journal	2001	Italy	Multicenter	332 CD	182 M/ 143F	2.1% CD	14.4% CD	10.9% CD	7.4% CD	–HBV prevalence higher than HCV in CD at all ages

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Table 4 (*continued*)

Author	Journal	Year of publication	Study area	Type of study	Patients/ Controls	Sex (M/F)	% HBsAg+	% Anti-HBs+	% HBcore+	% HCV(+)	Comments
					162 UC	87 M/75F	0.64% UC	15.8 % UC	11.5% UC	0.6% UC	–HCV prevalence is increased in young CD patients because of a greater need for surgery
					373 C	196 M/ 177F	2.1% C	7.7% C	5.1% C	5.1% C	–Higher HCV (not HBV) prevalence in CD to UC
Longo et al. [6]	Gastroenterol Clin Biol	2000	Nice	Hospital based	117 IBD 74 CD 43 UC	53 M/64F	Not investigated	Not investigated	Not investigated	5.98% all (7/ 117)	–HCV prevalence in France is 0.86% –Blood transfusion the only significant risk factor
Broome et al. [9]	Gut	1994	Stockholm	Prospective target group [Reference population n=1274 UC]	142 UC with abnormal liver tests		5/142	Not investigated	Not investigated	8/142 (5.6%)	–13/142 HBV or HCV positive –All patients had been transfused –4/5 HBV patients acute infection –9/13 chronic but non-fatal course of hepatitis

Table 5 Clinical outcomes in inflammatory bowel disease and other autoimmune diseases patients diagnosed or/and treated for hepatitis B.* = Lamivudine administered as prophylaxis [IBD = inflammatory bowel disease, CD = Crohn's disease, UC = Ulcerative colitis, SA = ankylosing spondylitis, RA = Rheumatoid arthritis, AZA = azathioprine, IFX = Infliximab, IFN = interferon].

Author	Journal	Year	No of patients	IBD diagnosis	Hepatitis diagnosis	Therapy (IFX doses)	Hepatitis therapy	IBD outcome	Hepatitis outcome	Comment
Ojiro et al. [21]	J Gastoenterol	2008	1	CD	HBV	IFX (4) 6-MP	Lamivudine 100 mg/d	Remission	Temporary reactivation	Temporary IFX discontinuation until response to lamivudine
Colbert et al. [22]	IBD journal	2007	1	CD	HBV	IFX, AZA Prednisone	Lamivudine	Relapse	Death	Ascites, fulminant hepatic failure after steroid, AZA and IFX withdrawal despite lamivudine
Madonia et al. [23]	IBD journal	2007	1	CD	HBV	IFX (6) prednizolone	Lamivudine	No change	Seroconversion	Pretreatment HBsAg was negative
Worns et al. [12]	Am J Gastro	2006	1	UC	HBV	Mesalamine Budesonide	Transplantation	Remission	Listed for retransplantation	De novo UC 2 months after transplantation for HBV
Milloning et al. [24]	World J Gastro	2006	1	CD	HBV	IFX (4) AZA	Lamivudine 150 mg/d	Remission	Favorable	Subfulminant HBV with transient encephalopathy
Ueno et al. [25]	Dig Dis Sci	2005	1	CD	HBV	IFX (1)	–	Remission	Favorable	Transaminase elevation-return normal with no antiviral therapy
Wendling et al. [26]	Ann Rheum Dis	2005	1	SA	HBV	IFX (3) Methotrexate	Lamivudine	–	Favorable	Reactivation of HBV
Sikorska et al. [27]	Med Wieku Rozwoj	2004	1	UC	HBV/ HCV	Mesalazine	IFNa		Therapeutic difficulties	HBV/HCV co-infection
Oniakitan et al. [28]	J Rheumatol	2004	1	SA	HBV	IFX (9)	Lamivudine*	–	No change	No effect of IFX on HBV therapy
del Valle Garcia-Sanchez et al. [29]	IBD journal	2004	1	CD	HBV	IFX (6)	Lamivudine*	Remission	No change	No effect of IFX on HBV therapy but persistent HBV replication
Esteve et al. [3,18]	Gut	2004	1	CD	HBV	IFX (4), AZA		Remission	Favorable	HBV reactivation
			1	CD	HBV	IFX (3), AZA			Fatal	
	IBD journal	2007	1	CD	HBV	IFX (3), AZA	Lamivudine*	Remission	Cirrhosis	Adefovir dipivoxil added
Papadakis et al. [30]	Gut	2004	1	CD	HCV		FK506 + Rapamycin	New onset	Transplantation	De novo CD at 11 months after transplantation
Ostuni et al. [31]	Ann Rheum Dis	2003	1	RA	HBV	IFX Methotrexate	Lamivudine	–	Favorable	Reactivation of HBV
Michel et al. [32]	J Rheumatol	2003	1	Adult Still's	HBV	IFX (2) Prednizolone	–	–	Liver transplant	Fulminant hepatitis but no signs of HBV reactivation
Kanazawa et al. [33]	Nippon Naik	2002	1	UC	HBV	Mesalazine	–	New onset		UC after acute exacerbation of HBV
Ramji et al. [34]	Dig Dis Sci	2002	1	CD	HBV		FK506 + AZA	New onset	Transplantation	De novo CD at 39 months after transplantation
Biancone et al. [35]	Gastro	2002	4	CD	HBV	AZA , Steroids IFX (1 patient)	–	Remission	Favorable	1 flare at steroid withdrawal, 1 proctocolectomy
Legaz Huidobro et al. [36]	Gastroenterol Hepatol	1996	1	UC	HBV	Mesalazine	IFNa	Remission	Seroconversion	Before HBV therapy better control before IBD
Yasumori et al. [37]	Nippon Sh.	1995	1	UC	HBV	Total colectomy	IFNa	Death		UC exacerbation at 1st day of IFN therapy

(HBsAb), HBV core antigen (HBcAb) as well as hepatitis B surface antigen (HBsAg) were detected using commercially available enzyme immunoassays. HBV-DNA was measured with using commercially available quantification methods.

Screening for anti-HCV was performed using a third generation enzyme-linked immunosorbent assay. Reactive samples underwent confirmatory testing by recombinant immunoblot assay (RIBA-3). HCV-RNA was tested in serum by nested-polymerase chain reaction after reverse transcription (RT-PCR) and quantified by branched-DNA signal amplification assay. HCV genotype—when applicable—was assessed in all HCV-positive patients by analysis of PCR products, carried out with specific DNA probes.

2.5. Treatment protocol for HBV therapy

Generally, all patients with HBV infection should be treated when they have both increased liver enzymes and positive HBV-DNA.[20] In addition, in all patients administered corticosteroids or immunomodulators prophylactic HBV treatment should be initiated despite HBV-DNA and transaminase levels. In our series, patients were treated with IFNa administration for 18 months as first choice of therapy in newly diagnosed HBV(+) patients meeting all available inclusion criteria for such therapy. In case of sustained response to IFNa patient is followed every six months.

In case of incomplete or non-response to IFNa patient is administered therapy with nucleot(s)ide analogues and is followed up every three months. In our IBD/HBV(+) patients and in the view of restricted literature on the topic, it was decided to favour therapy with nucleot(s)ide analogues rather than IFNa. Thus, IBD/HBsAg(+) were treated with lamivudine (Zeffix, Glaxo-Welcome, Research Triangle Park, NC) at a dose of 100 mg/d as this was the only therapy available during the previous decade.

On follow up, lamivudine administration was maintained unchanged in patients with normal liver function tests and HBV-DNA serology. In lamivudine-resistant patients therapy with adefovir dipivoxil (Hepsera, Gilead) or tenofovir (Viread, Gilead) was initiated.

2.6. Treatment protocol for HCV therapy

In our series, patients were treated with combination of pegylated (PEG)-IFNa and ribavirin as first choice of therapy when IBD/HCV(+)patients were meeting all available inclusion criteria for such therapy.[20] Thus, IBD/HCV(+) patients were accordingly treated (upon availability at the time of treatment initiation) with combination of IFNa 3MUI three times a week (or PEG-IFNa once a week) plus ribavirin. Treatment period is set to 3–18 months according to HCV genotype and early biochemical and virological responses.

2.7. Response to treatment

Responses to treatment were classified as previously described[5]: complete response-persistently normal ALT and viral clearance (HBV-DNA or HCV-RNA −ve) at the end of treatment, incomplete response −ALT normalization without viral clearance (HBV-DNA or HCV-RNA +ve), and sustained response-ALT normalization and hepatitis B or C virus clearance 12 months after the end of treatment.

2.8. Ethics committee approval

All IBD patients followed by our Department are attending the Northwest Greece IBD registry project. This project has been approved by the ethics Committee of the Ioannina School of Medicine. Therapies administered in our patients were all commercially available.

2.9. Statistical analysis

We reported all data as median and range. For all calculations we used the SPSS 16.0 working package (SPSS Inc., Chicago, IL).

3. Results

3.1. Prevalence of HBV and HCV

We diagnosed 15 patients (15/482, 3.1%) with chronic hepatitis B or C. Of these patients 11 were diagnosed with HBV (11/482, 2.3%) and 4 with HCV (4/482, 0.8%). Of note, four patients (4/15, 26.6%) were unaware of their hepatitis until IBD diagnosis. Follow up (median-range) was 11.6 (2–32) years for IBD and 13.4 (2–30) years for hepatitis. The clinical parameters and case analysis are presented in Tables 2 and **3** respectively.

3.2. Results of HBV therapy

Of the 11 IBD patients diagnosed with HBV, five were on 5-ASA, two on 5-ASA and azathioprine and five on azathioprine. On follow up three azathioprine-treated patients were switched to Infliximab.

Four patients with HBV before IBD diagnosis received the first choice therapy with IFNa—when available—for 18 months when criteria for therapy were fulfilled. On follow up, they were switched to lamivudine—when it was available—either because of an HBV flare (HBV-DNA or transaminase elevation) or because of IBD diagnosis and subsequent treatment. In one patient on low dose 5-ASA with HBV prior to IBD diagnosis and with bowel and liver disease long-term remission, therapy for HBV was not initiated.

Patients with HBV diagnosis concomitant to IBD or after IBD diagnosis received prophylactic lamivudine (4 patients) or IFNa (1 patient). In one patient on low dose 5-ASA with HBV concomitant to IBD diagnosis and bowel and liver disease quiescent phase, therapy for HBV was not initiated.

In total, nine of the eleven HBV patients received continuous antiviral therapy (8 lamivudine, 1 IFNa) either as prophylaxis (5 patients) or as continuing HBV therapy preceding IBD diagnosis (4 patients).

Continuous lamivudine was administered for 4.9 years (range 2–9 years). On follow up, only two of the eight patients on lamivudine had sustained response. In the remaining six, after the third year of therapy and due to incomplete response 5 lamivudine patients were switched to tenofovir and in one lamivudine patient adefovir dipivoxil was added. Patient on IFNa achieved sustained response and the two untreated

Table 6 Clinical outcomes in patients diagnosed or/and treated for hepatitis C, inflammatory bowel disease and other autoimmune diseases. [Abbreviations used in the Table: IBD = inflammatory bowel disease, CD = Crohn's disease, UC = Ulcerative colitis, HCV = Hepatitis C, AZA = azathioprine, IFX = Infliximab, PSC = primary sclerosing cholangitis IFN = interferon, PEG = pegylated, RIB = ribavirin, LFTs = Liver function tests, CyA = cyclosporine, UCDA = ursodeoxycholic acid].

Author	Journal	Year	No of patients	IBD diagnosis	Hepatitis diagnosis	IBD therapy	Hepatitis therapy	IBD outcome	Hepatitis outcome	Comment
Scherzer [2]	APT	2008	11	CD	HCV	8/11 patients	PEGIFNa2a/b + RIB	Symptoms may temporarily exacerbate	46% sustained response	Treatment in CD as in non-CD patients Moderate side effects of IFNa
Miike et al. [39]	Nippon Sh	2008	1	UC	HCV	Mesalazine	IFNa 2b	Moderate activity	Response to treatment	UC acute onset during I FN therapy
Abdelmalek et al. [40]	Am J Gastro	2007	1	CD	HCV (1)	Mesalazine IFX	PEG IFN + RIB	New onset in 5 weeks, response to treatment	Compensated cirrhosis	Successful treatment with concomitant PEG IFN and IFX
Goritsas et al. [11]	J Gastrointest Liver Dis	2007	1	CD	HCV/PSC	Mesalazine	UCDA	Remission	Response to treatment	No treatment for HCV
Tursi et al. [41]	IBD journal	2007	1	UC	HCV (1b)	Mesalazine Steroids	PEGIFNa 2b + RIB 1000 mg	Remission	Response to treatment	UC onset one week after the end of 1 year HCV therapy
Watanabe et al. [42]	Gut	2006	1	UC	HCV (1b)	Mesalazine Prednizone	PEGIFNa2b + RIB 800 mg	Exacerbation	PEG IFN discontinuation	Ablation for adenomatous hyperplasia of the liver (mesalazine discontinued by patient)
Bongiovanni et al. [43]	AIDS	2006	1	CD	HCV(3a)/ HIV	Mesalazine	PEG IFNa2b + 800 mg RIB	New onset in 3 months, response to treatment	Response to treatment	CD acute onset during PEG IFN therapy PEG IFN continued,
Salcedo-Mora et al. [44].	Digestion	2006	1	CD	HCV	Mesalazine AZA	IFNa 2b + RIB	Remission	Response to treatment	HCV therapy well tolerated
Sprenger et al. [45]	Gut	2005	1	UC	HCV (3a)	Mesalazine Prednizone	PEGIFNa2a + RIB 1000 mg	Relapse in 3.5 months Remission with 5-ASA	PEG IFN discontinuation	New onset UC
Villa et al. [1]	Eur J Gastr Hepatol	2005	1 1	UC UC	HCV HCV	Mesalazine Mesalazine	IFNa 6MUI 3/W + RIB both	Onset in 6 months, Onset in 10 days	Both IFN discontinuation	New onset of both UC cases, remission after therapy
Alderson et al. [46]	Med Gen Med	2005	1	CD (stoma)	HCV cirrhosis	AZA, IFX (1 dose)	IFN + RIB (5 years ago)	Fatal multiple organ aspergillosis	TIPS and liver transplant list	Aspergillosis resulting in respiratory failure and coma 11 days after IFX single infusion.
Nagai et al. [47]	J Gastroenterol	2005	1	UC, renal transplan	HCV	AZA, CyA, prednizolone	None	Leukapheresis 3/week Total colectomy	HCV clearance	HCV clearance 2 months after discontinuation of immunosuppression discontinuation

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Table 6 (*continued*)

Author	Journal	Year	No of patients	IBD diagnosis	Hepatitis diagnosis	IBD therapy	Hepatitis therapy	IBD outcome	Hepatitis outcome	Comment
Sawada et al. [48]	Dig Dis Sci	2005	1	CD	HCV (1b)	5 ASA, Granulo-cytapheresis,	IFNa + RIB	Favorable	Favorable	Intolerant to IFNa, Initially 5 consecutive Adacolumn 1/d then IFN 6 UI 3/w +800 mg RIB
Khalil et al. [49]	Gastroenterol Clin Biol	2005	1	CD	HCV	Mesalazine	IFN + RIB PEG IFN + RIB	New onset in 7 months	Remission	New onset of both CD cases after IFN therapy
			1	CD	HCV	AZA		New onset in 8 months	Remission	
Peterson et al. [50]	An Rheum Dis	2003	3	RA	HCV	IFX	None	–	Unchanged	IFX no effect on transaminases
Holtmann et al. [17]	Am J Gastro	2003	1	CD	HCV (1b)	IFX, AZA, IFX (1)	None	Remission	Lower LFTs	IFX no effect on liver disease in both cases
			1	CD	HCV (1)		None	Remission	Stable LFTs	
Sawada et al. [51]	Am J Gastro	2003	1	UC	HCV(1b)	5-ASA, prednisone, Granulocytapheresis	Granulocytapheresis then IFNa	Favorable	Favorable	Intolerant to IFNa Initially 5 consecutive Adacolumn sessions 1/d then IFNa 6UI 3/w and 1 Adacolumn/w for 24 wks
Awakawa et al. [52]	Nippon Sh	2003	1	UC	HCV	Mesalazine	IFNβ	Relapse in 7 days	IFN discontinuation	UC onset during IFN therapy
Niki et al. [53]	Nippon	2001	1	UC	HCV	Mesalazine Steroids	IFNa	Relapse in 2 months	IFN discontinuation	New onset UC
Campbell et al. [54]	Eur J Gastr Hepatol	2001	1	CD	HCV	IFX	IFNa 3MUI 3/w	Favorable	Not responding to therapy	IFX no effect on liver disease
Mavrogiannis et al. [55]	J Hepatol	2001	1	UC	HCV	Mesalazine Steroids	IFNa	Relapse in 14 days	IFN discontinuation	New onset UC, relapse under mesalazine and steroids during continuation of IFN
Usami et al. [56]	Rinshohin	1999	1	UC	Renal cancer	Sulfasalazine	IFNa, γ	Relapse in 12 months	IFN discontinuation	UC onset during IFN therapy
De Diego Lorenzo et al. [14]	Rev Esp Enfer Dig	1997	1	UC	HCV	Mesalazine	IFNa 2b	Remission	Response to treatment	HCV therapy well tolerated
Yamamoto et al. [57]	Nippon Sh	1995	1	UC	HCV	Sulfasalazine	IFNa	Relapse in 5 months	IFN discontinuation	IBD-like new onset during IFN therapy
Mitoro et al. [58]	Intern Med	1993	1	UC	HCV	Sulfasalazine	IFNa 9×10^6 6/w	Relapse in 23 days	Response to treatment	Sulfasalazine allowed IFN re-treatment with no UC flare
Honda et al. [59]	Nippon Sh	1993	1	UC	HCV	Sulfasalazine	IFNa	Relapse in 14 months	IFN discontinuation	UC exacerbation after readministration of IFN sulphasalazine allowed IFN readministration

Table 7 Therapeutic trials with interferon in inflammatory bowel disease patients. [Abbreviations: IBD = inflammatory bowel disease, CD = Crohn's disease, UC = Ulcerative colitis, HBV/HCV = Hepatitis B/Hepatitis C, AZA = azathioprine, IFN = interferon, PEG = pegylated, RIB = ribavirin, MMF = mycophenolate mofetil].

Author	Journal	Year of publication	No of patients	IBD diagnosis	Hepatitis diagnosis	IBD therapy	Hepatitis therapy	IBD outcome	Hepatitis outcome	Comment
Scherzer et al. [2]	APT	2008	11	CD	HCV	Mesalazine (4) AZA (3) MMF (1)	PEGIFN a or b +/−RIB	Temporarily exacerbation	Comparable to HCV therapy without CD	GI symptoms may temporarily exacerbate
Bargiggia et al. [5]	APT	2005	11 10	UC CD	HCV	Mesalazine AZA	IFN 6 MUI	Remission	Response to treatment	IFN is safe when IBD is in remission
Tilg et al. [16]	Gut	2003	60	UC	Patients without hepatitis	PEG IFN (0.5 or 1 μg/Kg)	–	No amelioration or worsening of IBD with IFN	–	PEGIFN safe but not effective as treatment for IBD
Madsen [62]	Am J Gastro	2001	16	UC	Patients without hepatitis	IFNa-2a 3-9MUI vs prednisolone enemas ×30 days	–	Significant depression of disease activity	–	Comparative study Mild IFN side efects
Cottone et al. [15]	Ital J Gastro	1995	7 7	UC CD	HBV/HCV	AZA Steroids	IFNa IFNa	Remission Remission (except 1 case)	Favorable Favorable	Mild IBD course during hepatitis B or C therapy
Sumer et al. [61]	Eur J Gastroent Hepatol	1995	28	UC	–	IFNa-2a 3-9MUI 6-12 months	–	82% responded		IFN well tolerated
Gasche et al. [60]	Dig Dis Sci	1995	12	CD	Patients without hepatitis	rhIFNa for 24 weeks	–	Unfavorable	–	No role for IFN Many side effects

patients remained at a quiescent phase with all tests at within normal limits.

Bowel disease was in remission in ten of the eleven patients. The eleventh patient, who was a 47-year-old male diagnosed with CD ileocolitis and treated with azathioprine for two years was diagnosed with small bowel carcinoid and was successfully operated. No patient had exacerbation of the IBD related to HBV therapy.

3.3. Results of HCV therapy

Of the four IBD patients diagnosed with HCV one patient was on 5-ASA, one on azathioprine, one on Infliximab and one permanent ileostomy patient received no treatment.

Two of the four HCV patients received antiviral therapy, IFNa 3MUI three times a week that was available at that period. Both patients were genotype 1a and received 18-month treatment, which was tolerated well. From the two remaining patients, both genotype 3, the first was an alcohol abuser and denied IFNa therapy while the other did not tolerate IFNa therapy and died 12 years after his hepatitis diagnosis from hepatocellular cancer.

Bowel disease was in remission in three of the four patients; one patient underwent total colectomy and permanent ileostomy prior to IFNa initiation so we cannot conclude on his IBD course during IFNa treatment.

3.4. Effect of azathioprine and Infliximab on HBV and HCV

In our IBD cohort 135 (135/482, 28%) patients (107 CD, 28 UC) are treated with thiopurines and 48 (48/482, 9.9%) patients are treated with Infliximab. The prevalence of HBV infection in patients treated or not with thiopurines was 7/135 (5.1%) and 4/347 (1.1%) respectively. The prevalence of HBV infection in patients treated or not with Infliximab was 4/48 (8.3%) and 7/434 (1.6%) respectively. It should be noticed herein that 3 of the 4 HBV patients on Infliximab were previously on azathioprine.

The prevalence of HCV infection in patients treated or not with thiopurines was 1/135 (0.7%) and 3/347(0.9%) respectively. The prevalence of HCV infection in patients treated or not with Infliximab was 1/48(2%) and 3/434 (0.7%) respectively.

In total 7/15 patients (six HBV, one HCV) received azathioprine. All six patients with HBV received continuous azathioprine at a dose of 2 mg/Kg for a median period of 7 years (range 2–16 years). Three of those six patients were treated with azathioprine before any administration of preventive antiviral treatment was possible. In two patients we observed a continuous low-increased HBV-DNA (up to 1200 c/μl) with normal transaminases and in one patient we observed transient ALT elevations that never exceeded two times upper the normal limit. Only one of three azathioprine-HBV patients achieved sustained biochemical and virological responses.

One 85-year-old HCV patient diagnosed with left-sided UC and treated with azathioprine for five years was diagnosed with hepatocellular cancer and died six months after diagnosis.

On follow up, 4/15 patients (3 HBV, one HCV) received Infliximab induction and then maintenance scheme at a dose of 5 mg/Kg for a median period of 2 years (range 1–6 years). Three patients were switched to Infliximab after azathioprine discontinuation and one patient received Infliximab monotherapy as initial treatment. Those patients were 3 males (aged 48, 53 and 62 years, two diagnosed with UC pancolitis and one with CD ileocolitis) and one 42-year old, left-sided UC female. All patients achieved with Infliximab remission in their bowel disease but experienced either biochemical (2 HBV, 1 HCV) or virological flare (1 HBV patient). All flares occurred during the first year of Infliximab infusions (approximately at eight infusions) and were asymptomatic with no further complications. Flares had a mild course regarding biochemical and virological parameters. In all three HBV patients lamivudine was switched to tenofovir and for the HCV patient we started on ursodeoxycholic acid.

4. Discussion

In this study we present our experience on the largest group of IBD patients with chronic HBV or HCV infection and antiviral therapy in Greece and in Western Balkans. In addition, we review all currently available literature on this topic.

Despite the limitations of its retrospective nature this is the first systematic attempt to describe the true dimensions of the problem in this area of major public health interest due to rapid political and demographic changes and the high rate of immigration of young population groups. Regional or global European policy on health care and prevention of transmittable diseases resides a lot in the information of such epidemiological studies. Along these lines health care consumption in chronic diseases is important for every country to further design health policy and health care priorities.

The prevalence of HBV and HCV in our IBD group of patients is 2.3% and 0.8% respectively and parallels that of the background population as it was observed in a study from Spain[8] and France[9] (Table 4).[3–9] This HBV and HCV prevalence reported herein is of the lowest ever reported in similar IBD studies and although limited data is available, our results are comparable to those reported from Italy[4] and Brasil[7] for HBV and from Spain[3] for HCV. Possible characteristics of our study population, as also the relatively low number of CD patients could be possible explanation for discrepant findings when compared with previous studies.

In IBD patients infected with HBV we favoured nucleot(s)ide therapy rather than IFNa due to the limited and conflicting data concerning a possible influence of IFNa on IBD relapse (Table 5).[3,12,18,21–37] The majority of the patients initially responding to lamivudine had to be switched to combination therapy either with adefovir dipivoxil or tenofovir due to biochemical or/and virological relapse.

Exacerbation of UC by the treatment with interferon for chronic hepatitis B has been reported.[36,37] Of note, the only HBV patient receiving IFNa did well. All data herein is discussed with reservations[33,38] as the activity of the disease was in remission at the time of clinical record review but it may be deduced that these patients had flares of the disease or chronic continuous inflammation because they needed chronic administration of immunosuppressants for disease control.

From the two patients with the difficult-to-treat HCV1a genotype one patient responded well but we cannot conclude for the effect of INFa to his bowel as he was colectomized on

Table 8 Outcomes of Infliximab therapy in patients with inflammatory bowel disease and other autoimmune diseases diagnosed with hepatitis B or C. [IBD = inflammatory bowel disease, CD = Crohn's disease, UC = Ulcerative colitis, RA = rheumatoid arthritis, AS = Ankylosing spondylitis, M = males, F = Females, HBV/HCV = Hepatitis B/Hepatitis C, AZA = azathioprine, IFX = Infliximab, IFN = interferon, PEG = pegylated, RIB = ribavirin]. * = Lamivudine prophylaxis prior to IFX.

Author	Journal	Year of publication	No of patients	IBD diagnosis	Hepatitis diagnosis	Therapy (IFX doses)	Hepatitis therapy	IBD outcome	Hepatitis outcome	Comment
Ojiro et al. [21]	J Gastoenterol	2008	1	CD	HBV	IFX (4) 6-MP	Lamivudine 100 mg/d	Remission	Temporary HBV reactivation	Temporary IFX discontinuation until response to lamivudine
Abdelmalek et al. [40]	Am J Gastro	2007	1	CD	HCV (genotype 1)	Mesalazine IFX	PEG IFN +RIB	New onset in 5 weeks, response to treatment	Well-compensated cirrhosis	Successful treatment with concomitant PEG IFN and IFX
Esteve et al. [3,18]	IBD journal	2007	1	CD	HBV	IFX (4), AZA		Remission	Favorable	HBV reactivation
			1	CD	HBV	IFX (3), AZA			Fatal	
	Gut	2004	1	CD	HBV	IFX (3), AZA	Lamivudine*	Remission	Cirrhosis	Adefovir dipivoxil added to lamivudine
Colbert et al. [22]	IBD journal	2007	1	CD	HBV	IFX, AZA Prednisone	Lamivudine	Relapse	Death	Ascites, fulminant hepatic failure after steroid, AZA and IFX withdrawal despite lamivudine
Madonia et al. [23]	IBD journal	2007	1	CD	HBV	IFX (6) Prednizolone	Lamivudine	No change	Seroconversion	Pretreatment HBsAg was negative
Milloning et al. [24]	World J Gastro	2006	1	CD	HBV	IFX (4) AZA	Lamivudine 150 mg/d	Remission	Favorable	Subfulminant HBV with transient encephalopathy
Alderson et al. [46]	Med Gen Med	2005	1	CD	HCV cirrhosis	IFX (1) AZA, Steroids	IFN+RIB (5 years ago)	Fatal multiple organ aspergillosis	TIPS and liver transplant evaluation	Complicated ileostomy Aspergillosis resulting in respiratory failure and coma 11 days after IFX
Ueno et al. [25]	Dig Dis Sci	2005	1	CD	HBV	IFX (1)	None	Remission	Favorable	Moderate transaminase elevation-return normal with no antiviral therapy
Wendling et al. [26]	Ann Rheum Dis	2005	1	SA	HBV	IFX (3) Methotrexate	Lamivudine	–	Favorable	Reactivation of HBV

(continued on next page)

Table 8 (*continued*)

Author	Journal	Year of publication	No of patients	IBD diagnosis	Hepatitis diagnosis	Therapy (IFX doses)	Hepatitis therapy	IBD outcome	Hepatitis outcome	Comment
del Valle Garcia-Sanchez et al. [29]	IBD journal	2004	1	CD	HBV	IFX (6)	Lamivudine*	Remission	No change	No effect of IFX on HBV therapy but persistent HBV replication
Oniakitan et al. [28]	J Rheumatol	2004	1	SA	HBV	IFX (9)	Lamivudine*	–	No change	No effect of IFX on HBV therapy
Holtmann et al. [17]	Am J Gastro	2003	1	CD	HCV (gen 1b)	IFX, AZA, Prednizolone	None	Remission	Slight lower transaminases	IFX no effect on liver disease in both cases
			1	CD	HCV (gen1)	IFX (1)	None	Remission	No change	
Michel et al. [32]	J Rheumatol	2003	1	Adult Still's	HBV	IFX (2) Prednizolone	–	–	Liver transplant	Fulminant hepatitis but no signs of HBV reactivation
Ostuni et al. [31]	Ann Rheum Dis	2003	1	RA	HBV	IFX Methotrexate	Lamivudine	–	Favorable	Reactivation of HBV
Peterson et al. [50]	An Rheum Dis	2003	3	RA	HCV	IFX	None	–	Unchanged	IFX no effect on transaminases
Biancone et al. [35]	Gastro	2002	4	CD	HBV	IFX (1 patient)	None	Remission	Favorable	Immunomodulatory drugs did not influence aymptomatic HBV or HCV
			4	CD	HCV	AZA (3 patients) Steroids (4 pts)				In 1 patient flare at steroid discontinuation and 1 proctocolectomy
Campbell et al. [54]	Eur J Gastr Hepatol	2001	1	CD	HCV	IFX	IFNa 3MUI 3/w	Favorable	Not responding to 6-month therapy	IFX no effect on liver disease

beforehand. An association between interferon therapy and the onset or flares of IBD has been described in HCV infected individuals (Table 6).[1,2,11,14,17,39–59] However, in these two HCV patients we did not observe flares of IBD during IFN therapy and we tend to support like others[5,13,15,44] that IFN does not appear to worsen the course of established IBD in patients already on maintenance IBD therapy. Of note, a study showed that gastrointestinal symptoms may be temporarily exacerbated and haematopoietic growth factors may be required.[2] By contrast, an interferon-beta- has induced remission of UC in a patient with HCV[39] and IFN has been used in therapeutic trials in IBD (Table 7).[2,5,15,16,60–62] It should be stressed herein that the experience using IFNa in this study is very limited to drawn conclusions. However do not suggest a bad influence on IBD outcome.

Attempting a critical review of the available literature in order to provide a possible explanation for the differences observed between studies showing a negative effect of IFNa on IBD activity and no effect in others we could briefly comment the following; IFNa is generally safe when IBD is in remission and cautious administration of concomitant to IFNa treatment is important. However, some UC patients may present an unpredictable acute flare shortly after IFNa initiation and this is probably related to individual immune factors.

Although we did not face difficult-to-treat HCV patients[27] it has been suggested that treatment of HCV is feasible in the presence of Infliximab.[40]

Immunomodulatory drugs such as azathioprine and methotrexate may increase hepatitis B and C viremia and reduce ALT levels, related to an increased intracellular viral replication.[24,61] We observed, like others[13,35], that immunomodulatory drugs appear not to influence the course of hepatic virus or acute flares.[63,64]

Infliximab use is safe in general[65,66] but in patients with HBV has been so far reported only in 19 patients (16 with IBD) including our 3 cases (Table 8).[3,17,18,21–26,28,29,31,32,35,40,46,50,54] The use of Infliximab appears safe in HBV patients with prophylaxis, that is, initiation of antiviral therapy possibly 4 weeks prior to anti-TNFa therapy and early intervention with frequent monitoring of HBV-DNA levels and liver enzymes to allow early detection and treatment.[22,67] Subfulminant hepatitis B[24], occult hepatitis B and Infliximab-induced HBV reactivation have been reported[21,23,29], and even after a single infusion.[25]

We have administered lamivudine prophylaxis in all our three patients as this was for many years the only available safe, well tolerated, and effective in preventing HBV reactivation nucleotide. However, in most of the patients we experienced lamivudine resistance[3] or/and Infliximab-induced flare and we switched to tenofovir. In fact, long-term therapy with lamivudine has been shown to induce resistance in the form of mutations in the Tyr-Met-Asp-Asp locus and between 16% and 32% of patients develop the YMDD mutation after 1 year of lamivudine therapy.[3,68] In our centre screening for hepatitis B and C and HIV as well as hepatitis B vaccination is routinely performed in all IBD patients.

Immunomodulatory drugs probably influence the course of HBV and HCV and may be dangerous if antivirals are not administered. Of interest, none of the patients in this study received combined immunosuppression. This is important since opportunistic infections in general reactivate in patients receiving two or more immunosuppressants. In this study severe acute flares were not observed probably due to the administration of preventive antiviral treatment.

Infliximab use in patients with HCV has been so far reported in 13 patients (10 with IBD) including our single case (Table 8). Based on the available data, it appears that TNFa antagonists have no adverse hepatic effects on patients with HCV. A mild elevation in liver function tests as happened in our case needs to be cautiously interpreted and careful follow up is mandatory.[13,46,54]

One of our patients was an alcohol abuser but none of the others was co-diagnosed with non-alcoholic fatty liver disease or steatohepatitis that may increase the vulnerability of the liver to HBV or HCV chronic infection.[69,70]

In conclusion, this study demonstrated that prevalence of chronic hepatitis B and hepatitis C infection in a large IBD cohort from Western Balkans is compared to that of the background population. IBD patients under immunosuppressants may apparently be treated with safety if preventive antiviral treatment is administered.

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