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REVIEW

Hepatobiliary manifestations in inflammatory bowel disease: The gut, the drugs and the liver

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Abstract

Abnormal liver biochemical tests are present in up to 30% of patients with inflammatory bowel disease (IBD), and therefore become a diagnostic challenge. Liver and biliary tract diseases are common extraintestinal manifestations for both Crohn's disease and ulcerative colitis (UC), and typically do not correlate with intestinal activity. Primary sclerosing cholangitis (PSC) is the most common hepatobiliary manifestation of IBD, and is more prevalent in UC. Approximately 5% of patients with UC develop PSC, with the prevalence reaching up to 90%. Cholangiocarcinoma and colon cancer risks are increased in these patients. Less common disorders include autoimmune hepatitis/PSC overlap syndrome, IgG4-associated cholangiopathy, primary biliary cirrhosis, hepatic amyloidosis, granulomatous hepatitis, cholelithiasis, portal vein thrombosis, liver abscess, and non-alcoholic fatty liver disease. Hepatitis B reactivation during immunosuppressive therapy is a major concern, with screening and vaccination being recommended in serologically negative cases for patients with IBD. Reactivation prophylaxis with entecavir or tenofovir for 6 to 12 mo after the end of immunosuppressive therapy is mandatory in patients showing as hepatitis B surface antigen (HBsAg) positive, independently from viral load. HBsAg negative and anti-HBc positive patients, with or without anti-HBs, should be closely monitored, measuring alanine aminotransferase and hepatitis B virus DNA within 12 mo after the end of therapy, and should be treated if the viral load increases. On the other hand, immunosuppressive therapy does not seem to promote reactivation of hepatitis C, and hepatitis C antiviral treatment does not influence IBD natural history either. Most of the drugs used for IBD treatment may induce hepatotoxicity, although the incidence of serious adverse events is low. Abnormalities in liver biochemical tests associated with aminosalicylates are uncommon and are usually not clinically relevant. Methotrexate-related hepatotoxicity has been described in 14% of patients with IBD, in a dose-dependent manner. Liver biopsy is not routinely recommended. Biologics-related hepatotoxicity is rare, but has been shown most frequently in patients treated with infliximab. Thiopurines have been associated with veno-occlusive disease, regenerative nodular hyperplasia, and liver peliosis. Routine liver biochemical tests are recommended, especially during the first month of treatment. All these conditions should be considered in IBD patients with clinical or biochemical features suggestive of hepatobiliary involvement. Diagnosis and management of these disorders usually involve hepatologists and gastroenterologists due to its complexity.

Key words: Inflammatory bowel disease; Hepatobiliary disorders; Extraintestinal manifestations; Primary sclerosing cholangitis; Drug-induced liver injury; Hepatotoxicity; Hepatitis B; Hepatitis C

Core tip: Hepatobiliary disorders are common extrain-

testinal manifestations of inflammatory bowel disease (IBD) that become a diagnostic challenge for the gastroenterologist. In this review, we have summarized the main diseases involving the hepatobiliary system in IBD and secondary liver toxicity to IBD treatment. This review also highlights the impact of immunosuppressive and anti-tumor necrosis factor treatment in hepatitis B and C, as well as its prophylaxis and treatment, according to current clinical practice guidelines.

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INTRODUCTION

Hepatobiliary diseases are relatively common in inflammatory bowel disease (IBD) and therefore become a diagnostic challenge. Liver and biliary tract disorders are typical extraintestinal manifestations in both Crohn's disease (CD) and ulcerative colitis (UC). In patients receiving immunosuppressive therapy, including biologics, the risk of hepatitis B reactivation is high, so patients undergoing this therapy should be screened for hepatitis B surface antigen (HBsAg) and anti-HBc prior to starting the treatment. Most of the drugs used for IBD treatment have also been associated with hepatotoxicity. All these conditions should be ruled out in IBD patients with clinical or biochemical features suggestive of liver involvement, as summarized in this review.

Bibliographic searches were performed in the MEDLINE electronic database up to February 2013 using the Medical Subject Headings terms: ("inflammatory bowel disease" OR "Crohn's disease" OR "ulcerative colitis") AND ("liver" OR "biliary tract" OR "primary sclerosing cholangitis" OR "hepatobiliary disorders" OR "small-duct PSC" OR "PSC/AIH overlap syndrome" OR "IgG4-associated cholangitis" OR "primary biliary cirrhosis" OR "hepatic amyloidosis" OR "granulomatous hepatitis" OR "cholelithiasis" OR "portal vein thrombosis" OR "liver abscess" OR "non-alcoholic fatty liver disease" OR "viral hepatitis" OR "hepatitis B" OR "hepatitis C" OR "drug-induced liver injury" OR "drug-induced hepatitis" OR "hepatotoxicity").

HEPATOBILIARY DISORDERS ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE

Hepatobiliary manifestations constitute some of the most common extraintestinal manifestations of IBD. They typically adopt an independent course irrespective of intestinal activity and are present in both UC and CD.

Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic fibrosclerotic disorder of the intrahepatic and extrahepatic biliary tree. and is the most common hepatobiliary manifestation of IBD. The association of PSC and IBD was described for first time in 1965[1].

Epidemiology: Approximately 70%-80% of patients with PSC have concomitant IBD and about 1.4%-7.5% of patients with IBD will develop PSC[2]; however the course of IBD is not related to PSC. It is more prevalent in males, in UC, and in young and middle-aged patients[3]. UC has been reported in 25 to 90 percent of patients with PSC[4]. In a Spanish multicenter study, based on a survey, UC was present in 44%[5]. Nevertheless, the real prevalence of UC in PSC is up to 90% when rectal and sigmoid biopsies are routinely obtained[6].

PSC is typically characterized by progressive inflammation, obliterative fibrosis, and destruction of intra- and extrahepatic bile ducts, leading to end-stage liver disease and portal hypertension[7]. Patients with PSC may also develop complications such as cholestasis-associated manifestations, biliary stricture, cholangitis, cholelithiasis, cholangiocarcinoma, and colon cancer. The diagnosis of PSC is usually previous to IBD, but PSC may be diagnosed over time, after a proctocolectomy in UC patients[8].

Etiology: The etiology of PSC remains unclear. Genetic, immunological, and environmental factors seem to contribute to its pathogenesis. First-degree relatives of patients with PSC show an increased risk of PSC and UC, supporting a genetic predisposition to these conditions[9]. Multiple genetic factors associated with susceptibility have been described, like HLA-B8, HLA-DRB1*0301 (DR3), HLADRB3*0101 (DRw52a), and HLA-DRB1*0401 (DR4)[10,11]. In addition, three UC susceptibility loci have been associated with PSC, harboring the presumed candidate genes REL, IL2, and CARD9[12]. An autoimmune mechanism has been suggested, since both are immune-mediated disorders, and are also associated with other autoimmune diseases. Several autoantibodies may be present, such as antinuclear antibodies (ANA) in 24%-53%, smooth muscle antibodies (SMA) in 13%-20%, and anti-perinuclear cytoplasmic antibodies (pANCA) in 65%-88% of patients[13-15]. Other autoantibodies, including anticardiolipin, thyroperoxidase, and rheumatoid factor may be present, but show uncertain clinical significance. In one study, 97% of cases with PSC were positive for, at least, one autoantibody, while 81% were positive for three or more[16]. An inflammatory response to chronic or recurrent bacterial infection into the portal circulation or ischemic damage to the bile ducts has also been postulated[17]. Therefore, the most plausible theory involves the exposure of genetically predisposed individuals to an environmental agent that provokes an anomalous immune response, leading to disease development.

IBD in PSC patients has a distinct behavior, as it shows a higher incidence of rectal sparing, backwash

ileitis, extensive colitis, pouchitis after ileal pouch anal anastomosis, colon dysplasia, colon cancer, and poorer prognosis[18-21]. Patients with UC and PSC usually have a lower grade of colon inflammation and a milder course, compared to patients without PSC[22]. In addition, severe progressive PSC requiring liver transplantation appears to reduce histological activity and the need for colectomy in UC[23,24].

Diagnosis: Most patients with PSC are asymptomatic at diagnosis. This disease should be considered in patients with IBD and abnormal liver biochemical tests, where a marked elevation of serum alkaline phosphatase is commonly found[25]. In symptomatic patients, fatigue and pruritus are common. Other features include abdominal pain, jaundice, and weight loss. Cholangitis occurs in 10%-15% of patients during the course of the disease. Biochemical tests usually show a cholestatic pattern. Aminotransferases levels are typically lower than 300 IU/L. Additional biochemical parameters are hypergammaglobulinemia (30% of cases), increased serum IgM levels (40%-50%), and p-ANCA (30%-80%). Serum albumin levels later decrease during the course of the disease, and the presence of hypoalbuminemia earlier may indicate active IBD.

Diagnosis is established by the demonstration of diffuse, multifocal strictures and dilations in the intra- and extrahepatic bile ducts. In 41% of cases, the gallbladder and cystic duct may also be involved[26]. In the early stages of the disease, superficial ulcerations of the bile ducts may be the only manifestation found. Endoscopic retrograde cholangiopancreatography (ERCP) is considered the gold standard technique for PSC diagnosis. It can be both diagnostic and therapeutic, and also may be useful in the early diagnosis of cholangiocarcinoma. Magnetic resonance cholangiography (MRCP) is a non-invasive alternative with high sensitivity and specificity, and without the risks related to the technique[27]. Liver biopsy is only recommended in cases of clinical suspicion of small-duct PSC, as it is rarely diagnostic of PSC[28]. The most specific histologic finding in PSC is fibrous obliteration of small bile ducts, with periductal concentric fibrosis in an "onion skin" pattern. Other abnormalities are non-specific and similar to those in primary biliary cirrhosis. Liver biopsy is helpful for staging the disease and determining prognosis. Ludwig described 4 stages of PSC based on morphologic features[29].

Prognosis: PSC is a progressive disease that, ultimately, results in portal hypertension, cirrhosis, and hepatic failure. The median survival time without liver transplantation is approximately 12 years. Survival is significantly worse in symptomatic patients at the time of diagnosis[30]. Coexisting IBD may also be related to a poorer prognosis, as it has been associated with a younger age at diagnosis, the development of malignant complications, dysplasia and/or colon cancer[31,32]. Patients with PSC usually develop complications of end-stage liver disease with portal hypertension, such as varices, ascites, and hepatic encephalopathy. The Mayo Risk Score based on age, serum bilirubin, albumin, aspartate aminotransferase, and the presence of variceal bleeding, has been used to assess disease progression and prognosis[33]. Other complications include steatorrhea and fat-soluble vitamin deficiency, secondary to chronic cholestasis, amyloidosis secondary to amyloid A protein deposition in tissues due to a progressive inflammatory process[34], dominant biliary strictures, cholangiocarcinoma, and colon cancer. The risk for cholangiocarcinoma is significantly increased in PSC and its development remains unpredictable. The annual incidence has been estimated as 1.5%[35]. Risk factors include the presence of IBD, cirrhosis, variceal bleeding, a dominant stricture in the bile duct, and alcohol intake[36]. Worsening jaundice, weight loss, and abdominal discomfort are suspicion symptoms. Diagnosis may be difficult, as imaging techniques and brush cytology show a lack of sensitivity for early detection. However, ERCP and cytology of bile duct strictures is highly specific[37]. Prognosis is devastating, with a survival rate of 10% two years after diagnosis[38] and a recurrence rate in the transplanted liver of about 20%-25%[39]. Patients with PSC have an increased risk for gallbladder cancer, pancreatic cancer and, in cirrhotic patients, hepatocellular carcinoma. A higher risk of colorectal dysplasia/cancer has also been described among UC patients with PSC[21], even after liver transplantation[40]. The severity and the duration of PSC have not been significantly associated with the risk of colon cancer[41]. In patients with ileal pouch-anal anastomosis, the risk for dysplasia persists after colectomy[42]. Therefore, surveillance for colorectal cancer should be strongly recommended in PSC patients with UC[43].

Treatment: Treatment of PSC associated with UC does not differ from PSC without IBD. As no pharmacologic therapy has proven effective for PSC, treatment goals are the control of symptoms and the management of complications. Ursodeoxycholic acid (UDCA) has been shown as effective in liver function improvement based on biochemical tests but it had no effect on liver histology, liver transplant-free survival, requirements for liver transplantation, development of cholangiocarcinoma, or incidence of death[44,45]. In a meta-analysis, UDCA does not appear to decrease either the risk of adenomas or colon cancer[46]. Immunosuppressants, chelators, and steroids have been used without any benefit.

Liver transplantation is the only therapy that can change the inevitable outcome. The appropriate moment for liver transplantation can be difficult to determine, as patients with advanced disease may not show signs of liver failure. Survival rates after hepatic transplant at 5 and 10 years are 85% and 70%, respectively[47]. However, in 20%-25% of cases, PSC recurs in the transplanted liver[39].

Endoscopic management of PSC is indicated in cases of cholangitis, exacerbate jaundice, or suspicion of cholangiocarcinoma. Endoscopic dilation of dominant

strictures, with or without stenting, has been shown to alleviate cholestasis and to improve laboratory test results, although it does not prevent disease progression[48].

Small-duct PSC

Small-duct PSC is characterized by laboratory and histological findings similar to PSC but with normal cholangiogram. The presence of coexisting IBD is required for the diagnosis of this entity[49]. In a large multicenter study, 80% of patients with small-duct PSC had concurrent IBD (78% UC and 21% CD)[50]. Progression of small-duct PSC to PSC was observed in 12%-23% of cases. Small-duct PSC has been associated with a better long-term prognosis as compared with large-duct PSC. Cholangiocarcinoma has not been previously described. Some patients may require liver transplantation for end-stage liver disease, and the disease may recur after liver transplantation. In IBD patients with cholestatic liver function tests altered and a normal cholangiogram by ERCP/MRCP, a biopsy is recommended to rule out small-duct PSC, after excluding other hepatobiliary disorders.

AIH/PSC overlap syndrome: AIH/PSC overlap syndrome has been described in patients with IBD, especially UC[51]. The diagnosis is suspected when features of AIH and PSC are present in the same patient, requiring a definitive diagnosis of AIH based on the International Autoimmune Hepatitis Group Criteria, which includes demographic, histologic, and laboratory markers[52]. Diagnosis, treatment, and prognosis of the overlap syndrome are controversial and so standardized diagnostic criteria are needed[53,54]. Previous studies have reported cases that initially presented with laboratory markers and histologic features of either AIH or both diseases with a normal cholangiography, only to develop pathologic characteristics of PSC during the follow-up[52,55,56]. Intrahepatic and extrahepatic bile ducts may be affected. Conventional corticosteroid therapy, alone or in conjunction with UDCA (13-15 mg/kg daily), has been variably effective, and cyclosporine, mycophenolate mofetil, and budesonide have been beneficial in selected patients. The cholestatic features that influence the prognosis of autoimmune hepatitis must be defined and incorporated into the definition of the syndrome[57].

IgG4-associated cholangiopathy

IgG4-associated cholangiopathy (IAC) is a biliary disease of unknown immunopathogenesis. Indistinguishable from PSC according to cholangiographic characteristics, it shows distinct histological findings. It is one of a variety of IgG4-related systemic disease and has been described in patients with concurrent UC[58]. Clinical diagnostic criteria for IgG4-related disease require systemic organ involvement, elevated serum IgG4 levels ($\geq$ 135 mg/dL), and histopathological findings[59]. IgG4 levels have also been reported in 9%-36% of patients with PSC, although these levels are usually lower than in patients with IAC[60,61]. The identification of IgG4 plasma cell infiltrating the bile duct and other organs is decisive in reaching the diagnosis[58,59]. Clinically, patients with IAC are older at diagnosis compared to patients with PSC. Obstructive jaundice can be the first symptom, whereas it is rarely present in PSC[62]. Steroids are the first-choice therapy of IAC, as they result in the resolution of jaundice, improve liver laboratory parameters, and reduce serum IgG4 levels and the reversal of strictures on cholangiogram[63]. Azathioprine (AZA) should be considered alongside those with proximal and intrahepatic stenosis, and those that relapse during and/or after corticosteroid therapy[64].

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) frequently accompanies various autoimmune diseases including Sjögren syndrome, chronic thyroiditis, and rheumatoid arthritis, but rarely IBD[65]. There are a few reported cases of both diseases in the literature[66,67]. The clinical presentation varies from typical PBC; affecting males more frequently, being diagnosed at younger age and at earlier stages of PBC, and usually associated with previously diagnosed mild left-side UC. Although the pathogenesis of this disease has not yet been clarified, environmental and genetic factors are considered important in the susceptibility to both diseases.

Hepatic amyloidosis

Secondary amyloidosis is an unusual complication of IBD, more frequent in CD than in UC (0.9% *vs* 0.07%)[68]. Chronic activity in the bowel contributes to amyloid deposition in the vasculatures and sinusoids of almost any organ, including the liver. It may present as asymptomatic hepatomegaly and is more common in men with colonic diseases. Treatment is based on controlling gut inflammation, thereby decreasing the release of the acute phase reactant serum amyloid A[69]. In some cases, colchicine can be effective.

Granulomatous hepatitis

Granulomatous hepatitis is another rare complication of CD, which is characterized by granulomas on the liver biopsy. The main manifestation is an increase in cholestatic enzymes such as alkaline phosphatase. Granulomatous hepatitis is often secondary to different medications, including sulfasalazine[70]. Other causes are malignancies, infections, or CD metastasis[71]. Corticosteroids and immunosuppressive drugs have been used in its treatment.

Cholelithiasis

It has been estimated that patients with CD have a doubled risk for gallstones comparing to IBD-free controls, while UC is not associated with an increased risk[72]. The incidence of gallstones is raised in patients with Crohn's ileitis or ileal resection, ranging from 13% to 34%[73]. Risk factors associated with its development are CD location at diagnosis, surgery, and extent of ileal resection. Other factors include the age of the patient, frequency

of clinical recurrences, length of hospital stay, and the use of total parenteral nutrition. The pathophysiology of cholelithiasis in CD is not well defined. Abnormal malabsorption of bile acids that interfere with enterohepatic circulation has been proposed. Moreover, reduced gallbladder motility has been described in CD and increased gallstone cholesterol concentrations have been identified in patients with ileoanal anastomosis[74].

Portal vein thrombosis

IBD is associated with an increased risk of vascular complications, such as arterial and venous thromboembolisms, which are considered extraintestinal manifestations. Portal vein thrombosis is a rare but potentially life-threatening complication, with an incidence in IBD patients higher than that of the general population. In a Mayo Clinic study, portal/mesenteric vein thrombosis was reported in 1.3% of IBD cases, with a mortality of 50%[75]. Recent abdominal surgery, younger age, and female gender are associated with a higher incidence of portal vein thrombosis[76]. The factors involved in this pathogenesis are diverse. Acquired prothrombotic factors can be identified, such as inflammation, immobilization, extent of colon disease, surgery, central catheters, corticosteroids, and smoking[77,78]. Furthermore, patients with IBD have increased platelet counts, factor V and Ⅷ levels, and fibrinogen, along with decreased antithrombin Ⅲ levels. Anticoagulants, such as low-molecular-weight heparin and warfarin, are mainstays of therapy, even in the setting of gastrointestinal bleeding[73]. In the presence of a congenital hypercoagulable state, lifelong systemic anticoagulation should be considered, although in other prothrombotic conditions, a six-month course provides adequate coverage[79].

Liver abscess

The association between liver abscesses and IBD is uncommon[80,81], but hepatic abscesses can be an initial manifestation of CD[82]. The mechanism of abscess development may be related to direct extension of intra-abdominal abscesses or due to portal pyemia, secondary to an increase in intestinal mucosa permeability. Among associated risk factors, intra-abdominal abscesses, fistulizing disease, malnutrition, and treatment with steroids and metronidazole have been reported.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological syndrome with a histologic spectrum ranging from benign steatosis to non-alcoholic steatohepatitis (NASH)[83]. Steatosis is described in up to 50% of abnormal liver biopsies in IBD patients and has been related to colitis severity. It was presumed secondary to severe illness, with malnutrition, hypoproteinemia, and corticosteroids primarily responsible[84]. On the other hand, NAFLD occurs in 8.2% of the IBD population, which is much lower than the frequency reported in the United States general population (33.6%). Those patients who developed NAFLD tended to be older, and developing IBD at an older age normally requires small bowel surgery[85]. It has been reported that IBD patients develop NAFLD with fewer metabolic risk factors than non-IBD NAFLD patients. In multivariate analysis, hypertension (OR = 3.5), obesity (OR = 2.1), small bowel surgeries (OR = 3.7), and use of steroids at the time of imaging (OR = 3.7) were independent factors associated with NAFLD. NAFLD is also less common among patients who received antibodies against tumor necrosis factor alpha (anti-TNF-α) therapy.

VIRAL HEPATITIS AND IBD

Chronic hepatitis B and C are two common diseases. The WHO estimates that 350 million people in the world suffer from chronic hepatitis B, and more than 200 million from hepatitis C[86,87]. Hepatitis B infection is transmitted during delivery or early childhood. Hepatitis C is a bloodborne disease spread mainly *via* blood product transfusion and misuse of illegal drugs. Around 20% of patients with chronic hepatitis B show cirrhosis progression and 5% are at risk of developing hepatocellular carcinoma.

Chronic hepatitis B infection is a dynamic process, owing to the interaction between the hepatitis B virus and the host immune system. Its natural history is covered by five different phases[88] (Table 1): (1) Immunotolerant phase: characterized by positive hepatitis B e antigen (HBeAg), higher HBVDNA titre, and normal or near normal ALT levels. Liver biopsy at this phase shows mild or no inflammatory lesions and scarce non-progressive fibrosis; (2) Immunoclearance phase: positive HBeAg, lower HBVDNA, and raised aminotransferase levels. Liver histology shows necroinflammatory activity together with fibrosis progression. Spontaneous HBeAg clearance and anti-HBe seroconversion could occur at this phase; (3) HBsAg inactive carrier: characterized by negative HBeAg, positive anti-HBe, residual viremia (HBVDNA lower than 2000 IU/mL), and ALT levels under the normal limit. Liver histology shows minimal or no lesions; (4) Chronic hepatitis B: HBeAg negative could appear after unsuccessful seroconversion. HBVDNA remains quantifiable and ALT levels are fluctuant. Fibrosis progression is common; and (5) Resolved infection: characterized by loss of HBsAg and could be a stable phase, with negative HBsAg and non-detectable HBVDNA with normal ALT levels and excellent prognosis.

Chronic hepatitis C is a progressive liver disease that could evolve to cirrhosis. Risk factors associated with fibrosis progression are alcohol consumption, HIV coinfection, and adult age at infection.

Chronic hepatitis B patients showing HBVDNA > 2000 IU/mL and at least moderate necroinflammatory activity or fibrosis in a liver biopsy should be treated with entecavir or tenofovir and, in selected cases, with peginterferon α-2a. In patients with chronic hepatitis C and positive HCVRNA, antiviral treatment should be started. In genotype 1, protease inhibitor-based triple therapy is

Table 1 Phases of chronic hepatitis B infection

Phase	Characteristics	HBVDNA	ALT	Liver histology
Immune tolerant	HBeAg positive	> 2000000 UI/mL	Normal	Normal or mild inflammation
Immune active	HBeAg positive	> 200000 UI/mL	Elevated	Chronic hepatitis Active cirrhosis
Inactive carrier	HBeAg negative Anti-HBe positive	< 2000 UI/mL	Normal	Normal or mild inflammation Mild fibrosis Inactive cirrhosis
HBeAg negative chronic hepatitis	HBeAg negative Anti-HBe positive	> 20000 UI/mL	Elevated (fluctuating)	Chronic hepatitis Active cirrhosis
Remission	HBsAg negative Anti-HBc positive	Indetectable in serum and detectable in liver	Normal	Normal Mild fibrosis Inactive cirrhosis

HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen.

the first choice and, in non-1 genotype, standard peginterferon plus ribavirin.

Viral reactivation during immunosuppressive therapy is a major concern in viral hepatitis B and C. Viral reactivation is defined by an increase of 1 log in viral load or re-appearance of the virus after previous clearance. A flare of ALT is common and in some cases may develop into acute liver failure.

Hepatitis B reactivation depends on two main factors: (1) type of immunosuppressive drug used, and (2) hepatitis B phase prior to treatment. In a recent meta-analysis including 14 studies and 485 HBsAg-positive patients undergoing chemotherapy, one in three patients developed hepatitis and the mortality rate reached 7%. Positive HBeAg and detectable HBVDNA, together with steroids or rituximab in hematologic neoplasms, were independent factors associated with the risk of developing reactivation[89]. In patients with HBsAg loss, reactivation risk was around 3%-10% and mainly associated with the combination of steroids and rituximab in hematologic neoplasms[90].

Hepatitis B reactivation prophylaxis is recommended from one week before chemotherapy to 12 mo after cessation of this therapy. Lamivudine has shown to decrease mortality rate[89]. However, it has been associated with an increased risk of developing resistant variants, so drugs with a higher genetic barrier, like entecavir or tenofovir[91], are recommended if immunosuppressors need to be used for more than one year.

Hepatitis C reactivation management is controversial, due to both its frequency and clinical manifestations remaining unclear. Hepatitis has been reported in 11% of cases and reactivation in 36% of the few patients with HCVRNA evaluated before and after chemotherapy, mainly in those treated with rituximab for hematologic neoplasms[92]. Interferon-based therapy is not recommended for hepatitis C reactivation prophylaxis. Further combination of direct antiviral drugs could be useful in avoiding hepatitis C reactivation in this setting.

As immunosuppressive drugs, like AZA, methotrexate (MTX), and anti-tumor necrosis factor α (TNFα), are being used more frequently in IBD, concerns about viral reactivation are increasing.

Hepatitis B and IBD

At the beginning of this century, hepatitis B infection prevalence was slightly higher in patients with IBD than in the general population, which was mainly related to increased surgical procedures and blood transfusions[93,94]. However, recent studies in France and Spain did not confirm these data. Prevalence of hepatitis B in IBD has been estimated to be similar to the general population as a consequence of several health system measures, like overall vaccination, safe transfusions, and surgical procedures. Prevalence of anti-HBc was 7.1% in CD and 8% in UC in a Spanish population[95,96].

Hepatitis B reactivation is a major health problem. Patients undergoing immunosuppressive therapy are at risk of developing hepatitis B reactivation. Acute liver failure requiring orthotopic liver transplantation has been reported in a patient under AZA and steroid treatment[97]. TNFα plays a role in hepatitis B virus replication, so anti-TNFα drugs could promote hepatitis B reactivation[98]. Infliximab, together with AZA or steroids, have been implicated in hepatitis B reactivation in seven cases from several series[94,99-102]. No cases have been reported in patients receiving adalimumab or certolizumab pegol. Nevertheless, hepatitis B reactivation seems to be a class-effect, so more cases should be expected with the continuing use of these new drugs. In patients with HBsAg loss reactivation is infrequent, but one case treated with infliximab has been reported[103]. A collaborative multicenter and retrospective Spanish study (REPENTINA) showed a reactivation rate of 36% (9/25) in patients with positive HBsAg; six out of nine developed liver failure, three underwent liver transplantation, and one died. No HBsAg-negative patients developed hepatitis B virus reactivation. In this study, the key factor for reactivation was the combination of two or more immunosuppressive drugs, independently of agent type. The absence of reactivation was associated with the use of only one drug for a short period of time[104].

Clinical practice guidelines from AEEH, EASL, and ECCO revised this topic and recommended prophylaxis of hepatitis B reactivation in patients with IBD receiving immunosuppressive agents[104-106]. HBsAg, anti-HBc, and anti-HBs should be tested before immunosuppressive

therapy with two goals: avoid possible fatal complications and use antiviral drugs to control hepatitis B virus replication: (1) HBV serologically-negative patients should receive vaccination. Vaccination rates in IBD are variable. In Spain, only 56% of young people showed anti-HBs antibodies[95]. Vaccine response was around 46% using double doses in patients with IBD receiving anti-TNF drugs. However, AZA seems not to influence vaccine response. In non-responders a new complete vaccination course should be recommended. Hepatitis B screening is highly recommended immediately after the diagnosis of IBD, and vaccination is indicated in serologically-negative patients[107]; (2) Patients showing HBsAg positive and HBVDNA > 2000 IU/mL should be treated with tenofovir or entecavir as chronic hepatitis B patients; (3) Patients showing HBsAg positive and HBVDNA < 2000 IU/mL or undetectable levels, and patients with HBsAg negative and HBVDNA positive should be treated with tenofovir or entecavir for 6 to 12 mo after the end of immunosuppressive therapy. ALT levels and HBVDNA titre should be monitored every three months during treatment; and (4) Patients showing HBsAg negative and anti-HBc positive with or without anti-HBs should be closely monitored every 1 to 3 mo, measuring ALT and HBVDNA until 6 to 12 mo after the end of therapy. For patients with an increase in viral load, entecavir or tenofovir therapy should be immediately started.

Hepatitis C and IBD

The prevalence of hepatitis C infection was increased in IBD patients younger than 50-year-old in comparison with the general population in studies of the last decade of the twentieth century[94]. However, recent studies have demonstrated a similar prevalence to the general population both in Spain (2.3% in CD and 1.3% in UC) and France (0.79% in CD and 1.59% in UC)[96,97].

The impact of immunosuppressive therapy for IBD on hepatitis C remains controversial. Steroids could promote viral replication, as demonstrated after liver transplantation. However, steroids have been used to treat hepatitis C without success or adverse events. ALT flares have been reported after stopping steroid therapy in patients with IBD[108]. Steroid therapy should be avoided in patients with hepatitis C, and patients should be closely monitored after any withdrawal or tapering process. Immunosuppressive drugs like AZA, MTX, cyclosporine, and mycophenolate mofetil have been largely used in the liver transplantation setting, showing a slight antiviral activity against hepatitis C[109-111]. MTX did not affect hepatitis C disease in patients with arthritis[112]. Therefore, immunosuppressive therapy with these drugs seems to be safe. Indeed, in a Spanish study, 16% (8/51) of patients with chronic hepatitis C and IBD receiving immunosuppressive therapy developed non-severe liver dysfunction, seven related to steroids, and one case with AZA[104].

TNFα plays a major role in the pathogenesis of chronic hepatitis C and associated metabolic abnormalities. TNFα is crucial in hepatitis C-induced insulin resistance, but could also modulate interferon response. Increased TNFα levels have been associated with impaired sustained virological response (SVR)[113]. Thus, TNFα inhibition could be more beneficial than harmful in the management of chronic hepatitis C. Etanercept improved SVR in patients with chronic hepatitis C receiving peginterferon plus ribavirin[114]. Patients suffering from rheumatoid arthritis and hepatitis C treated with etanercept or infliximab did not show any changes in transaminases level or viral load[115]. Although etanercept is not effective on IBD, a class-effect should be expected, and the use of anti-TNFα could be safe in hepatitis C associated with IBD.

CD is characterized by a Th1 response. Interferon seems to play an immunomodulatory activity-enhancing Th1 response, and can cause outbreak of CD[116]. On the other hand, some authors have suggested that interferon could be safely used in patients with IBD, due to a lack of negative impact on the gut[117,118]. In a prospective study including 11 patients with IBD and hepatitis C, peginterferon plus ribavirin achieved SVR in a similar way to non-IBD patients. During treatment six patients developed gastrointestinal symptoms that required optimization of immunosuppressive agents without impacting antiviral treatment[119]. Several case reports showed a beneficial effect of interferon-alpha and beta on patients with UC[120,121]. A systematic review, including three prospective studies, demonstrated no effect of interferon-alpha on UC[122], although new cases or exacerbation of UC have been seen in patients treated with interferon-alpha[123,124]. Higher doses of interferon used in hepatitis C, in comparison with lower doses in UC trials, could partially explain this discrepancy. Finally, 10 patients with CD and 10 with UC in remission or showing mild bowel activity underwent antiviral therapy for hepatitis C. No patient developed reactivation of IBD during treatment or the 12 mo of follow-up[125], confirming data from a recent review concluding that interferon does not impair IBD course[126].

In summary, hepatitis C antiviral treatment has no influence on IBD natural history, and immunosuppressive therapy for IBD does not promote reactivation of hepatitis C. Currently, no therapeutic option for reactivation prophylaxis nor vaccination are available for hepatitis C, but in the near future interferon-free regimen combining protease, polymerase, and NS5A inhibitors could be useful in the management of hepatitis C in IBD.

DRUG-INDUCED LIVER INJURY IN IBD

Approximately 30% of patients with IBD show abnormalities in liver biochemical tests during the course of the disease. Most of the drugs used in IBD have potential hepatotoxicity[127] (Table 2).

Aminosalicylates: Sulfasalazine and mesalazine

Sulfasalazine, an association between sulfapyridine and 5-aminosalicylate (5-ASA), was the first aminosalicylate used in the treatment of IBD. This drug has been replaced in the last two decades by mesalazine or 5-ASA,

Table 2 Drug induced hepatobiliary manifestations in inflammatory bowel disease

Manifestation	Drug
Drug induced hepatitis	Azathioprine 6-mercaptopurine Methotrexate Cyclosporine Infliximab
Reactivation of hepatitis B	Anti-TNF therapy Corticosteroids
Drug induced pancreatitis	Azathioprine 6-mercaptopurine Methotrexate
Hepatosplenic T-cell lymphoma	Combination of anti-TNF and immunosuppressive therapy

TNF: Tumor necrosis factor.

due to its adverse effects. Mesalazine is indicated for the induction and maintenance of the clinical remission in patients with UC with mild-moderate activity. The efficacy of this drug in CD remains controversial.

The anti-inflammatory effect of aminosalicylates is unclear. Synthesis inhibition of prostaglandins and leukotrienes (which show antioxidant and immunomodulatory activity) are well known. Aminosalicylates are safe drugs, and rarely lead to severe adverse effects such as bone marrow aplasia, pancreatitis, nephropathy, or hepatotoxicity. Altered liver function tests (cytolysis or cholestasis) may be detected during treatment with them. These abnormalities usually have no clinical relevance, although hepatotoxicity induced by acute hypersensitivity and acute liver failure has been described. In clinical trials, abnormalities in liver biochemical tests have been observed in 2% of UC patients treated with mesalazine[128]. The United Kingdom's Committee on Safety of Medicines observed that, between 1991 and 1998, the incidence of toxic hepatitis was 3.2 and 6 cases per million of prescriptions for mesalazine and sulfasalazine, respectively, and the presence of rheumatoid arthritis was a stronger risk factor than IBD[129]. Therefore, given the low risk of hepatotoxicity, a close monitoring of liver biochemical tests is not necessary in patients treated with aminosalicylates.

Methotrexate

Methotrexate (MTX) has both anti-proliferative and immunosuppressive activities, impairing DNA synthesis (*via* inhibition of dihydrofolate reductase) as well as decreasing the production of proinflammatory cytokines and inducing lymphocyte apoptosis, respectively. The main indication in IBD is maintenance of clinical remission in steroid-dependent CD patients, after adverse effects or lack of efficacy of thiopurines. MTX efficacy in UC is controversial. On the other hand, MTX is contraindicated in pregnancy. Regarding adverse effects, myelosuppression and hepatotoxicity are dose-dependent. These effects were documented in up to 25% of patients with rheumatoid psoriatic arthritis, highlighting the association with obesity, alcoholism, diabetes, previous abnormalities in biochemical liver tests and, especially, an accumulated dose higher than 15 g, as risk factors. Currently, liver fibrosis and cirrhosis are less frequent, probably due to close monitoring of liver parameters, proper selection of patients, and simultaneous treatment with folic acid, which decreases MTX-related adverse effects. Sabeni *et al*[130], in Italy, detected hepatotoxicity in 14.3% of patients with IBD treated with MTX during a mean follow-up of 26 mo. Te *et al*[131], in the United States, carried out a study in 20 IBD-patients treated with MTX with a mean follow-up of 131 mo and accumulated doses of 2.6 g. Liver fibrosis in biopsies was detected in one patient; the rest of the patients showed mild histological changes only. No association between abnormalities in liver biochemical tests and liver histology was found[131]. Regular liver laboratory studies are recommended in patients treated with MTX[132]. Nowadays, liver biopsy is not recommended routinely during MTX treatment[133]. However, it should be performed in cases of persistent alteration of transaminases (especially if they do not decrease after reducing the drug dose) and in patients with high accumulated doses, together with other risk factors. On the other hand, transient elastography (Fibroscan®) is emerging as diagnostic method of liver fibrosis in these patients. Treatment needs to be discontinued in cases of liver fibrosis or cirrhosis[134].

Anti-TNFα: Infliximab and adalimumab

Infliximab and adalimumab are monoclonal antibodies against TNFα, indicated in several rheumatologic, dermatologic, and gastrointestinal diseases. The main indication is the induction and maintenance of clinical remission in steroid-resistant or steroid-dependent CD and UC patients without response to immunosuppressive therapy. Early on, they are recommended in CD associated with risk factors or in the presence of severe perianal disease. Biological agents inhibit TNFα, preventing the release of proinflammatory cytokines, leukocyte migration, expression of endothelial molecules, fibroblast proliferation, and prostaglandin synthesis.

The main adverse effects of these drugs are opportunistic infections, hepatitis B virus reactivation, lymphoproliferative diseases, neurological diseases, and autoimmune diseases, such as lupus-like syndromes. Severe hepatotoxicity is a very rare condition in biological therapy, being most frequent in patients treated with infliximab. It is difficult to determine cause-effect associations between liver damage and these drugs in some cases due to confounding factors, like the presence of other drugs and other concomitant diseases. The drug label of infliximab (Remicade®) showed that, in clinical trials, ALT raised more than three times in 4.9% of patients with CD and in 2.5% of patients with UC, without clinical relevance. In contrast, serum ALT levels were less altered in the placebo group. On the other hand, the drug label of adalimumab (Humira®) indicates that serum ALT levels were similar in patients with IBD and a placebo.

According to infliximab indications, jaundice has been an uncommon finding, as well as infectious hepatitis, with liver failure being a very rare condition[135]. The Food and Drug Administration considers infliximab a hepatotoxic drug[136]. Recently, hepatotoxicity by these drugs has been evaluated in the United States (2003-2011), where only 34 cases were found, confirming the peculiarity of this adverse effect. Most cases (76%) were related to infliximab, showing a hepatocellular or cholestatic pattern with autoimmune characteristics, and improving after discontinuation of the drug[137]. Cross hepatotoxicity has not been documented in anti-TNF agents. In fact, in cases of infliximab-induced hepatotoxicity, adalimumab has been shown to be safe[138].

Thiopurines (azathioprine and 6-mercaptopurine)

AZA and its metabolite, 6-mercaptopurine (MP), are the immunosuppressive agents most commonly used in IBD. They are purine analogues, which interfere in nucleic acid synthesis and inhibit the proliferation of B and T lymphocytes, although the most relevant action is the apoptotic activation of T lymphocytes. The main indication of these drugs in CD and UC is the maintenance of clinical remission, preventing the use of steroids.

The active metabolites of AZA and MP are the 6-thioguanine nucleotides. In the liver, AZA is modified to MP, which is metabolized by xanthine oxidase and thiopurine methyltransferase (TPMT) in 6-thiouric acid and 6-methylmercaptopurine, resulting ultimately in 6-thioguanine nucleotides by hypoxanthine phosphoribosyltransferase. The decreased activity of TPMT facilitates the increasing in 6-thioguanine nucleotide levels, which are related to adverse effects. In fact, the efficacy of AZA and MP is limited owing to their adverse effects, which are responsible for treatment discontinuations in up to 15% of patients. Adverse effects are classified as dose-independent, dose-dependent, or idiosyncratic (which appears during the first two weeks of treatment). Regarding dose-independent adverse effects, the most common are allergic reactions (fever, exanthema, myalgias, and arthralgias) and acute pancreatitis. Among dose-dependent adverse effects, gastrointestinal intolerance and myelotoxicity are present in 2%-5% of patients. In retrospective studies, hepatotoxicity affected 3% of patients with an annual incidence of 1.4%, while these results are higher in prospective studies (10%)[139]. AZA and MP are able to damage the vascular endothelium, especially sinusoids and terminal veins, promoting veno-occlusive disease, regenerative nodular hyperplasia, and liver peliosis. These complications could be detected between 3 mo and 3 years after the beginning of treatment, and generate portal hypertension[140,141]. In general, mechanisms for AZA and MP hepatotoxicity remain unclear. It is thought that the main reason is the intracellular accumulation of 6-thioguanine nucleotides due to the decreased activity of TPMT.

It is recommended to determine levels of TPMT before the beginning of treatment with AZA or MP and routinely perform liver biochemical tests, especially during the first months of treatment, to detect myelotoxicity and/or hepatotoxicity. Mild abnormalities in liver parameters, without clinical relevance, allow the continuation of treatment at a lower dose. However, jaundice or persistent alterations in spite of reduced dose require an immediate stop to treatment[142].

CONCLUSION

Hepatobiliary disorders are common extraintestinal manifestations of IBD, and PSC represents the most prevalent disease among them. Abnormal liver biochemical tests are present in up to 30 percent of patients with IBD and emerge as a diagnostic challenge. Drug-induced hepatotoxicity should always be rule out, as most IBD treatments have been associated with liver toxicity, although the incidence of serious complications is low. Hepatitis B screening and vaccination is recommended in patients with IBD. Reactivation prophylaxis with entecavir or tenofovir is mandatory in patients under immunosuppressive therapy showing HBsAg positive, independently from viral load. HBsAg negative and anti-HBc positive patients, with or without anti-HBs, should be closely monitored, and treated if the viral load increase. Diagnosis complexity often requires a joint gastroenterologist and hepatologist approach.

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