Liver disease is exceptional in patients with inflammatory bowel disease. The most common manifestation, sclerosing cholangitis, characterized by inflammation and fibrosis of the intra- and/or extrahepatic bile ducts, is unusual in patients with inflammatory bowel disease. Conversely, inflammatory bowel disease (mainly chronic ulcerative colitis) is not infrequent in patients with sclerosing cholangitis. Gallstone disease, portal vein thrombosis, and hepatic abscesses are complications directly related to inflammatory bowel disease. Drugs prescribed for the treatment of inflammatory bowel disease can be the cause of rare but potentially serious hepatic manifestations which must be recognized and detected early. Recent studies have demonstrated the role of purine analogues in the development of nodular regenerative hyperplasia. Because of the poor prognosis, patients taking purine analogues should be monitored regularly to search for inaugural signs such as an elevation of serum alkaline phosphatase or low platelet counts (which may not necessarily reach thrombopenia). The risk of methotrexate-induced fibrosis is exceptional in inflammatory bowel disease. Patients should be monitored with non-invasive tests to recognize the development of fibrosis. Finally, because of the risk of viral reactivation, patients should be screened for hepatitis B virus surface antigen before introducing infliximab; chronic carriers should be given preventive treatment with nucleoside or nucleotide analogues.

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Résumé Les manifestations hépatiques sont rares au cours des maladies inflammatoires de l’intestin. La cholangite sclérosante est la manifestation hépatobiliaire la plus fréquente.
et se caractérise par une atteinte inflammatoire et fibrosante des voies biliaires intra- et/ou extrahépatiques. Elle est fréquemment associée à une maladie inflammatoire de l’intestin (rectocolite hémorragique le plus souvent) alors qu’inversement elle est rare chez les malades ayant une maladie inflammatoire de l’intestin. La lithiase biliaire, la thrombose de la veine porte et les abcès hépatiques sont des complications hépatobiliaires directement en rapport avec les maladies inflammatoires de l’intestin. Les manifestations hépatiques induites par les traitements prescrits au cours des maladies inflammatoires de l’intestin, bien que rares, sont potentiellement graves et nécessitent donc d’être connues et dépistées précocement. L’hyperplasie nodulaire régénérative, induite par les analogues des purines, doit être dépistée le plus tôt possible en recherchant régulièrement une cholestase et une chute du taux des plaquettes (sans obligatoirement de thrombopénie). Le risque de fibrose induite par le méthotrexate semble exceptionnel. Un dépistage régulier de la fibrose par les marqueurs non invasifs de quantification de la fibrose pourrait être un moyen pour suivre les malades. Enfin, le dépistage d’un portage chronique de l’antigène HBs, et en cas de positivité, un traitement préventif par un analogue nucléosidique ou nucléotidique doivent être réalisés avant d’initier un traitement par infliximab en raison du risque de réactivation virale.

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Introduction

Routine liver tests are frequently perturbed in patients with inflammatory bowel disease (IBD), specifically ulcerative colitis and Crohn’s disease [1,2]. Elevated levels of alkaline phosphatase and/or alanine aminotransferase (ALT) have been reported in 11 to 49% of patients, but without any systematic link with disease activity [3–6]. In some patients, the liver problem is related to the IBD itself, while in others the cause is attributed to their treatment. In still other patients, neither of these elements appears to be involved. Most treatments used for IBD are known to induce hepatic complications. A rigorous search for the causal mechanism is thus necessary to avoid missing an iatrogenic mechanism or conversely, wrongly accusing a useful treatment.

Hepatic manifestations during inflammatory bowel disease

Intra- and/or extrahepatic bile duct involvement

Sclerosing cholangitis

Generalities. Primary sclerosing cholangitis is an inflammatory and fibrosing disease of the intra- and/or extrahepatic bile ducts. Sclerosing cholangitis can be primary, i.e. arising from an unknown cause which nonetheless probably involves a dysimmune mechanism in which case it is often associated with inflammatory colitis, or secondary to a recognized biliary disease (notably ischemia). Schematically, the association of IBD with sclerosing cholangitis is generally considered to correspond to an inappropriate inflammatory reaction arising in the intestines of patients with a particular genetic susceptibility [7]. The two main risks are the constitution of secondary biliary cirrhosis and cholangiocarcinoma.

Inaugural manifestations vary depending on the series reported; presentations have changed over time. Compared with past experience, the diagnosis of primary sclerosing cholangitis is currently generally established in older sparsely symptomatic patients who often have IBD [8].

The diagnosis is based on the association of four types of signs listed in Table 1. There is a weak correlation between biological, histological and radiographic findings.

Antitissue antibodies are not specific and not constant. Sensitivity is highly variable for perinuclear antineutrophil cytoplasmic antibodies (pANCA) (26–85%) and specificity is only fair because these antibodies are also found in IBD and autoimmune hepatitis. Phosphatase alkaline elevation may be minimal or even absent [9]. Consequently, the diagnosis of primary sclerosing cholangitis should be entertained as a possibility when the routine work-up fails to identify the cause of chronically abnormal liver tests.

Histological diagnosis. The most common histological feature, fibrous obliterating cholangitis, is absent in more than two thirds of the biopsy specimens due to the heterogeneous distribution of lesions within the liver. The histology report thus generally mentions lesions “compatible” with the diagnosis of bile duct disease: periportal portal inflammation, discrete atrophy of the bile ducts without periductal fibrosis, proliferative ductal reaction or ductopenia [10]. The biopsy is found normal in 5–10% of cases [11]. Consequently, when the context is suggestive, a normal or nearly normal nonspecific liver biopsy cannot rule out the diagnosis of primary sclerosing cholangitis. A four-stage classification system has

<table>
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<th>Table 1 Diagnostic aspects of primary sclerosing cholangitis.</th>
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<tr>
<td>Biology: cholestasis (may be minimal)</td>
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<tr>
<td>Liver tests</td>
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<tr>
<td>Radiology (intra- and/or extrahepatic anomalies of the bile ducts)</td>
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<tr>
<td>MR cholangiography</td>
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<tr>
<td>Histology (signs of biliary disease)</td>
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<tr>
<td>Liver biopsy</td>
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<tr>
<td>Association with inflammatory bowel disease</td>
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<td>Colonoscopy (always with biopsies)</td>
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<tr>
<td>If no other etiology can be identified, the diagnosis of primary sclerosing cholangitis is retained in the presence of two of these four criteria including at least one histology or radiology argument</td>
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been proposed: in stage I, injury is limited to portal lesions (image of cholangitis); stage II is a periportal stage where the inflammation and/or fibrosis overrides the portal space; stage III corresponds to extensive fibrosis without cirrhosis; stage IV corresponds to overt cirrhosis with the presence of regenerative nodules.

**Morphological diagnosis.** The gross aspect of the bile ducts is often the key to diagnosis. Ultrasound, computed tomography or endoscopic ultrasound can demonstrate suggestive anomalies and rule out other causes of cholestatic jaundice. Heterogeneous involvement of the bile ducts is often the origin of marked hepatic dysmorphism. Nevertheless, diagnosis of primary sclerosing cholangitis cannot be ruled out on the basis of normal morphological explorations.

Direct opacification of the bile ducts, generally using endoscopic retrograde cholangiopancreatography (ERCP). Long multiple zones of stenosis are commonly found, usually without clear upstream dilatation. A beaded appearance of irregular dilatation is typical. Wall anomalies, sometimes with a diverticular aspect, may be seen [12]. Both intra- and extrahepatic ducts are usually involved. Lesions are confined to the intrahepatic ducts in less than 20% of cases and the extrahepatic ducts in less than 10%. Cystic duct, gallbladder and pancreatic duct involvement have been described. ERCP is difficult and an important source of post-ERCP morbidity when performed for diagnostic purposes. The complication rate can reach 12% in patients with primary sclerosing cholangitis.

Magnetic resonance (MR) cholangiography now offers a non-invasive means of visualizing the biliary tree. In the hands of expert centers, this method has demonstrated usefulness in primary sclerosing cholangitis (sensitivity 88—90%, specificity 91—97%). It should be noted, however, that patients included in these studies had advanced disease so the conclusions cannot be readily applied to early-stage disease. Zones of minimal narrowing may be missed and the length of overt stenosis may be overestimated. It is also difficult to interpret minimal anomalies of the intrahepatic ducts. Interobserver agreement has been only moderate [14]. MR cholangiography is now a first-intention exploration, ERCP being performed only for therapeutic purposes, or rarely when complementary diagnostic information is needed.

**Prevalence of IBD during primary sclerosing cholangitis.** The prevalence of IBD in patients with primary sclerosing cholangitis varies greatly depending on the study and geographic area (from 21 to 98%). In Europe, there appears to be a north-south gradient. In France, primary sclerosing cholangitis is associated with IBD in about two thirds of patients. The variable methodologies used for the diagnosis of IBD could explain part of these differences since colonoscopy is not systematically used by all authors.

Ulcerative colitis is the main IBD involved. Ulcerative colitis associated with primary sclerosing cholangitis has characteristic features: usually pancolitis (beyond the left angle in 90% of cases), minimally active disease (indications for corticosteroids or hospitalization less frequent than for ulcerative colitis without primary sclerosing cholangitis), or totally quiescent disease [15]. Cases of uniquely histological involvement (with a normal endoscopy) have been reported as has been rectal sparing [16]. It is estimated that the prevalence of primary sclerosing cholangitis is about 5% when the colitis is active beyond the left angle and only 0.5% in the event of distal colitis. The work-up for primary sclerosing cholangitis should systematically include a colonoscopy with biopsy because of a potentially asymptomatic colitis. Ulcerative colitis is diagnosed before primary sclerosing cholangitis in about two thirds of patients but the inverse is also possible; the colitis may even begin after liver transplantation. There is no correlation between the severity of ulcerative colitis and the severity of primary sclerosing cholangitis; colectomy does not appear to modify the course of the primary sclerosing cholangitis. In patients with ulcerative colitis, it is estimated that primary sclerosing cholangitis is responsible for 40% of the chronic anomalies of the liver battery. Other causes are steatosis, excessive alcohol intake, viral hepatitis, granulomatosis, septic processes, or drug toxicity [17].

The prevalence of Crohn’s disease during primary sclerosing cholangitis varies from 1 to 17%. A characteristic feature of Crohn’s disease associated with primary sclerosing cholangitis is that the IBD always involves the colon. The prevalence of primary sclerosing cholangitis may reach 9% in patients with colonic Crohn’s disease. The presence of all four signs is generally considered anecdotal; the diagnosis of primary sclerosing cholangitis can be retained in the presence of two criteria (including at least one histological or radiological criterion) in patients with no other identifiable etiology [13]. A rigorous work-up is thus indispensable to avoid a phase of probable “under-diagnosis” of primary sclerosing cholangitis, for example in the event of minimal anomalies on the liver battery and non-specific lesions of the intrahepatic bile ducts on the MR cholangiogram.

**Management.** The initial work-up for primary sclerosing cholangitis should include a physical examination, blood tests (liver battery), imaging explorations (ultrasound and MR cholangiography), liver biopsy, and colonoscopy (unless colonic disease is known). Liver biopsy may not be indispensable but is generally recommended because it can provide important prognostic information and in the event of an atypical presentation, diagnostic arguments.

Because of the possible asymptomatic presentation of primary sclerosing cholangitis, the following protocol has been proposed for screening purposes:

- at the diagnosis of IBD: routine liver tests (bilirubin, transaminases, gamma glutamyltransferase (GGT), alkaline phosphatase);
- at follow-up: annual liver tests in patients with pancolitis.

**Specific forms of primary sclerosing cholangitis**

These forms illustrate the heterogeneous nature of the disease and should be well understood.

**Small-duct primary sclerosing cholangitis.** Histological evidence of sclerosing cholangitis can be observed even with normal radiographic findings. The diagnosis of small-duct primary sclerosing cholangitis, formally called pericholangitis, is classically retained if the following criteria are present: biological cholestasis, histology compatible with primary sclerosing cholangitis, normal cholangiography, association with IBD without other cause of cholestasis [18]. Nevertheless, recent series do not consider IBD as necessary for diagnosis. The discussion includes other causes of
Liver and inflammatory bowel disease

Cholestasis and chronic inflammatory bowel disease with normal cholangiogram
Liver biopsy
Autoimmune hepatitis and chronic inflammatory bowel disease
MR cholangiography
Treatment-resistant autoimmune hepatitis
MR cholangiography
Cholangiocarcinoma and/or association with pancreatic anomalies
IgG4

Table 2  Unusual presentations of sclerosing cholangitis.

<table>
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<tr>
<th>Cholestasis and chronic inflammatory bowel disease with normal cholangiogram</th>
<th>Liver biopsy</th>
<th>Autoimmune hepatitis and chronic inflammatory bowel disease</th>
<th>MR cholangiography</th>
<th>Treatment-resistant autoimmune hepatitis</th>
<th>MR cholangiography</th>
<th>Cholangiocarcinoma and/or association with pancreatic anomalies</th>
<th>IgG4</th>
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</table>

Cholestasis in macroscopically normal ducts such as primary biliary cirrhosis, sarcoidosis, and drug-induced cholangitis, in addition to small-duct primary sclerosing cholangitis. The prevalence is usually less than 10% in series where all patients had a high-quality cholangiography [18]. This form might be an initial stage of primary sclerosing cholangitis since secondary involvement of large ducts has been described. This development appears to be relatively rare since it has been reported in only 25% of cases after mean follow-up of about 10 years [19]. Although there have been rare case reports of advanced-stage liver disease in patients who apparently never had small-duct primary sclerosing cholangitis, the long-term prognosis is better than "classical" primary sclerosing cholangitis. Cholangiocarcinoma has never been described. Thus, in the majority of cases, small-duct primary sclerosing cholangitis would not be an early stage observed in all types of primary sclerosing cholangitis, but rather a specific disease of the bile ducts with a different natural history.

IgG4 cholangitis. This entity was recently identified [20] and has been described under various terms: sclerosing pancreatocholangitis, autoimmune pancreatocholangitis. IgG4 cholangitis has the following characteristics: increased serum levels of IgG4, IgG4 plasma cell infiltration of the bile ducts, preferential involvement of the extrahepatic ducts, frequent association with another fibrosing condition, particularly autoimmune pancreatitis (> 50%) and spectacular regression of the biliary stenosis with corticosteroid therapy [21]. It is now known that the forms without an associated pancreatic disease can occur and that association with ulcerative colitis is a possibility. In clinical practice, the diagnosis should be entertained (and IgG4 assay ordered) in men beyond the fifth decade with rapid onset symptoms (overt jaundice) and of course pancreatic anomalies. The pathogenic mechanisms are poorly elucidated because of the limited number of cases reported. An autoimmune or allergic mechanism has been proposed, but it is difficult to determine whether IgG4 cholangitis is an atypical form of primary sclerosing cholangitis or a different entity. The presence of these specific forms suggest that search for arguments in favor of primary sclerosing cholangitis should be undertaken in patients with unusual presentations (Table 2).

Differential diagnosis
Several steps are involved:

- does the patient have sclerosing cholangitis?
- is the sclerosing cholangitis primary or secondary?

The diagnosis is essentially based on radiographic anomalies of the bile ducts. If the cholangiography is not normal, the main differential diagnoses are:

- cholangiocarcinoma, in which case the differential diagnosis is particularly difficult or even impossible if a tumor mass is not found; in addition, cholangiocarcinoma can be associated with primary sclerosing cholangitis. Utmost precaution is required before retaining the diagnosis of primary sclerosing cholangitis in a patient with a unique stenosis;
- congenital or acquired anomalies of the bile ducts (Caroli, lymphoma, tuberculosis, portal cavernoma...). Stone-filled biliary dilatations have been recently reported in patients with mutations of the ABCB4 (DR3) gene [22]. If the anomalies are strictly intrahepatic, other differential diagnoses include cirrhosis, malignant spread to the liver, granulomatosis, or amylosis. Liver biopsy is indispensable.

When the diagnosis of sclerosing cholangitis has been established, its primary or secondary nature must be determined. The presence of IBD is a strong argument in favor of primary disease. The main causes are: lithiasis of the common bile duct, history of biliary surgery, injection of a caustic product into the bile ducts, human immunodeficiency virus infection, or ischemia [23]. Gallstone disease has been observed in patients with primary sclerosing cholangitis [24]. Consequently, the presence of stones in the bile ducts is not sine qua non to secondary sclerosing cholangitis.

Gallstone disease
The prevalence of gallstone disease in IBD is similar to that observed in the general population, excepting in patients with Crohn’s disease of the ileum or after resection of the terminal portion of the ileum [1]. The incidence of gallstone disease in IBD varies from 13 to 34% [1]. In a Swedish cohort, 26.4% of patients with Crohn’s disease had gallstone disease versus 15% in the general population [25]. An Italian team also studied the incidence of gallstones in a cohort of 429 patients with Crohn’s disease and 205 patients with ulcerative colitis [26]. They compared these patients with 634 controls matched for age, gender, and body mass index. The incidence of gallstones was 14.3 per 1000 person/years in Crohn’s disease and 7.75 in controls; the figure was 7.5 in patients with ulcerative colitis. Factors predictive of gallstone disease are ileocolonic involvement, disease known for more than 15 years, more than three episodes of clinical relapse, ileal resection of more than 30 cm, more than three hospitalizations, parenteral nutrition, and long hospital stay. The authors found that the extra risk of gallstones is linked only with Crohn’s disease, stone formation being related to ileal involvement and/or ileal resection. Generally, the cholesterol stones are related to altered intestinal absorption of bile salts and reduction of the circulating pool, leading to decreased biliary secretion and over-saturation of cholesterol in the bile.
Because of the higher prevalence of gallstone disease, prophylactic cholecystectomy could be warranted in patients undergoing ileal resection. An Australian team compared a group of patients with operated ileal Crohn’s disease (n = 89) with a group of patients with ileal Crohn’s disease treated medically (n = 45) [27]. Patients were contacted by phone; 20 had symptomatic gallstones (18/89 with ileal resection and 2/45 with medical treatment). In this work, the prevalence of cholecystectomy was the same in the two groups. Thus cholecystectomy would not appear to be warranted during ileal resection for Crohn’s disease.

Diseases of the hepatic parenchyma

Autoimmune hepatitis and primary biliary cirrhosis

The association of autoimmune hepatitis and IBD is exceptional. When associated, the two conditions appear to have a similar course [1,2]. Search for an atypical form of primary sclerosing cholangitis should be undertaken in patients with autoimmune hepatitis. About 20 cases have been reported of patients with primary biliary cirrhosis and IBD [28,29].

Granulomatous hepatitis

Granulomatous hepatitis has been reported in less than 1% of patients with IBD, mainly Crohn’s disease [30]. The disease is generally asymptomatic, but cases with fever, hepatosplenomegaly and/or cholestasis without jaundice have been reported. Histology is required for diagnosis. Outcome is generally favorable and progression to cirrhosis is exceptional. Symptomatic treatment is indicated and one case of regression after colectomy has been reported [30].

Hepatic steatosis

In addition to causes usually observed in the general population, other potential etiologies include corticosteroid therapy, malnutrition, and sometimes parenteral nutrition [1,2]. Recent work suggests that anti-TNF treatments could have a beneficial effect on the metabolic syndrome observed during Crohn’s disease despite the accumulation of intra-abdominal fat [31]. Among 11 patients with Crohn’s disease, repeated infusions of infliximab were associated with a significant decrease in blood glucose and glycosylated hemoglobin, particularly in patients with a low baseline level. Conversely, serum lipids, HDL and LDL cholesterol as well as triglycerides, were initially normal and were not modified by the treatment [31]. A decrease in insulin resistance during infliximab treatment for rheumatoid polyarthitis has also been reported [32]. An ultrasound study in 511 patients with IBD found hepatomegaly in 25.7% and moderate to severe hepatic steatosis (defined by the intensity gradient between the liver and the kidney) in 39.5% of patients with Crohn’s disease and 35% of those with ulcerative colitis [6]. The prevalence of hepatitis-steatosis lesions and pseudo-alcohol lesions which could potentially progress to extensive fibrosis and cirrhosis has not been determined.

Liver abscesses

Liver abscesses are not exceptional in patients with IBD, particularly Crohn’s disease, irrespective of the disease duration or localization [33], and are sometimes inaugural [34]. IBD is generally in an active phase. The potential favoring effect of corticosteroids, immunosuppressive treatment or anti-TNF has been suggested but not specifically evaluated. One case of liver abscess complicating Staphylococcus aureus cholecystitis has been reported in a patient given infliximab [35]. Most patients have multiple abscesses preferentially located in the right lobe [33]. Clinical signs are not specific or may be misleading due to the coexistence of IBD manifestations. Thus in the event of infection in a patient with Crohn’s disease, morphological explorations, including ultrasound and computed tomography, are needed to establish the diagnosis. Unlike the liver abscesses observed in other conditions, the infection is generally caused by a single germ, in decreasing frequency: Streptococcus milleri, Fusobacterium nucleatum, Bacteroides fragilis, numerous Gram negative bacilli, and S. aureus [31]. Antibiotics adapted to the germ(s) identified, ideally by guided needle puncture, are needed in addition to drainage.

Vascular diseases of the liver and chronic inflammatory bowel disease

Portal vein thrombosis

In patients with IBD, the prevalence of deep vein thrombosis is increased [36,37], reported in 1 to 8% of patients in clinical series and up to 41% in autopsy series. Cases of portal vein thrombosis have been included in clinical case reports [36,37]. The pathogenesis associates locoregional factors and systemic prothombotic factors which must be explored to adapt treatment, particularly long-term anticoagulation. Among the acquired factors favoring portal vein thrombosis, inflammatory syndrome (activity of the IBD) and its impact on coagulation factors are important in addition to smoking, oral contraception, and prolonged bed rest [36,37]. The majority of cases of portal vein thrombosis reported in the literature have been observed during an acute phase of the disease or after surgery [38].

Portal vein thrombosis associated with portal vein gas or sepsis (pylephlebitis) has been reported. An analysis of 19 cases of portal vein thrombosis associated with portal vein gas [39,40] found that eight cases had a predisposing regional factor (enterovenous fistula for two, colonoscopy or barium enema for four, and abdominal trauma for two) [39]. Mortality appears to be high (2/19, 11%). The few published cases of pylephlebitis have concerned patients with infectious complications of IBD, particularly abscesses [40]. In one case the portal vein thrombosis was the first manifestation of Crohn’s disease [40].

Peliosis hepatis and sinusoidal dilatation

Peliosis hepatis, typically seen as moderate to severe dilatation of certain hepatic sinusoidal spaces, is generally asymptomatic but can be complicated by portal hypertension and/or anicteric cholestasis. There have been reports of peliosis hepatis associated with IBD, even outside a context of oral contraception or azathiprine intake [41]. Diagnostic magnetic resonance imaging can show low or high intensity signals on the T1 sequences or high intensity signals on the T2 sequences [42].
Budd-Chiari syndrome

An association of IBD and Budd-Chiari syndrome is exceptional and should always trigger a search for associated thrombophilia. Among the cases reported, ulcerative colitis is involved more often than Crohn’s disease [43–45]. Like portal vein thrombosis, surgery or a prothrombotic state are favoring factors [45]. Two cases have been reported in adolescents with ulcerative colitis [43,44].

Hepatotoxicity and precautions for using treatments prescribed for inflammatory bowel disease

Aminosalicylic acid

Derivatives containing 5-aminosalicylic acid (5-ASA) are widely prescribed for mild to moderate episodes of IBD and for the prevention of relapse. The main hepatotoxic effects observed in patients given 5-ASA are listed in Table 3.

Sulfasalazine

Sulfasalazine is rarely a cause of acute hepatitis, generally with elevated transaminases [46]. A few severe cases, sometimes requiring transplantation or even with fatal outcome, have been reported in adults and children [47]. The sulfamide fraction (sulfapyridine) is often the culprit and good potential tolerance to 5-ASA can often be demonstrated. Prudent reintroduction of 5-ASA under strict inpatient surveillance can be proposed if required to control IBD after sulfasalazine-induced hepatitis [48].

Mesalazine

The hepatotoxicity of 5-ASA has been documented, but more rarely, with mesalazine [46,49]. Among 15 studies mentioning adverse hepatic effects of mesalazine, the liver tests were found to be perturbed in up to 21% of the cases. Acute transaminase elevation, generally to a moderate level without liver failure, has been reported as has been cholestasis [50]. Manifestations of hypersensitivity such as fever and hypereosinophilia are often associated with hepatitis [47]. One case of chronic hepatitis has been reported; the histology showed portal and periporal fibrosis associated with segmental necrosis [51]. The liver tests returned to normal when 5-ASA was discontinued. No cases of cirrhosis have been reported [49]. There was one case of granulomatous hepatitis attributed to 5-ASA in a patient with ulcerative colitis [52]. Another case of acute hepatitis was reported in a patient taking azidosalicylate (Dipentum®) [53].

Purine analogues (azathioprine, 6-mercaptopurine, 6-thioguanine)

In the Césame cohort in France, 54% of the 12,463 patients with Crohn’s disease and 26% of the 7679 patients with ulcerative colitis were given azathioprine or 6-mercaptopurine [54]. Excepting dose-dependent hepatotoxicity or a context of hypersensitivity, thiopurines can induce injury to the hepatic sinusoidal endothelium [55]. The main effects observed in the liver in patients taking purine analogues are listed in Table 3.
The prevalence of abnormal liver tests in patients with IBD treated with purine analogues was recently studied in 161 patients followed prospectively for a median period of 271 days. Abnormal liver tests, defined by serum ALT and/or alkaline phosphatase levels twice the upper limit of normal, were observed in 21 patients (13%). ALT levels were elevated more often than alkaline phosphatase levels [56]. In 50% of cases, these anomalies appeared within the first three months. Treatment was definitively discontinued in 31% of cases. In 44% of cases, the azathioprine dose was temporarily reduced before later returning to the initial dose. In certain cases, the hepatotoxicity of azathioprine was related to dose, associated treatments, nutritional status, or drug interactions. Gisbert et al. analyzed all studies evaluating the frequency of liver injury induced by azathioprine or 6-mercaptopurine [55]. Taking into account only those studies with a follow-up, 2992 patients were given treatment during 6952 years follow-up. The incidence of hepatotoxicity (defined as elevated serum ALT) was 1.4% per patient-year of treatment.

Dubinsky et al. reported a correlation between 6-methylmercaptopurine level greater than 5700 pmol/8 × 10^8 erythrocytes and hepatotoxicity of azathioprine or 6-mercaptopurine [57]. In that work, among 16 patients with adverse liver effects secondary to azathioprine or 6-mercaptopurine treatment, the median level of 6-methylmercaptopurine was significantly higher than measured in patients with normal liver tests [57]. The risk of developing hepatotoxicity was three-fold higher when the 6-methylmercaptopurine level was greater than 57 pmol/8 × 10^8 erythrocytes [57]. The level of 6-thioguanine was not correlated with hepatotoxicity of azathioprine/6-mercaptopurine nor with azathioprine/6-mercaptopurine dose. All teams have not, however, found similar results, so such findings should be interpreted with caution [58]. A few cases of chronic hepatitis or cirrhosis have also been reported [53,58].

### Anomalies of the hepatic vascularization: nodular regenerative hyperplasia and sinusoidal obstruction syndrome

#### Nodular regenerative hyperplasia

Anomalies of the hepatic vascularization are classically considered to be complications of thiopurine treatment. In the early 2000s, 6-thioguanine was proposed with some success in IBD patients who were unable to tolerate azathioprine or 6-mercaptopurine because of pancreatitis, immunooallergic manifestations or hepatitis [59]. It was nevertheless noted that this treatment was frequently complicated by nodular regenerative hyperplasia, so that it was almost totally abandoned [59]. Dubinsky et al. studied the liver tests and blood counts of 111 patients given 6-thioguanine [60]. Twenty-nine patients (26%) had abnormal liver test results and/or hematological toxicity induced by 6-thioguanine. Elevated liver enzymes and platelet counts less than 200,000/mm^3 were the most common findings. During treatment with 6-thioguanine, among patients with abnormal liver tests (n = 29, group 1) the median serum transaminase level and the median alkaline phosphatase level increased while the platelet count decreased; in group 2 these levels remained unchanged. Liver biopsy was performed in 17 of the 29 patients in group 1 and nine of the 82 in group 2. Nodular regenerative hyperplasia was identified in 13/17 (76%) of the patients in group 1 and in 3/9 (33%) of those in group 2. There was no association between duration of treatment, total cumulative dose, and level of 6-thioguanine nucleotides.

The GETAID study reported 36 cases of regenerative nodular hyperplasia in IBD patients given purine analogues [61]. Twenty-nine of the patients were men [61]. Thirty-one had portal hypertension at diagnosis and 14 of them presented a severe complication (digestive bleeding for nine due to esophageal varices and ascites in five). Twenty-one patients underwent ileal resection (14 had several resections). Two factors were associated with risk of nodular regenerative hyperplasia: male gender and ileal resection. Thrombophilia was observed in 10/15 cases examined. Cosnes et al. reported 13 cases of nodular regenerative hyperplasia after a median 44 months of azathioprine treatment in a cohort of 1860 patients [62]. This series gave a prevalence estimate of 0.7%, which might be considered an underestimate since liver biopsy was performed only in patients with thrombopenia. Similar to the GETAID study, risk factors for nodular regenerative hyperplasia were male gender and a history of ileal resection. Thus, in men with an ileal resection treated with azathioprine, the actuarial rate of nodular regenerative hyperplasia was 11.4 ± 5.1% 10 years after starting azathioprine [62].

These observations underscore the gravity of nodular regenerative hyperplasia and the frequency of associated thrombophilia, particularly hyperhomocysteinemia which can be favored by a deficit in folic acid and/or vitamin B12 (deficits frequently observed in IBD, whether related to malabsorption or insufficient intake).

The natural history of nodular regenerative hyperplasia is not fully elucidated, whether in patients who continue taking the drug or in those who have discontinued. In a series of four cases of biopsy-proven nodular regenerative hyperplasia in men with IBD treated with azathioprine whose diagnosis had been established early (between six and 12 months after starting azathioprine), liver tests and platelet counts returned to normal in three of four cases, but the outcome and potential regression or worsening of the hyperplasia was not reported [63].

The discovery of this serious complication has two practical implications for the management of patients taking purine analogues. The first is to screen for potential anicteric cholestasis (even with minimal GGT elevation) and/or decreased platelet counts. The second is to order morphological explorations in order to identify the etiology of the observed biological anomalies. Magnetic resonance imaging is contributive and a liver biopsy sample may be necessary for reticulin staining [64]. This should be sufficient to avoid late diagnosis (by insufficient surveillance) as well as over-diagnosis where all liver anomalies would be wrongly attributed to this etiology and this drug class. It is important to recognize the usefulness of a liver biopsy rather than relying on a presumptive diagnosis. The prevention of certain cases will require supplementation with vitamin B12 and folic acid which should be assayed regularly in patients with ileal resection. Finally, liver tests...
should be ordered regularly in patients with regenerative nodular hyperplasia in addition to surveillance of esophageal varices and ultrasound assessment of the parenchymal structure.

**Syndrome of sinusoidal obstruction**

*Generalities.* The syndrome of sinusoidal obstruction is often associated with partial or total non-thrombotic fibrous obstruction of the centrolobular veins. The diagnosis is histological and is based on the presence of variable sinusoidal dilatations within the centrolobular zones associated with atrophy then necrosis of the hepatocytes, and, in the more severe forms with nodular regenerative hyperplasia [65,66]. Generally, portal hypertension with progressive ascites is the main manifestation. Anicteric cholestasis is observed, associated in advanced forms with thrombopenia consecutive to the hypersplenism induced by portal hypertension. Magnetic resonance imaging can show left lobe hypertrophy often associated with a prothrombotic state, which is also related to sinusoidal obstruction and nodular regenerative hyperplasia.

Prothrombotic phenomena associated with sinusoidal obstruction and nodular regenerative hyperplasia. Sinusoidal obstruction and nodular regenerative hyperplasia are often associated with a prothrombotic state, which is also observed in IBD patients [61,70]. Hillaire et al. reported a series of 23 patients with idiopathic intrahepatic portal hypertension who underwent hemostasis explorations; 12 (52%) presented an associated prothrombotic state [70] which was a myeloproliferative syndrome in five (latent in four) associated with protein S deficiency in two, protein S deficiency in two other patients, protein C defect in one patient, and antithrombin III deficiency in five.

**Hepatocellular carcinoma.** Excluding other predisposing liver diseases, four cases of hepatocellular carcinoma have been reported in three patients with Crohn’s disease and one with ulcerative colitis [71,72]. These four patients were treated with azathioprine or an azathioprine-infliximab combination for one of them [72]. Two of these patients were young (22 and 28 years) and exposed to azathioprine for three to six years.

**Methotrexate**

Methotrexate-induced hepatotoxicity was initially described in the treatment of severe psoriasis and rheumatoid polyarthriti [73]. The main liver diseases attributed to methotrexate are given in Table 3.

The main histological anomalies are macrovesicular steatosis, inflammatory infiltration of the portal spaces, hepatocellular necrosis, fibrosis, and cirrhosis [73]. Fibrosis and cirrhosis are usually observed after a cumulative dose of greater than or equal to 1.5 g. The prevalence of cirrhosis during psoriasis varies from 0 to 26% [74]. Most of these studies have not however considered risk factors associated with chronic liver disease (virus, alcohol, metabolic syndrome...) [73]. More recent studies taking into account these factors have shown a lower level of fibrosis [75]. Aithal et al. obtained 121 liver biopsies from 66 patients treated with methotrexate for psoriasis [75]. None of the samples revealed cirrhosis after a median 280 weeks treatment and a median cumulative dose of 3206 g. The estimated cumulative probability of advanced fibrosis (Ishak score ≥ 4) was 0%, 2.6%, 2.6%, 8.2%, and 8.2% for 1500, 3000, 4500, 5000, and 6000 mg dose respectively. Only two of the 24 patients with liver biopsy results before methotrexate introduction had advanced fibrosis.

**Specificity during IBD**

Among 306 IBD patients treated with methotrexate within the framework of nine therapeutic trials, transaminase levels were elevated in 18, giving a prevalence of 6% [76,77]. Lemann et al. observed persistently anomalous liver tests in three of 49 patients treated with methotrexate for more than six months for their Crohn’s disease [77]. Eleven of the 49 patients had a liver biopsy for the following reasons: cumulative dose greater than or equal to 1500 mg (n = 3), persistently anomalous liver tests (n = 3), surgery (n = 3), reason not specified (n = 2). None of the biopsy specimens revealed cirrhosis, and at most moderate periportal fibrosis, observed in one case [77]. The risk of methotrexate-induced fibrosis and cirrhosis is thus an exception in IBD.

**Blood tests for surveillance**

Routine surveillance of blood cell counts and liver tests is useful in patients taking methotrexate. A liver battery should be ordered weekly during the first month. Thereafter, every three months has been found adequate: (http://www.getaid.org/03-fiches/documents/methotrexate.pdf). If the results show an altered function, tests should be ordered at closer intervals and if the anomalies persist at three successive tests, two solutions are possible, sometimes together, withdrawal of methotrexate and search for hepatic fibrosis. Persistent elevation of serum enzymes is correlated with histology [78].

**Evaluation of hepatic fibrosis**

The role of non-invasive tests for the evaluation of hepatic fibrosis is not well established in patients with IBD. Preliminary work in 54 patients with Crohn’s disease, including 21 with a cumulative dose of methotrexate greater than 1500 mg, and 33 methotrexate naive, was conducted to
evaluate hepatic fibrosis using Fibrotest® and Fibroscan® [79]. The fibrosis score determined by elastometry was not significantly different between the two groups of patients. Evaluation of fibrosis by one and/or the other method can be proposed before starting methotrexate treatment followed by regular tests during the treatment course in patients with favoring factors such as chronic viral hepatitis, steatosis, and/or alcoholism. While waiting for the validation of this diagnostic approach, liver biopsy remained a case-by-case indication, for example after prolonged transaminase elevation.

Infliximab and other blockers of alpha tumor necrosis factor

The main liver diseases observed during treatment with anti-TNF are given in Table 3.

In the Accent I trial, transaminase elevation was observed with infliximab in 42% of patients [80]. In a phase III trial in rheumatoid polyarthritis patients, moderate transaminase elevation was observed in 37% of the treated patients versus 29% in the placebo group [81].

After ruling out other causes of hepatitis, eight cases of acute hepatitis were associated with infliximab in patients with inflammatory colitis, psoriatic rheumatism, or rheumatoid polyarthritis [82–84]. Acute hepatitis was diagnosed after 1 to 12 infliximab infusions. The course was generally favorable after withdrawal of infliximab, but one patient developed fulminant hepatitis and required liver transplantation [83]. Antinuclear antibodies were identified in four cases [83,84] and high-titer antismooth muscle antibodies in one [84].

Data in the literature are scarce on the hepatotoxic effects of adalimumab and certolizumab. Moderate transient elevation of liver enzymes in serum has been noted in pivotal studies performed in patients with Crohn’s disease [85]. In a study conducted in 214 patients with rheumatoid polyarthritis treated with adalimumab, 17 and 26 patients developed elevated serum enzymes, i.e. ALT (7.9%) and alkaline phosphatase (12.1%). These cases were not documented [86]. For certolizumab, a few cases of moderate transient elevation of liver enzymes have been reported in the two main clinical trials conducted in Crohn’s disease patients [87,88]. These cases were not documented.

Precautions for use of immunomodulators and hepatitis B virus

Immunosuppressive treatments expose patients to the risk of viral reactivation [89]. Treatments which induce immune tolerance favor viral replication; their withdrawal, which leads to restored immunity, in turn leads to a destruction of hepatocytes expressing the nucleocapside antigens. Reactivation of hepatitis B virus (HBV) has been observed in patients given infliximab for a rheumatological disease or IBD [90–92]. Most of these patients developed fulminant hepatitis. Among the three patients treated with infliximab who were positive for the hepatitis B surface antigen (HBs) reported by Esteve et al., the first died of fulminant hepatitis, the second presented HBe seroconversion, and the third was treated preventively with lamivudine, allowing HBe seroconversion before introduction of infliximab (which then did not induce viral reactivation) [90]. Patients should be screened for HBs before starting immunosuppressive treatment [93]. There is no specific guideline concerning patients with isolated anti-HBc antibodies. Treatment with a new generation analogue could be proposed for first-line treatment. Entecavir (Baraclude®) or tenofovir (Viread®) both have powerful antiviral action and very low rate of resistance emergence. Agreement on the appropriate therapeutic approach is less well defined in HBs-positive patients who need azathioprine or methotrexate. These patients do, however, need close surveillance after interruption of their immunomodulator treatments.

Precautions for use of immunomodulators and hepatitis C virus

Treatment of chronic hepatitis C virus (HCV) infection associates pegylated interferon and ribavirin. In a patient with HCV infection and IBD, it is important to recognize interactions between the different drugs prescribed over the course of these two diseases as well as their consequences for each disease.

Interferon and IBD

Bargiggia et al. conducted a case-control study comparing the efficacy of standard interferon in a single drug regimen in 21 patients with HCV infection and quiescent or moderately active IBD (10 patients with Crohn’s disease and 11 with ulcerative colitis) versus a group of 63 patients with isolated HCV infection matched for age and gender [94]. After 12 months treatment, the virological response was identical in the two groups (42% versus 35%), as was sustained response (24% versus 18%). The adverse effects were also identical in the two groups and there was no exacerbation of the IBD during the 12 months of treatment.

Interaction between ribavirin and azathioprine

Hematological toxicity is noted in 1.4 to 7% of patients treated with azathioprine. Blockade of inosine monophosphate dehydrogenase (IMPDH) with ribavirin could increase the level of methylated derivatives of azathioprine which are known to be associated with higher risk of hematological toxicity. Five cases of severe pancytopenia have been observed in patients taking azathioprine for IBD and a biotherapy regimen of pegylated interferon and ribavirin. In a patient with HCV infection and IBD, it is important to recognize interactions between the different drugs prescribed over the course of these two diseases as well as their consequences for each disease.
methyltransferase (TPMT) level and three were no mutations of its gene. It is thus preferable to avoid associating IMPDH inhibitors such as ribavirin with azathioprine.

Hepatosplenic lymphomas and immunomodulators

Exceptional cases of hepatosplenic T-cell lymphoma have been reported in patients taking infliximab and purine analogues for IBD [96]. These subjects were young and predominantly male. Most had Crohn’s disease (9/10) for five to 21 years, had been treated with purine analogues for two to six years, and had received one to 24 infliximab infusions. Outcome was fatal in six cases at the time of publication. At this stage, the risk factors and the mechanisms involved have not been elucidated, particularly concerning the respective roles of the two treatments. Hepatosplenic T-cell lymphomas constitute a subgroup of peripheral non-Hodgkin T cell lymphomas [97]. The clonal population often expresses gd receptor but in certain cases can express ab receptor (seven and three respectively of the 10 published cases of IBD). Generally, hepatosplenomegaly was the clinical presentation of the cases complicating IBD, but cases of hepatitis (two of the IBD cases published) and fever or thrombopenia have also been observed.

Conclusion

Beyond the classical association of IBD and primary sclerosing cholangitis, attention has been focused in recent years on the vascular toxicity of azathioprine and its derivatives which can lead to a wide spectrum of pathological lesions from sinusoidal dilatation to nodular regenerative hyperplasia. A declining platelet count, associated or not with cholestasis, can be an early sign of toxicity, even without reaching the stage of thrombopenia. In patients on long-term methotrexate, cirrhosis is exceptional during IBD; regular screening for fibrosis can be useful (Fibroscan®). Search for chronic carriers of the hepatitis B surface antigen is important before initiating anti-TNF treatment. Preventive treatment with a nucleoside or nucleotide analogue is important before initiating anti-TNF treatment. Preventive treatment with a nucleoside or nucleotide analogue is important before initiating anti-TNF treatment.

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Liver and inflammatory bowel disease

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