Hepatobiliary Disorders Associated with Inflammatory Bowel Disease

Hepatobiliary manifestations are common in inflammatory bowel disease (IBD) frequently manifesting in abnormal hepatic biochemical tests. Of these disorders, Primary Sclerosing Cholangitis (PSC) carries the most significant clinical implications and remains a highly challenging disease to manage. Cholangiocarcinoma is a potential risk in PSC and has a poor prognosis in most cases. The presence of PSC is associated with increased risk of colorectal cancer in patients with ulcerative colitis. Hepatotoxicity can occur with nearly all medications in the treatment of IBD. Discontinuation of drug, or dose reduction in some cases, is indicated when abnormalities are detected. This article reviews the hepatobiliary manifestations of IBD and the hepatotoxic effects of the medications used in its management. The importance of routine monitoring of hepatic biochemical tests and an awareness of the implications and causes of abnormal hepatic biochemical tests in patients with IBD is emphasized.

INTRODUCTION

Ulcerative colitis (UC) and Crohn’s disease (CD) are idiopathic conditions that primarily affect the gastrointestinal tract, but also are associated with a variety of systemic or extra-intestinal manifestations. These extra-intestinal manifestations may implicate multiple organ systems. For some of these disorders there is evidence that the severity and duration of the inflammatory bowel disease (IBD) may influence the course of the extra-intestinal manifestations, whereas others are independent of the underlying bowel disease. The pathogenesis of these manifestations remains elusive.

Hepatobiliary complications commonly occur in IBD (Table 1). Of these complications, primary sclerosing cholangitis (PSC) is the most serious and is an
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Table 1
Hepatobiliary Manifestations of IBD
- Primary Sclerosing Cholangitis (PSC)
- Cholangiocarcinoma
- “Small duct” PSC
- Autoimmune hepatitis
- Steatosis
- Cholelithiasis
- Hepatic amyloidosis
- Granulomatous hepatitis
- Liver abscess
- Medication-induced hepatotoxicity

important indication for liver transplantation (1). This article reviews the hepatobiliary manifestations of IBD and the hepatotoxic effects of the medications used in its management.

PRIMARY SCLEROSING CHOLANGITIS (PSC)
PSC is characterized by progressive inflammation, fibrosis and stricturing of intra- and extra-hepatic bile ducts (2,3). The disease is usually progressive, often leading to cirrhosis, portal hypertension and liver failure (4).

The pathogenesis of PSC is unknown. Bacteria, toxins, viral infections, immunologic and genetic factors have been proposed. It has been postulated that PSC is the result of recurrent or chronic cholangitis stemming from the recurrent entry of enteric bacteria through the more permeable colonic mucosa associated with chronic colitis (5–7). Animal models of small intestinal bacterial overgrowth have revealed changes in the appearance of bile ducts similar to those seen in PSC (8). However, the absence of portal vein phlebitis in patients with PSC, a typical finding in recurrent portal bacteremia, undermines this hypothesis (9,10).

It has also been proposed that abnormal absorption of toxic bile acid metabolites or toxins produced by enteric bacteria play a role in the pathogenesis. However, there is no evidence to support this hypothesis (11).

The fact that only a small number of patients with inflammatory bowel disease develop PSC (2.5% to 7.5% of UC patients and rarely in CD) suggests that other factors play a role in the pathogenesis. An increasing body of evidence, although largely indirect, points to immunologic and genetic factors in the pathogenesis of PSC.

A high prevalence of elevated autoimmune markers is seen in patients with PSC. These include perinuclear antineutrophilic cytoplasmic antibodies (p-ANCA), immunoglobulins IgG and IgM and autoantibodies, such as antinuclear antibodies and anti-smooth muscle antibodies (12–14). Furthermore, human leukocyte antigen (HLA) haplotypes HLA-B8 and HLA-DR3, which are associated with autoimmune disorders such as celiac disease, myasthenia gravis and diabetes mellitus, are present at increased frequency in patients with PSC (12).

The prevalence of PSC in the general population is low estimated at 1 to 6 per 100,000 persons in the United States (18). The mean age at diagnosis is 39 years and men are affected more than twice as often as women (19). PSC occurs primarily in patients with inflammatory bowel disease (20–23). The prevalence of UC in PSC patients varies in different studies from 25% to 80% (18,20,24,25). Although there is no correlation between the severity of PSC and that of the colon disease, PSC is more common in patients with extensive colonic involvement (18,24,25).

PSC can also develop years before onset of IBD and years after total colectomy (26). Approximately 2.5% to 7.5% of patients with UC have or will develop PSC (27–29). Although PSC is usually suspected in IBD patients with abnormal hepatic biochemical tests, reported cases of PSC in asymptomatic patients with normal hepatic biochemical tests suggest that PSC in patients with IBD may be more prevalent than reported (30).

Although PSC is more commonly associated with UC than with CD, the prevalence of PSC in Crohn’s patients with large bowel involvement approximates that of UC patients (31). Therefore, PSC should be considered in the differential diagnosis in patients with colonic CD in cases where hepatic biochemical tests produce abnormal results.

The classic histologic finding in PSC is concentric rings of connective tissue surrounding degenerating bile duct epithelium. Unfortunately, these lesions commonly referred to as onionskin lesions, (Figure 1) are rarely seen on liver biopsy of PSC patients. Liver
biopsy findings are usually non-specific and are subject to considerable sampling error and, for this reason, are useful only as an adjunct to the diagnosis (18).

Cholangiography is required for definitive diagnosis. The findings of multifocal strictures and dilatations of the intra- and extra-hepatic bile ducts on cholangiogram giving the characteristic “beaded appearance” is diagnostic of sclerosing cholangitis (Figure 2). Nevertheless, it is important to rule out secondary causes of sclerosing cholangitis that can produce similar cholangiographic findings. These include chronic bacterial cholangitis, or recurrent choledocholithiasis, ischemic bile duct injury secondary to intraarterial treatment with floxuridine, cholangiopathy associated with acquired immune deficiency syndrome (AIDS), previous biliary surgery, congenital biliary-tree abnormalities and cholangiocarcinoma (18).

The majority of patients with PSC are asymptomatic at the time of diagnosis. The diagnosis is usually suspected on the basis of abnormal hepatic biochemical tests, particularly elevated alkaline phosphatase or \( \gamma \)-glutamyltransferase levels. However, normal levels have also been reported at the time of diagnosis (30). Often, with advancing disease, patients develop symptoms of pruritus, fatigue, jaundice and weight loss. Progression to cirrhosis, portal hypertension and end-stage liver disease is the natural course of the disease in many patients and death usually ensues shortly thereafter, in the absence of liver transplantation. The median survival rate is 9 to 11 years from time of diagnosis and even less in patients who are symptomatic at the time of diagnosis. Kim, et al devised a model for reliably estimating patient survival in a setting of PSC (32). The model is designed around a formula which incorporates five variables (age, bilirubin, albumin, aspartate aminotransferase and history of variceal bleeding) upon the basis of which a risk score for PSC patients can be calculated (Table 2). The result is then used to determine the estimated survival of the patient up to 4 years (Table 2).

To date, there is no medical therapy that has proven effective in the treatment of PSC. A small number of studies have demonstrated that ursodeoxycholic acid at standard doses of 13 to 15 mg/kg/d significantly improved liver biochemistries but did not alter the clinical course of disease with respect to progression to cirrhosis, time to transplantation or death (33–36). Prelim-

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The mainstay of treatment has been in the management of the symptoms and complications associated with PSC namely, portal hypertension, pruritis, malabsorption, biliary strictures, cholelithiasis, cholangitis and osteopenia/osteoporosis. Currently, liver transplantation remains the only curative therapy for PSC in eligible patients. Recurrence of PSC, however, has been reported in approximately 9% to 14% of grafts after orthotopic liver transplantation (40,41).

PSC patients are at increased risk of cholangiocarcinoma and colorectal cancer. Cholangiocarcinoma occurs in 6%–20% of patients with long-standing PSC (42–44). Alcohol consumption is an independent risk factor (45).

Several clinical studies have shown that the risk of developing colorectal carcinoma and dysplasia is greater in patients with UC and PSC than in patients with UC alone (46–50). In a case control study involving matched controls of patients with UC and PSC and patients with UC alone the absolute risk of colorectal carcinoma or dysplasia was significantly greater in patients with both UC and PSC (46). The risk increased substantially with the length of time that had elapsed following diagnosis (10 years: 9% vs 2%), (20 years: 31% vs 5%) and (25 years: 50% vs 10%). Recent studies have shown that administration of ursodeoxycholic acid may reduce the risk of colorectal cancer and dysplasia in patients with PSC and UC (51,52). However, to date the most effective strategy to address the risk lies in stringent colorectal cancer screening guidelines. No screening guidelines have yet been established for UC patients with PSC. We propose annual screening in patients with ulcerative colitis once a diagnosis of PSC has been made.

### CHOLANGIOCARCINOMA

The diagnosis of cholangiocarcinoma is usually extremely difficult. Distinguishing cholangiocarcinoma from benign biliary strictures by cholangiogram is challenging, as PSC often resembles a benign dominant stricture. The onset of jaundice, weakness, weight loss, right upper quadrant pain, fever and rapidly rising serum bilirubin are suggestive of cholangiocarcinoma, but these clinical conditions are usually present only at advanced stages of the disease (43). Combining use of serum tumor markers CEA, and CA 19-9 has been shown to facilitate more accurate diag-

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**Table 2**

Revised Natural History Model to Estimate Patient Survival in PSC

\[
\text{Risk Score (R)} = 0.03 \times (\text{age in years}) + 0.54 \times \log e (\text{total bilirubin in mg/dl}) + 0.54 \log e (\text{AST in U/L}) + 1.24 \times (\text{variceal bleeding}^*) - 0.84 \times (\text{albumin in g/dl})
\]

\[
\text{Estimated Survival Probability % (S_{1–4 \text{ years}}) = S_0^\psi(R-1.00)}
\]

\* previous history of variceal bleeding = 1, No previous a history of variceal bleeding = 0; \(S_0\) (at 1 year) = 0.963, \(S_0\) (at 2 years) = 0.919, \(S_0\) (at 3 years) = 0.873, \(S_0\) (at 4 years) = 0.833

The risk score and estimated survival probability can be obtained using a user-friendly online worksheet (http://www.mayoclinic.org/gi-rst/mayomodel3.html)
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Table 3
Mayo Model Risk Score

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<thead>
<tr>
<th>Variables</th>
<th>Risk Score</th>
<th>Actuarial survival</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Low (≤4.4)</td>
<td>1 year = 100%</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td></td>
<td>7 years = 100%</td>
</tr>
<tr>
<td>splenomegaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic stage</td>
<td>Moderate (4.4 &gt; 5.3)</td>
<td>1 year = 68.6%</td>
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<tr>
<td>Stage 1 = cholangitis or portal hepatitis</td>
<td>7 years = 68.6%</td>
<td></td>
</tr>
<tr>
<td>Stage 2 = periportal fibrosis ± periportal hepatitis</td>
<td>7 years = 68.6%</td>
<td></td>
</tr>
<tr>
<td>* Stage 3 = septal fibrosis or bridging necrosis</td>
<td>High (≥5.3)</td>
<td>1 year = 54.6%</td>
</tr>
<tr>
<td>Stage 4 = cirrhosis</td>
<td></td>
<td>7 years = 46.8%</td>
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</tbody>
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Risk score (r) = 0.041 × (age in years) + 0.535 × loge (total bilirubin in mg/dl) + 0.705 (splenomegaly score) + 0.486 × (histologic stage*)

*A multiplication factor of 2 is given for histologic stage 3 and a multiplication factor of 3 is given to histologic stage 4

The diagnosis of cholangiocarcinoma in patients with PSC (53). Ramage, et al devised an index combining the two tumor markers using the formula [CA19.9 + CEA × 40]. A cut off value of 400 yielded a sensitivity specificity, positive predictive value, negative predictive value and accuracy of 66%, 100%, 100%, 81% and 86% respectively (53).

The benefits of endoscopic retrograde cholangiography with bile duct brushings for cytology in routine screening of patients with PSC remain questionable. Although this modality is highly specific, its sensitivity is low (54–58). Combining cytology and DNA image analysis from bile duct brushing may increase its diagnostic sensitivity as compared with cytology alone (59). Currently, no guidelines have been established for cholangiocarcinoma screening in patients with PSC. However, combining routine testing for the tumor markers CEA and CA 19-9 with endoscopic retrograde cholangiography and bile duct brushings for cytology and DNA analysis should increase diagnostic yield (60).

For patients who have developed cholangiocarcinoma the prognosis is poor with a median survival of 7 months (61). Most patients have unresectable disease and recurrence is common. In one study of highly selected patients with hilar cholangiocarcinoma survival rates were reported to be from 33% to 46% at 5 years following extensive surgical resection in patients with localized tumors and negative resection margins (62).

Liver transplantation for patients with cholangiocarcinoma has typically yielded poor outcomes and for this reason transplantation has been considered contraindicated for most patients. In a recent study PSC patients with cholangiocarcinoma had a 35% 5-year survival rate following transplantation (63). However, in highly selected patients with localized perihilar cholangiocarcinoma, tumor size <3 cm and negative regional lymph nodes, neoadjuvant chemotherapy followed by liver transplantation gave a 5-year 80% actuarial survival rate (64,65).

It is not clear whether early detection of cholangiocarcinoma in patients with PSC improves overall prognosis after liver transplantation. Nashan, et al proposed the Mayo Model Risk Score (Table 3) as a screening tool for identifying patients with PSC who could benefit from early transplantation (66). According to this study, a group of PSC patients with Mayo Model risk scores of <4.4 (low risk), had actuarial survivals of 100% at 7 years, while those with risk scores of 4.4 > 5.3 (moderate risk) and >5.3 (high risk) had actuarial survivals of 68.6% and 46.8% respectively (66). However, the group did not include PSC patients with biliary malignancy. Where biliary malignancy was detected at transplantation the actuarial survival was 30% at 1 year and 0% at 6 years. In the study a risk score above 4.4 was associated with a marked increase in the incidence of biliary malignancies. Based on the data, the authors recommended that liver transplanta-

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The following be considered for PSC patients with low Mayo Model risk scores (<4.4) where prognosis was better because of the lower risk of developing biliary malignancy (66).

“SMALL DUCT” PSC

“Small duct” PSC, as the name implies, primarily affects the small bile ducts. It comprises about 5% of all cases of histologically confirmed PSC (67,68). The condition shares many clinical and histologic features with PSC and is considered part of the disease continuum. The clinical course of small duct PSC, however, is more benign with only 12% of patients progressing to large duct PSC (67–69). The diagnosis is difficult to establish due to the normal appearance of the biliary tree on cholangiogram and can only be reliably made in the setting of IBD.

AUTOIMMUNE HEPATITIS

It is widely believed that inflammatory bowel disease has an autoimmune component. However, its association with autoimmune hepatitis (AIH) is limited to case reports. In the majority of cases reported, AIH has been found to coexist with PSC as an “overlap syndrome,” primarily in association with UC (70–72). Rare cases have also been reported in patient’s with CD (73). Therefore, an evaluation for PSC with cholangiogram should be considered in all patients with AIH and colitis.

The onset of autoimmune hepatitis can result in rapid progression of liver disease and should be tested for in patients with PSC who present with high serum levels of aminotransferases or rapid deterioration in liver function (74). When a diagnosis of AIH is made, standard treatment with prednisone and azathioprine should be considered, although the response has usually been poor where “overlap syndrome” is present. (70).

STEATOSIS

Liver steatosis is the most common pathological liver finding in patients with IBD (75). In a prospective, single center, controlled study of 511 patients with IBD the prevalence of liver steatosis detected using sono-
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ment rarely occurs without concurrent involvement of other organ systems such as kidney, spleen, pancreas, bone marrow, gastrointestinal tract and heart (87).

In the largest retrospective analysis to date, 6 of 3,050 of patients with inflammatory bowel disease whose records were reviewed had hepatic amyloidosis. Three of these presented with hepatomegaly and the remaining three were diagnosed at autopsy (87). Given the rarity of the condition and the need for liver biopsy for reliable diagnosis, the true incidence of hepatic amyloidosis and its prognosis in inflammatory bowel disease is unknown. However, as with other causes of secondary amyloidosis, reversibility is probably achievable with treatment of the underlying condition.

GRANULOMATOUS HEPATITIS

Granulomatous hepatitis is an uncommon complication of CD occurring in less than 1% of patients (88). Patients are usually asymptomatic presenting with elevated levels of alkaline phosphatase as the main laboratory abnormality. The condition generally has no clinical sequela and usually requires no treatment. The most common cause of granulomatous hepatitis in the setting of IBD is secondary to a medication, usually sulfazalazine, but the condition may also result from other causes such as malignancy, infectious and idio-pathic, such as sarcoidosis (89).

LIVER ABSCESS

Liver abscess in IBD is rare, but is more prevalent in patients with CD than in the general population (90). Intra-abdominal abscesses, fistuluous disease, intestinal perforation and metronidazole or corticosteroid therapy have been reported to be important predisposing factors (91,92). Most common clinical manifestations of liver abscess include fever, chills, anorexia and abdominal pain with right upper quadrant tenderness (90,91). Leukocytosis and abnormal hepatic biochemical tests, particularly elevated alkaline phosphatase are among the more common laboratory findings (90,91). An overall mortality of 21% for liver abscess in CD has been reported, and immunosuppressive treatment and delayed diagnosis of liver abscess may increase mortality in IBD (90). Early diagnosis with an imaging study (abdominal ultrasound or CT scan), percutaneous drainage and antibiotic treatment improve outcome (91,93,94).

Liver abscess is rarely reported in patients with UC (95,96). Despite the fact that biliary infection is a common source of pyogenic liver abscess in the general population, it is surprising that it does not occur more frequently in patients with UC and PSC who are at increased risk of developing ascending cholangitis.

MEDICATION INDUCED HEPATOTOXICITY

Liver injury is a potential complication of nearly every medication used in the treatment of patients with IBD. Although medication induced hepatotoxicity in IBD is rare and usually manifests as mild elevations in amino-transferases, fatal and near fatal reactions may occur.

The majority of drug related reactions are idiosyn-cratic. These reactions occur at therapeutic doses at a frequency of 1 in every 1,000 to 100,000 patients and are characterized by a variable delay or latency period ranging from 5 to 90 days from the initial dose (97). Liver injury is usually reversible following discontinuation of medication but, upon rechallenge, a more severe reaction often occurs (97,98).

Some drugs used in the treatment of inflammatory bowel disease can cause liver injury in a dose-dependent fashion. These include methotrexate, cyclosporine and azathioprine. Although the reactions are considered idiosyncratic, the individual or cumulative dosage plays a role in liver toxicity (97).

5-AMINOSALICYLATES

The 5-aminosalicylates (pentasa, mesalamine, sulfaza-lazine) although rarely implicated may cause hepatoxicity through an idiosyncratic type reaction. The most common manifestation is a mild elevation of aminotransferases. However, hepatocellular, cholesta-tic, granulomatous and immunological types of reac-tions have been described (89,99–103). The latter type of reaction is more commonly associated with sulfaza-lazine and results, most likely, from the sulfa compo-nent. A rare fatal case of fulminant liver failure attrib-uted to sulfazalazine was reported in a 24-year-old

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patient who was rechallenged years after an episode of hepatitis. In the majority of cases, however, the effects are reversible upon discontinuation of the drug.

**Azathioprine and 6-Mercaptopurine**

Azathioprine (AZA) and 6-mercaptopurine (6-MP) can cause a hepatocellular or cholestatic pattern of liver injury in a dose dependent fashion or through an allergic hypersensitivity reaction (104–107). The majority of cases are asymptomatic with mild amino-transferase elevations occurring in approximately 2% of patients (105). A retrospective chart review of pediatric patients with CD or UC revealed that as many as 13 of 95 (13.7%) patients receiving treatment with AZA or 6-MP had elevated aminotransferases. Levels normalized after dose reduction or discontinuation of drug (107). Rare cases of severe cholestatic jaundice have been reported which improved after discontinuation of drug (104,105).

Patients receiving treatment with AZA and 6-MP should undergo routine testing of liver biochemistries at regular intervals. Mild elevations in aminotransferases can be managed by reducing the dose of AZA and 6-MP by 25% to 50% while closely monitoring hepatic biochemical tests (107). The presence of more severe or persistent elevations in hepatic biochemical tests, or unexplained hyperbilirubinemia, requires immediate discontinuation of medication (108).

**Methotrexate**

Methotrexate can cause macrovesicular steatosis, hepatic fibrosis and cirrhosis in a cumulative dose dependent manner. Methotrexate-induced hepatotoxicity is well known in patients with psoriasis and rheumatoid arthritis. Liver biopsy is recommended before initiation of therapy for patients in both groups and is strongly indicated where risk factors for liver disease such as chronic hepatitis B and C infection, prior excessive alcohol consumption, and persistently abnormal hepatic biochemical tests are known to exist (109,110).

In a retrospective study of 20 patients with inflammatory bowel disease who received cumulative methotrexate doses of at least 1.5 grams, 19 experienced only mild histologic abnormalities on liver biopsy. Although liver biopsy of the remaining patient revealed signs of hepatic fibrosis, the finding could not clearly be attributed to methotrexate as there were multiple coexisting risk factors for liver disease in the patient (112).

Obesity, diabetes mellitus and alcohol consumption increase the risk of methotrexate related liver injury (113). It is of particular importance that all patients be counselled on strict avoidance of alcohol during treatment with methotrexate. Finally, in addition to routine screening for hepatic biochemical tests, folic acid supplementation is recommended in all patients receiving methotrexate, since many of the toxic effects are thought to be mediated by the depletion of folate stores (114).

**Cyclosporine**

Cyclosporine can cause reversible hepatotoxicity in a dose dependent manner. Hepatotoxicity is predominantly cholestatic and is likely the result of cyclosporine on inhibiting excretion of bile acids into bile (115). Cyclosporine induced-hepatotoxicity is rare in IBD in the absence of coexisting hepatobiliary disease, since cumulative dosage rarely exceeds levels that can cause liver injury commonly seen in renal transplant patients. In a retrospective study of 86 patients treated with intravenous cyclosporine for severe UC, 2 patients (2.3%) had elevated hepatic biochemical tests over twice the upper limit of normal (116). In a study of 13 patients receiving cyclosporine therapy for relapsing CD, hepatotoxicity occurred in a single patient in whom the serum cyclosporine level was four times the upper limit of the therapeutic level (117).

**Infliximab**

Infliximab is a relatively new drug in the treatment of IBD. There is very little evidence linking infliximab to hepatotoxicity. However, post marketing information
A variety of potential hepatobiliary manifestations can occur in patients with IBD. All of these usually manifest in abnormal hepatic biochemical tests. Of the hepatobiliary complications of IBD, PSC carries the most significant clinical implications and remains a highly challenging disease to manage. No medical management has proven effective in the treatment of PSC, liver transplantation offering the only prospect for cure in eligible patients. Cholangiocarcinoma and colorectal neoplasia remain a potential risk in PSC. The therapeutic potential of ursodeoxycholic acid has shown promise in reducing the risk of colonic malignancy. However, at present, the most effective strategy for addressing the increased risk of developing cancer lies in reliable and effective screening guidelines.

Hepatotoxicity can occur with nearly all medications in the treatment of IBD. Although severe drug-induced hepatotoxicity is rare with medications commonly used in IBD, routine monitoring through hepatic biochemical tests is advisable. Discontinuation of drug, or dose reduction in some cases, is indicated when abnormalities are detected.

The importance of an awareness of the implications and causes of abnormal hepatic biochemical tests in UC and CD patients—because the wide range of possible complications and the risks associated with the medications used to treat and manage them—cannot be overemphasized. Hepatic biochemical tests should be the routine for these patients. When abnormalities are detected, the general approach should be to test for and exclude the more common manifestations and then proceed to test for the less common ones until a reliable diagnosis can be made.

**CONCLUSION**

on the drug makes reference to occasional cases of acute liver failure, jaundice, autoimmune hepatitis and cholestasis (118). Of the trials reported, only one randomized, controlled, double blind trial of infliximab for the treatment of severe to moderately severe UC referred to abnormal hepatic biochemical tests in one of 42 patients (119). One case report attributed cholestatic liver disease in a 44-year-old woman with CD to infliximab. The condition resolved after discontinuation of the medication (120).

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