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Review

Hepatobiliary Impairments in Patients with Inflammatory Bowel Diseases: The Current Approach

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Abstract: Inflammatory bowel disease (IBD) refers to chronic conditions with a low mortality but high disability. The multisystemic nature of these diseases can explain the appearance of some extraintestinal manifestations, including liver damage. Abnormal liver biochemical tests can be identified in approximately one third of patients with IBD and chronic liver disease in 5% of them. Among the liver diseases associated with IBD are primary sclerosing cholangitis, cholelithiasis, fatty liver disease, hepatic amyloidosis, granulomatous hepatitis, drug-induced liver injury, venous thromboembolism, primary biliary cholangitis, IgG4-related cholangiopathy, autoimmune hepatitis, liver abscesses or the reactivation of viral hepatitis. The most common disease is primary sclerosing cholangitis, a condition diagnosed especially in patients with ulcerative colitis. The progress registered in recent years in the therapeutic management of IBD has not eliminated the risk of drug-induced liver disease. Additionally, the immunosuppression encountered in these patients increases the risk of opportunistic infections, including the reactivation of viral hepatitis. Currently, one of the concerns consists of establishing an efficiency and safety profile of the use of direct-acting antiviral agents (DAA) among patients with hepatitis C and IBD. Early diagnosis and optimal treatment of liver complications can improve the prognoses of these patients.

Keywords: hepatobiliary impairments; inflammatory bowel diseases; disability; treatment; prognosis

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1. Introduction

Inflammatory bowel disease (IBD), mainly represented by Crohn's disease (CD) and ulcerative colitis (UC), refers to chronic idiopathic inflammatory diseases. A study that followed the epidemiological evolution of IBD reported 6.8 million IBD cases worldwide in 2017 [1]. The same study identified an increase in the prevalence rate of IBD from 79.5 cases/100,000 inhabitants in 1990 to 84.3 cases/100,000 inhabitants in 2017 [1]. For the same period, a decrease in the mortality rate of IBD patients (0.61 deaths/100,000 inhabitants in 1990 vs. 0.51 deaths/100,000 inhabitants in 2017) and a doubling of the years lived with disability (YLDs) were reported [1]. Regarding the geographical distribution, the highest prevalence rates of IBD were recorded in regions with a high socio-demographic index, such as the United States (464 cases/100,000 inhabitants) and United Kingdom (449 cases/100,000 inhabitants), and the lowest prevalence rates in were recorded in the Caribbean (6.7 cases/100,000 inhabitants) [1]. This phenomenon can be explained by certain differences in the distribution of risk factors, such as lifestyle choices, diets high in meat and low in fiber, smoking, air pollution, hygienic environments, exposure to infectious agents during childhood, urbanization and genetic susceptibility [2–6]. Another explanation can be the easier access to diagnostic tools in developed countries [3].

Beyond the important rates of morbidity and mortality, IBD is associated with a significant economic burden [1]. Thus, both the medical care costs of these patients and the indirect costs entailed by sick leave and early retirement are high [7,8].

The impact on the quality and length of life is secondary to both the direct consequences of IBD on the gastrointestinal tract, and to the extraintestinal manifestations. These are reported in more than one third of IBD patients [9]. An important category of extraintestinal manifestations is that of liver diseases (Table 1) [10]. If defined, chronic liver disease can be present in approximately 5% of IBD patients; abnormal liver biochemical tests are recorded in approximately 30% of these patients [11]. Mendes et al. followed a group of 544 patients with IBD and reported a prevalence of abnormal liver biochemical tests in 27% of patients with active disease and 36% of those in remission [11]. The same authors identified a 4.8-fold increase in age-adjusted risk of death in patients with abnormal laboratory liver function tests [11]. The pathophysiological mechanism behind liver damage in IBD is not completely elucidated. Until now, genetic, immunological and environmental factors have been blamed [12,13]. From a clinical point of view, patients with hepatobiliary disease can be completely asymptomatic, a situation in which the diagnosis is suggested by some biochemical or imaging changes, or they can present symptoms such as pruritus, jaundice, nausea or vomiting [14]. Initial evaluations begins with clinical history and a physical examination, aiming to identify potential risk factors for liver diseases, such as alcohol consumption, as well as signs of chronic liver disease (jaundice, telangiectasias, ascites, etc.) [14,15]. Biochemical evaluations can reveal elevations of liver enzymes, alkaline phosphatase (AP) and bilirubin [14,15]. An abnormal serum albumin and prothrombin time can be secondary to malnutrition in IBD, but it can also reflect impaired hepatic synthetic function [14,15]. Among the imaging methods that can contribute to the establishment of a positive diagnosis are abdominal ultrasound (US), magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) [14]. A liver biopsy is usually not necessary to establish a positive diagnosis, but it can be useful in patients with small-duct primary sclerosing cholangitis or overlap syndrome [14]. The diagnostic and therapeutic management for each liver disease is presented below.

Table 1. Hepatic manifestations in IBD [10,16–19].

Hepatic Impairments	Occurrence Rate in CD	Occurrence Rate in UC
Primary sclerosing cholangitis	3%	2–7%
Cholelithiasis	11–34%	5.5–15%
Non-alcoholic fatty liver disease (NAFLD)	33–55%	33–55%
Hepatic amyloidosis	0.94–2.27%	0.94–2.27%
Granulomatous hepatitis	<1%	<1%
Drug-induced liver injury	2–50%	2–50%
Venous thromboembolism	3.72%	3.72%
Primary biliary cholangitis	Sporadically reported	Sporadically reported
IgG4-related cholangiopathy	Sporadically reported	Sporadically reported
Autoimmune hepatitis	0.6–1.6%	0.6–1.6%
Liver abscesses	Very rare	Very rare
Reactivation of viral hepatitis	<40% of patients with resolved viral hepatitis	<40% of patients with resolved viral hepatitis

2. Primary Sclerosing Cholangitis (PSC)

PSC is a chronic cholestatic disease characterized by inflammation, fibrosis and strictures at the level of intrahepatic and extrahepatic bile ducts [20]. PSC can be identified in approximately 2–7% of UC and 3% of CD patients [20]. The etiopathogenesis of PSC associated with IBD is believed to be multifactorial and includes altered gut microbiota, chronic portal bacteriemia, immune-mediated processes and genetic predisposition [21,22]. Activated lymphocytes from the colon can migrate through the enterohepatic vascular pathway and produce liver inflammation [21]. Graham et al. recently debunked the potential

specificity of aberrant T-cell homing in PSC [23]. Liwinski et al. highlighted that different dysbiosis in PSC-IBD vs PSC has not definitely been established, as most studies report no difference and only a few do [24]. Karlsen et al. reported HLA-B8, HLADRB1*0303 (DR3) and HLADRB1*0101 (DRw52a) as genetic susceptibility factors for PSC-IBD [25].

Patients with PSC-IBD present certain clinical and endoscopic peculiarities. Colitis is identified at a younger age compared to patients with IBD alone [26]. Intestinal damage is more extensive, but less active [10,26]. Thus, in patients with PSC and UC, pancolitis with rectal sparing and backwash ileitis is more frequently identified, and in patients with PSC and CD, extensive colitis is more frequently identified [14].

Most patients with PSC are asymptomatic at the time of diagnosis [10]. Over time, they may develop symptoms such as fatigue, pruritus, jaundice, discomfort in the right hypochondrium and weight loss [10]. In approximately half of patients, hepatomegaly and splenomegaly can be identified [10]. PSC can also lead to a series of complications, including liver failure, cirrhosis, portal hypertension, gallstones, cholecystitis, gallbladder carcinoma, cholangitis and cholangiocarcinoma, as well as pouchitis and colorectal cancer [10,27–30]. Usually, the diagnosis of cholangiocarcinoma is established in the first 1–3 years after diagnosis of PSC. An advanced age at the time of PSC diagnosis is associated with an increased risk of developing cholangiocarcinoma [31]. A meta-analysis that comparatively evaluated the risk of colorectal cancer among patients with PSC and UC, and patients with UC alone, reported an increased risk in the first group [30]. Additionally, the risk of colorectal cancer persists even after liver transplantation [10,30]. Thus, colonoscopy screening is recommended every 1–2 years from the moment of PSC diagnosis [32]. The association of PSC in patients with UC and ileal pouch-anal anastomosis increases the risk of pouchitis and the risk persists even after liver transplantation [33,34].

From a biological point of view, cholestasis syndrome and increased serum values of alkaline phosphatase and aminotransferases are more frequently identified [25]. Later, increased titers of anti-perinuclear antibodies (pANCA in 65–88% of cases), anti-nuclear antibodies (ANAs in 24–53% of cases) and smooth muscle antibodies (SMAs in 13–20% of cases) can be highlighted [35]. Cholangiography usually shows multifocal strictures and a dilation of the intra- and extrahepatic bile ducts [14]. ERCP is another accurate imaging diagnostic method, but it is associated with the risk of bacterial cholangitis and pancreatitis [36]. There are also some variants of PSC, such as small-duct PSC, PSC-autoimmune hepatitis overlap and IgG4-associated cholangitis with particular characteristics [14]. In these situations, a liver biopsy may be necessary to establish a positive diagnosis [14]. IgG4-related disease is now recognized as a separate disease entity, and IgG4 cholangitis is its biliary manifestation. Therefore, this is a condition that needs careful diagnosis in order to differentiate it from PSC because the treatment response and prognosis differ significantly [37].

All patients with PSC require a colonoscopy evaluation, even those without symptoms suggestive of intestinal damage [20]. It is also recommended to take random biopsies even in the case of a macroscopically normal mucosa [20].

The therapeutic options for PSC are limited and the include the control of symptoms and the management of possible complications. The use of ursodeoxycholic acid (UDCA) is associated with an improvement in serum liver markers but not with an improvement in symptomatology, histological liver abnormalities or survival rate [38]. A meta-analysis that followed four studies (281 patients) also reported the lack of influence of UDCA use on the risk of developing adenomas or colorectal carcinoma [39]. A series of immunosuppressive agents, such as infliximab, ciclosporin, azathioprine and budesonide, have been used, but none have proven to be effective [40–42]. In case of strictures at the level of extrahepatic ducts, repeated ERCP sessions with balloon dilation and/or biliary prostheses placement can be performed [14]. The last therapeutic resource for PSC patients remains liver transplantation, with 5-year survival rates of 80–90% and PSC recurrence rates of approximately 20% [43].

The latest data from the specialized literature suggest that PSC, PSC-IBD and IBD might be three different disease entities [44,45]. A study that followed 579 patients with PSC

identified an association with IBD in 66% of them [45]. The same authors highlighted the presence of pancolitis in 94% of PSC-UC patients and colitis in 95% of PSC-CD patients [45]. Additionally, backwash ileitis and rectal sparing were more frequently identified in PSC-UC patients [45].

3. Cholelithiasis

The prevalence of cholelithiasis in the general population ranges from 5.5% to 15% [46]. In CD, the risk of developing gallstones is double (prevalence rate 11–34%), while in UC, no differences in the prevalence of gallstones compared to the general population were identified [46,47]. The risk factors for cholelithiasis in CD patients are age at CD diagnosis, disease duration (>15 years), ileo-colonic localization of the lesions, length of ileal resection (>30 cm), frequency of clinical recurrences (>3), long hospital stay, number of hospitalizations (>3) and total parenteral nutrition [48]. Among the pathophysiological mechanisms underlying cholelithiasis in CD are the following: bile acid malabsorption; solubilization of bilirubin by unabsorbed bile acids in the colon; dysbiosis with bile acid dysmetabolism; reduced gallbladder motility; activation of Th1-mediated immune response; PSC associated with IBD; and hemolysis induced by drugs [49–52]. The only indication for cholecystectomy remains complicated cholelithiasis [53]. Even in patients with CD who require ileocolonic resection, prophylactic cholecystectomy is not recommended [54]. Navaneethan et al. demonstrated an increased risk of postoperative complications in IBD patients [55].

4. Non-Alcoholic Fatty Liver Disease (NAFLD)

The prevalence of NAFLD among patients with IBD varies between 33–55% [56–59]. A study that followed 384 patients with IBD, with no significant alcohol intake, reported the presence of NAFLD in 32.8% of them and the presence of significant liver fibrosis in 12.2% [57]. The independent predictors for NAFLD were higher body mass index (BMI), older age and higher triglycerides [57]. For liver fibrosis, the independent predictors were older age and higher body mass index (BMI) [57]. Extrahepatic diseases, such as chronic kidney disease and cardiovascular disease, proved to be more frequently diagnosed among patients with IBD and NAFLD compared to those with IBD alone [57]. The pathophysiological mechanisms that can explain the increased risk of NAFLD among patients with IBD are chronic relapsing inflammation, an alteration in intestinal microbiota, parenteral nutrition, potentially hepatotoxic drugs and surgery [58–60]. Moreover, dysbiosis has been associated with both the severity of IBD and NAFLD, which suggests a pathogenic link between the two conditions [58,59]. Restellini et al. suggested the need to initiate noninvasive screening strategies (transient elastography) among patients with IBD and high-risk factors of NAFLD [57]. The objectives of these screening strategies are early diagnosis and the early initiation of therapeutic measures, such as weight loss or lipid-lowering medication [57]. On the other hand, biological treatments used for IBD, such as infliximab, have been shown to improve liver histological changes in patients with NAFLD [61]. Monitoring adherence to treatment is also necessary. The absence of NAFLD secondary symptoms, such as upper right abdominal pain or asthenia, among some patients with chronic digestive disorders may explain the lower adherence to the therapeutic measures that NAFLD requires [57]. The importance of adherence to treatment derives from the risk of the evolution of this condition toward irreversible liver fibrosis and even cirrhosis.

5. Granulomatous Hepatitis

Granulomatous hepatitis is a rare complication of CD [10]. However, this condition can be secondary to treatment with mesalamine or sulfasalazine, or it can have malignant or infectious etiologies [62–64]. From a clinical point of view, granulomas are usually asymptomatic [10]. In extensive disease, hepatomegaly or jaundice can be detected [10]. A diagnosis is usually suggested by imaging identification of a liver mass or an unexplained increase in cholestatic enzymes [65]. A positive diagnosis is established by a liver

biopsy [10]. The first-line treatment for granulomatous hepatitis, after the exclusion of infectious etiology, consists of systemic corticosteroids [66]. In case of corticosteroid resistance, immunomodulatory drugs such as azathioprine or methotrexate and anti-TNF-α agents can be used [67]. Paradoxically, cases of granulomatous hepatitis and extrapulmonary sarcoidosis have also been reported in patients with CD who are on anti-TNF-α treatment [68]. Decock et al. identified 90 cases of sarcoidosis-like lesions associated with anti-TNF therapy in the literature [68]. In most cases, these were patients with rheumatic disease (rheumatoid arthritis, ankylosing spondylitis, psoriasiform arthritis) and the most prescribed drug among them was etanercept. Only six patients had IBD as the underlying disease [68]. In 71 of these patients, the partial remission of liver disease was obtained by withdrawing biological treatment, initiating treatment with corticosteroid or both therapeutic measures [68]. The reintroduction of treatment with anti-TNF agents led to the reactivation of liver disease in 7 out of 20 patients [68].

6. Hepatic Amyloidosis

Secondary amyloidosis can be a complication of chronic inflammatory diseases. This condition is rare among IBD patients, occurring in less than 1% of them [46]. If in CD the prevalence of hepatic amyloidosis varies between 0.9–3%, in UC it does not exceed 0.07% [46]. Hepatic amyloidosis is more common in men and the average age at diagnosis is approximately 40 years. Additionally, a more frequent association of this condition with the colonic localization of CD has been reported [46]. The patients are usually asymptomatic, and a diagnosis is suggested by the identification of hepatomegaly during imaging examination. The treatment consists of controlling the underlying CD and reducing the release of acute-phase reactant serum amyloid A [46,69]. Gottenberg et al. claimed that anti-TNFα agents can reduce the release of amyloid precursors and the formation of amyloid deposits, contributing to the clinical improvement of these patients [69]. Another drug with long-term benefits in patients with amyloidosis and CD has been shown to be colchicine [70]. Secondary systemic amyloidosis was associated with an increased risk of infections, sepsis and multi-organ system involvement, but without influencing in-hospital mortality in IBD patients [71].

7. Venous Thromboembolism (VTE)

VTE is a condition with significant morbidity and mortality. In the United States, more than 500,000 hospitalizations and 100,000 deaths attributed to VTE are registered annually [72]. Compared to the general population, patients with IBD have a two-to three-fold higher risk of developing VTE [73]. Bruining et al. reported an incidence rate for portal thrombosis of 1.7% among patients with CD [74]. In patients with IBD undergoing surgery, the incidence rate of superior mesenteric thrombosis can reach up to 4.8% [75]. The pathophysiological mechanisms of VTE in IBD are incompletely elucidated. Currently, the following several risk factors are incriminated: age; genetics factors; pregnancy; active and more extensive disease; hospitalization; surgery; and medications (corticosteroids or tofacitinib) [76]. IBD is characterized by a procoagulant status attributed to the upregulation of inflammatory and coagulation systems [77]. In these patients, during an IBD flare, the following were identified: increased levels of fibrinogen; products of fibrin; thrombin formation; von Willebrand factors; and coagulation factors V, VII, VIII, X, XI and XII [78,79]. During active disease periods, lower levels of antithrombin and protein S, thrombocytosis and increased platelet activity were also highlighted [80,81]. The increased risk of thrombotic events seems to be particular to IBD, not occurring in other chronic inflammatory diseases, such as celiac disease or rheumatoid arthritis [74,82]. Compared to age, there was a significantly higher risk of VTE in young people, but also in elderly patients [83]. Nylund et al. reported an increased risk of VTE among hospitalized IBD adolescents compared to non-IBD hospitalized adolescents [84]. Another study that followed 872,122 patients with IBD reported an increase in the risk of VTE with advancing age [85]. If in the age group 31–40 years, the risk of VTE was 2.1; in the age group 41–50 years, the risk was 2.08; in the

age group 51–65 years, the risk was 3.74; in the age group 66–80 years, the risk was 4.04; and in the age group > 80 years, the risk reached 3.06 [86].

The first-line paraclinical investigation that can identify portal vein thrombosis is abdominal ultrasonography, but the gold standard remains the CT scan. The therapeutic management of patients with IBD and portal thrombosis includes the following: cessation of smoking and consumption of oral contraceptives; anticoagulant treatment with low-molecular-weight heparin (LMWH) or warfarin; and, in severe cases, thrombolysis; surgical interventions; or intravascular thrombectomy devices [87].

Currently, there are no clear recommendations regarding VTE prophylaxis among IBD patients. However, all guidelines recommend VTE prophylaxis in hospitalized patients, with no hemodynamically significant bleeding, during an IBD flare [83]. The extent of post-discharge VTE prophylaxis in patients with high thrombotic risk remains unclear [83].

8. Infection

8.1. Pyogenic Liver Abscess Is a Rare Complication of IBD, Especially CD

If in the general population the incidence of liver abscess is 8–16 cases/100,000 inhabitants, in patients with CD it can reach up to 11–297 cases/100,000 inhabitants [10]. Compared to the general population, patients with liver abscesses and CD are younger and show more frequent multilocular damage [10]. The pathogenic mechanisms incriminated are portal pyemia with a secondary seeding of germs at the level of liver parenchyma or direct hepatic extension of an intra-abdominal abscess [86]. Other factors with a potential pathological role in the occurrence of liver abscesses are fistulizing disease phenotype, glucocorticoid use, abdominal surgery, diabetes mellitus and malnutrition [86]. The presence of a liver abscess can mimic a CD flare. Thus, these patients can present abdominal pain, fever, diarrhea and leukocytosis [86]. Imaging investigations can identify a liver lesion, but a positive diagnosis is established by the biochemical and bacteriological analysis of purulent aspirate [86]. Treatment involves the administration of antibiotics and in selected cases, ultrasound or CT-guided percutaneous drainage or surgical drainage [88]. Li et al. compared the effectiveness of ultrasound-guided percutaneous catheter drainage (US-PCD) vs. surgical drainage among 120 patients with liver abscesses and septic shock [89]. US-PCD was associated with a shorter extubation time, lower postoperative complication rate, shorter hospital stay and higher survival rate [89]. These authors concluded that US-PCD can be an effective therapeutic method for the drainage of liver abscesses and can improve the prognosis of these patients [89].

8.2. Reactivation of Viral Hepatitis

Treatment with corticosteroids, immunomodulators and biological agents used in patients with IBD increase the risk of opportunistic infections. Additionally, patients with a history of viral hepatitis are at risk of the reactivation of liver disease because of the immunosuppression induced by these treatments [90]. Most viral reactivations occur at the time of tapering or withdrawing of immunosuppressive therapy [91,92]. This phenomenon can be explained by the response of the immune system to the viral replication with the destruction of infected hepatocytes [91]. The use of two or more immunosuppressive drugs has been shown to be an independent predictor for viral hepatitis B reactivation [93]. Other risk factors for opportunistic infections in IBD patients are older age, malnutrition, chronic diseases, diabetes mellitus or congenital immunodeficiency [94]. The spectrum of clinical manifestations can vary from the absence of symptoms to fulminant, life-threatening hepatitis [91].

The 2021 European Crohn's and Colitis Organization (ECCO) guidelines recommend serological screening for hepatitis A, B and C viruses, Epstein–Barr virus, varicella zoster virus, cytomegalovirus, measles virus and human immunodeficiency virus (HIV) for all IBD patients before and during immunosuppressive treatment [95]. Additionally, vaccination against hepatitis B is recommended in all seronegative patients (hepatitis B core antibody (anti-HBc) negative and hepatitis B surface antigen (HBsAg) negative) [95]. The goal of

vaccination is to obtain an anti-HBs titer > 10 IU/L [95]. A meta-analysis that followed 1688 IBD patients reported a response rate to vaccination of 61% [96]. In patients with IBD and previous HBV infection (anti-HBc positive and HBsAg negative), prophylactic antiviral treatment is not recommended [92]. In patients with IBD and chronic hepatitis B, antiviral treatment with nucleoside analogues is recommended [95]. The use of antiviral treatment in these patients reduces the risk of hepatitis B reactivation from 47.4% to 7.1% [97,98]. The mortality rate in patients with hepatitis B reactivation who receive immunosuppressive treatment is approximately 5% [99].

The prevalence of hepatitis C in patients with IBD varies between 1% and 6% [100]. For patients with IBD and hepatitis C, the ECCO guidelines recommend antiviral treatment [95]. In patients using direct-acting antiviral agents (DAAs), the same guidelines recommend the careful monitoring of disease exacerbation in 2021 [95]. A multicenter retrospective study published in 2022, which followed 79 patients with IBD and hepatitis C treated with DAAs, reported an increased efficiency and safety of this antiviral treatment [100]. A sustained virologic response was obtained in 96.2% of the patients included in the study [100]. Adverse effects were reported in seven patients, five of whom were probably related to DAAs, but in 100% of cases there were mild adverse effects [91]. Thus, in patients with IBD and hepatitis C, antiviral treatment with DAAs seems to be effective, with cure rates > 90% and a good safety profile [100].

9. Drug-Induced Hepatotoxicity

The therapeutic management of IBD patients has seen impressive progress in recent decades. However, the risk of developing some adverse reactions persists. Many of the drugs used in IBD patients can lead to liver injury (Table 2) [10,101–105].

Table 2. Drug-induced hepatotoxicity in IBD patients.

Drugs	Drug-Induced Hepatotoxicity
Corticosteroids	Hepatomegaly Non-alcoholic steatohepatitis
Aminosalicylic acids	Hepatic biochemical abnormalities (mesalazine/sulfasalazine) Granulomatous hepatitis (sulfasalazine)
Methotrexate	Increase in the serum level of aminotransferases Hepatic steatosis Hepatic fibrosis Cirrhosis
Azathioprine 6-mercaptopurine	Increase in the serum level of aminotransferases Acute cholestatic hepatitis Nodular regenerative hyperplasia Chronic liver disease by peliosis and veno-occlusive disease
Anti-tumor necrosis factor (TNF) agents	Increase in the serum level of aminotransferases Cholestatic liver disease
Anti-interleukin 12/23 antibody	Increase in the serum level of aminotransferases
Anti-integrin antibodies	Hepatic steatosis Increase in the serum level of aminotransferases and/or bilirubin
Tofacitinib	Increase in the serum level of aminotransferases

Koller et al. followed, for one year, 251 patients with IBD in order to quantify the liver injury burden [106]. These authors defined two degrees of liver injury, respectively: grade 1 alanine transaminase (ALT), 1–3 × the upper limit of normal (ULN); grade 2 ALT, > 3 × the ULN [106]. The presence of a grade 1 liver injury was identified in 26.3% of patients and grade 2 was identified in 2% [106]. New biological treatments have been associated with a lower frequency of drug-induced liver injury (DILI), but even in these cases a liver function test follow-up is recommended [107]. Hepatotoxicity is

frequently transient and usually does not require major changes in the therapeutic management of IBD patients [106]. A meta-analysis published in 2021 reported a link between liver injury and thiopurine treatment, but not with anti-TNFα therapies [108]. In 50% of cases, a thiopurine-induced liver injury was diagnosed in the first three months of treatment [108]. The appearance of hepatotoxicity led to the withdrawal of thiopurine treatment in 31% of cases [108]. Hepatotoxicity was dose-dependent rather than immunologically induced [108]. Another study that followed 229 patients with IBD who received azathioprine or 6-mercaptopurine reported the presence of liver injury in only 9% of them [109]. These authors identified a difference in BMI between patients who developed a liver injury compared to those who did not develop hepatotoxicity (BMI 27.6 vs. BMI 24.2; $p = 0.002$) [109]. Worland et al. followed the occurrence of adverse liver reactions among 175 patients with IBD under infliximab treatment [110]. Abnormal liver biochemistry was identified in one third of patients, but only one patient met the RUCAM (Roussel Uclaf Causality Assessment Method) criteria for DILI secondary to infliximab [111]. Predictive factors for the development of DILI among IBD patients receiving infliximab treatment were male sex, NAFLD or another pre-existing liver disease [110].

Anti-TNFα therapies can lead from slight increases in the serum level of aminotransferases to rare cases of acute hepatitis. Frequently in patients who develop acute hepatitis secondary to anti-TNFα agents, increases in anti-nuclear, anti-double-stranded DNA and anti-smooth muscle antibodies are identified [111]. The pathophysiological mechanism of hepatotoxicity is incompletely known. In vitro studies have demonstrated that infliximab or adalimumab treatments have no direct hepatotoxic effect on HepG2 cells [111]. Additionally, treatment with infliximab can be used in patients with pre-existing liver disease, but it is suggested to avoid or even stop the treatment in patients with aminotransferase values exceeding three times the ULN [112].

Ustekinumab is rarely associated with transient mild–moderate increases in aminotransferases levels, abnormalities that are resolved despite continued treatment [113]. Regarding vedolizumab therapy, less than 2% of patients may experience mild-moderate increases in serum aminotransferases or bilirubin [114]. A study that followed 63 patients with IBD who received vedolizumab treatment reported the presence of a liver injury in 6.5 % of them [115]. In none of these patients was it necessary to stop the treatment or reduce the dose of vedolizumab [115].

10. Conclusions

Patients with IBD are prone to the risk of developing extraintestinal manifestations, including hepatic injuries. The spectrum of liver lesions that can be associated with IBD is varied, including cholestatic liver diseases, NAFLD, gallstones, infections, DILI or portal vein thrombosis. A careful monitoring of liver function is therefore recommended by evaluating serological markers, such as serum aminotransferases, alkaline phosphatase gamma glutamyl transpeptidase or bilirubin. Subsequent imaging studies are indicated by clinical manifestations and biological changes. Despite the impressive progress in the therapeutic management of IBD patients, the risk of DILI still persists. Biological therapies are associated with a small risk of adverse liver reactions and when they occur, the adverse reactions are mild. Usually, the hepatic manifestations do not require the adjustment or interruption of biological treatment.

IBD can be associated with other autoimmune diseases, such as PSC, primary biliary cholangitis or autoimmune hepatitis. The use of UDCA in PSC-IBD patients was associated with an improvement in serum liver markers but not with an improvement in symptomatology, liver histological abnormalities, the risk of developing adenomas or colorectal carcinoma and survival rates [38,39]. Patients who present endoscopically approachable bile duct strictures can benefit from balloon dilatation and/or biliary stent placement. The last therapeutic resource for these patients remains liver transplantation, with 5-year survival rates of 80–90% and PSC recurrence rates of approximately 20% [43,116].

Compared to the general population, IBD patients also have a two- to three-fold higher risk of developing thrombotic events, including portal vein thrombosis, with all its secondary complications [73,117]. Currently, there are no clear recommendations regarding antithrombotic prophylaxis among IBD patients. However, all guidelines recommend antithrombotic prophylaxis during hospitalization in patients with an IBD flare [81].

Immunosuppression secondary to the treatment used in IBD patients increases the risk of opportunistic infections and the reactivation of viral hepatitis. The ECCO guidelines recommend vaccination against hepatitis B virus in all seronegative IBD patients and the association of antiviral treatment with nucleoside analogues in patients with chronic hepatitis B [85]. The current data on the use of DAAs in patients with hepatitis C and IBD support a good profile of efficacy and safety but are limited [100].

An early diagnosis and initiation of specific therapeutic measures can improve the prognosis of IBD patients. Additionally, these patients must be informed about the risk of developing liver diseases and the need to eliminate other potentially hepatotoxic factors, such as alcohol consumption. Working in multidisciplinary teams is the key to success in the care of these multisystemic diseases.

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