DAVIDE DE MARCO
MDCM

Dr. Davide De Marco is a fourth-year gastroenterology and hepatology resident at McGill University. He completed his medical school training at McGill University in 2020 and his Internal Medicine residency at McGill University in 2023. He has a wide range of clinical interests in gastroenterology including inflammatory bowel diseases and hepatology.

Affiliations:
Division of Gastroenterology and Hepatology, McGill University, Montreal, Quebec, Canada

AMINE BENMASSAOUD
MDCM, MSc, FRCPC

Dr. Amine Benmassaoud completed his medical training and specialty training in Gastroenterology at McGill University. He then pursued an advanced fellowship in hepatology at the Sheila Sherlock Liver Centre, Royal Free Hospital, London England thanks to the support of the Canadian Association for the Study of the Liver Clinical Fellowship award. He recently completed his Master's in Experimental Medicine at McGill University. He is currently an assistant professor of medicine, and member of the Division of Gastroenterology and Hepatology at McGill University Health Centre in Montreal. As an early career clinician-investigator, his special interest is the evaluation and management of portal hypertension.

Affiliations:
Division of Gastroenterology and Hepatology, McGill University, Montreal, Quebec, Canada

PRACTICAL APPROACH TO ABNORMAL LIVER ENZYMES IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

Introduction

Inflammatory Bowel Diseases (IBD) are chronic inflammatory conditions that can impact organ systems beyond the gastrointestinal tract. Extraintestinal manifestations (EIMs) of IBDs are common and can occur at any stage of the disease.[1] While EIMS most commonly involve the musculoskeletal system, up to 35% of individuals with IBD exhibit hepatobiliary involvement at some point during the course of their disease, often independently of disease activity.[2] Chronic hepatobiliary diseases are noted in 5% of patients with IBD.[3] These diseases manifest with indicative symptoms, abnormal liver biochemistry tests, or radiological abnormalities. This review provides a comprehensive outline and approach to abnormal liver enzymes in individuals with IBD.

Approach to Liver Dysfunction in individuals with IBD

Liver biochemical tests are widely utilized to help diagnose and monitor liver damage or disease. These tests include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT). ALT and AST are enzymes found throughout the body, including hepatocytes. Elevated levels of ALT and AST can be indicative of hepatocellular injury. ALP is an enzyme found in the intestine, bone, placenta, and liver. The hepatic origin of ALP is confirmed by elevated levels of GGT, which is indicative of cholestatic injury.[4] Calculating the R-factor, defined as (ALT ÷ Upper Limit of Normal [ULN] ALT)/(ALP ÷ ULN ALP) with cutoff values defined in **Table 1**, can help determine the nature of the injury: hepatocellular, cholestatic, or mixed.[5] Common causes of chronically abnormal liver enzymes are illustrated in **Figure 1**.[4]

R Factor		
<2	2-5	>5
Cholestatic	Mixed	Hepatocellular

Table 1. *R Factor Thresholds; courtesy of Davide De Marco, MD and Amine Benmassaoud, MD"*

The liver performs vital functions including producing certain products such as glucose, proteins (including albumin and coagulation factors), and fat, detoxifying blood (medications, drugs, pathogens), storing glycogen, handling bilirubin, regulating circulation, and converting thyroid hormones. Abnormalities in the liver's vital functions are referred to as liver synthetic dysfunction. When assessing liver abnormalities in patients with IBD, it is important to consider the type of enzyme elevation, duration (acute [< 6months] or chronic), timing (flare, surgery, new medication, or routine follow-up), presence of synthetic dysfunction (jaundice, coagulopathy, encephalopathy), and degree of hepatic fibrosis. Assessing fibrosis can be achieved with non-invasive tools such as the Fibrosis-4 (Fib 4) score calculated using (Age*AST)/(Platelets x √(ALT)) defined in **Table 2** and elastography in outpatients without acute hepatic injury.[6]

All patients with elevated liver enzymes (ELEs) should undergo repeat testing.[5] Initial assessment should review risk factors for viral diseases, metabolic syndrome, toxins, including drugs, medications, alcohol, and natural products, as well as associated systemic, auto immune, or genetic diseases. Subsequent evaluation will depend on the pattern of the ELE and evidence of synthetic dysfunction.[5] Initial evaluation and management of patients with hepatocellular injury is outlined in **Figure 2** and cholestatic injury in **Figure 3**.[5] In patients with IBD, most ELEs are transient and unrelated to IBD activity.[7,8] Risk factors for ELEs include elevated body mass index, advanced age, and longer disease duration.[7,8] ELEs hold prognostic significance in IBD, with an age-adjusted risk of death 4.8 times higher in patients with persistent ELEs.[7]

Fibrosis 4 Score (Fib-4)				
Significant Fibrosis Excluded	1.3*	Indeterminate	3.25	Advanced Fibrosis

Table 2. *Fibrosis 4 (Fib-4) Score Thresholds ; courtesy of Davide De Marco, MD and Amine Benmassaoud, MD*
**<2.0 in patients > 60 years old*

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD), the most common liver disease in the general population, is equally prominent among patients with IBD. A meta-analysis was conducted to examine the prevalence of NAFLD among 7,640 patients with IBD. The findings indicated a prevalence of NAFLD among patients with IBD of 32% compared with 25.2% in the general population.[9] The study went on to report that advanced hepatic fibrosis was seen in 10.3% of patients with IBD.[9] In addition, obesity, diabetes, older age, prior surgical interventions for IBD, and longer disease duration were found to be important risk factors for NAFLD in this population.[9] Exposure to certain hepatotoxic drugs, such as methotrexate and biologics, can alter the body's metabolic state and increase the risk of NAFLD.[9,10]

NAFLD is largely asymptomatic and is commonly identified incidentally in patients with IBD, although abnormal liver enzymes or decompensated cirrhosis may be present. Similar to IBD, NAFLD is associated with changes in the gut microbiome.[9,10] Underlying inflammatory and surgical changes observed in IBD can also disrupt bile acid metabolism in the ileum, leading to decreased levels of

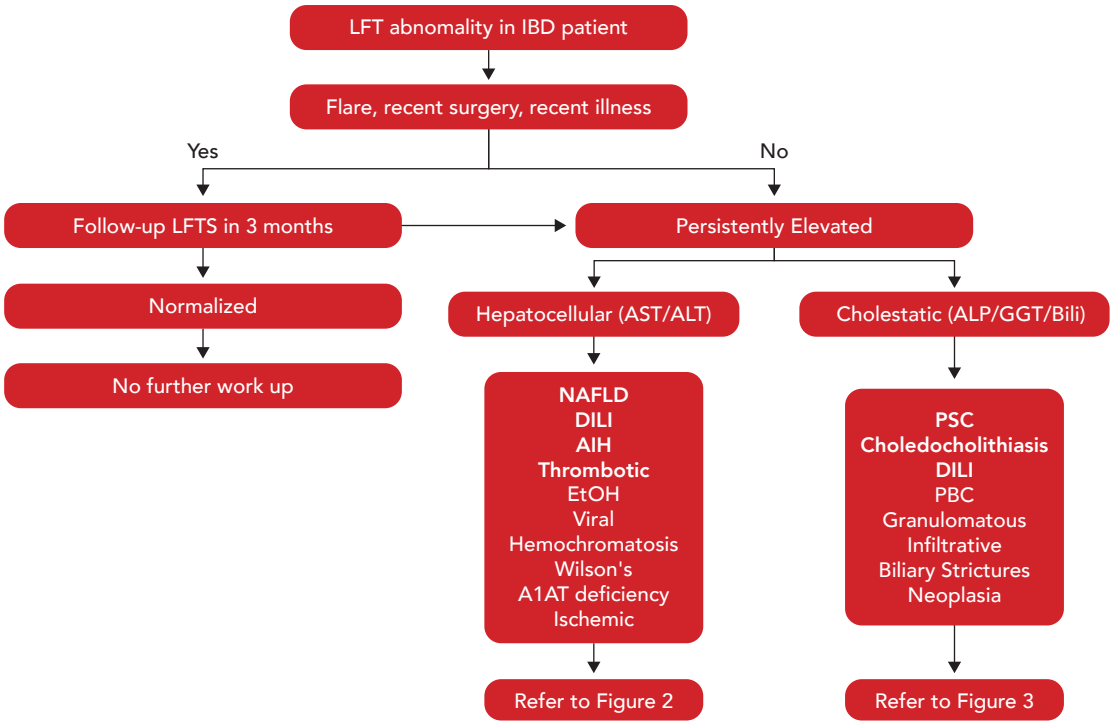

Figure 1. *Simplified Approach to Liver Enzyme Abnormalities in IBD (Inflammatory Bowel Disease) Patients; courtesy of Davide De Marco, MD and Amine Benmassaoud, MD*

A1AT: Alpha-1-antitrypsin, AIH: Autoimmune hepatitis, ALP: Alkaline Phosphatase, ALT: Alanine Transaminase, AST: Aspartate aminotransferase, DILI: Drug Induced Liver Injury, EtOH: Alcohol, GGT: Gamma-Glutamyl Transferase, NAFLD: Non-alcoholic Fatty Liver Disease, PBC: Primary Biliary Cholangitis, PSC: Primary Sclerosing Cholangitis. Adapted from 2017 AGA guidelines.

circulating fibroblast growth factor 19 (FGF 19), an important factor in lipid metabolism.[9,11] In those identified incidentally, the first step is to obtain liver biochemistry tests, exclude co-contributing diseases, and establish the degree of hepatic fibrosis non-invasively using the Fib-4 or the NAFLD fibrosis score.[12] In patients with suspected significant hepatic fibrosis, confirmation by elastography and referral to hepatology should be considered. First line treatment for NAFLD is centred around diet, exercise, weight loss, and gaining control of metabolic co-morbidities.[13] Screening becomes increasingly important because these patients are more likely to have concurrent extrahepatic disease, such as cardiovascular disease, emphasizing the importance of early identification and intervention.[14]

Primary Sclerosing Cholangitis

A systematic review that included 776,700 patients with IBD found the prevalence of primary sclerosing cholangitis (PSC) to be 2.16%, with a higher prevalence among individuals with ulcerative colitis (UC) than in those with Crohn's disease (CD) (OR 1.69, 95% CI 1.24-2.29).[15] The prevalence of PSC may be underestimated among patients with IBD, as demonstrated by a study that assessed 322 patients who were screened with magnetic resonance cholangiopancreatography (MRCP), and found a prevalence of 7.5%.[16] Conversely, studies have reported that 23-77% of patients with PSC have concomitant IBD.[17,18] PSC is closely linked to disease severity. Patients with extensive UC were six times and patients with ileocolonic CD were four times more likely to develop PSC than their ileal counterparts.[15] Moreover, a recent meta-analysis demonstrated a four-fold increase in colon cancer amongst patients with PSC and UC compared to those with UC alone.[19] The diagnosis of PSC is based on the presence of characteristic features such as biliary strictures, "beads on a string" appearance on MRCP, and exclusion of secondary causes.[18] Histological confirmation is only necessary when small-duct PSC, with normal MRCP, is suspected.[18] Patients can be asymptomatic or can experience fatigue, jaundice, pruritus, and even decompensated cirrhosis. There is no clear explanation for the relationship between PSC and IBD, though 3 candidate genes, *REL*, *IL2* and *CARD9*, are associated with both UC and PSC. Emerging research highlights the influential role of gut microbiota in the pathogenesis of PSC.[20] Treatment options for PSC remain limited. In addition, the efficacy of ursodiol (ursodeoxycholic acid) therapy remains uncertain. Liver transplantation is considered for those with decompensated cirrhosis or recurrent cholangitis, with a reported 5-year relapse rate of 20%.[21] Given the strong association between PSC and malignancies, patients with PSC and IBD should undergo annual colonoscopy and abdominal imaging every 6 to 12 months, ideally with MRI Liver/MRCP, for surveillance of hepatobiliary malignancies.[18]

Autoimmune hepatitis

Patients with autoimmune hepatitis (AIH) and concurrent IBD demonstrate distinct characteristics, including younger age at onset, refractoriness to AIH treatment, higher rates of liver transplantation, and increased mortality.[22] The diagnosis of AIH is based on evidence of hepatocellular injury, elevated IgG, positive results of serological markers, exclusion of other causes of ELEs, compatible histological abnormalities,

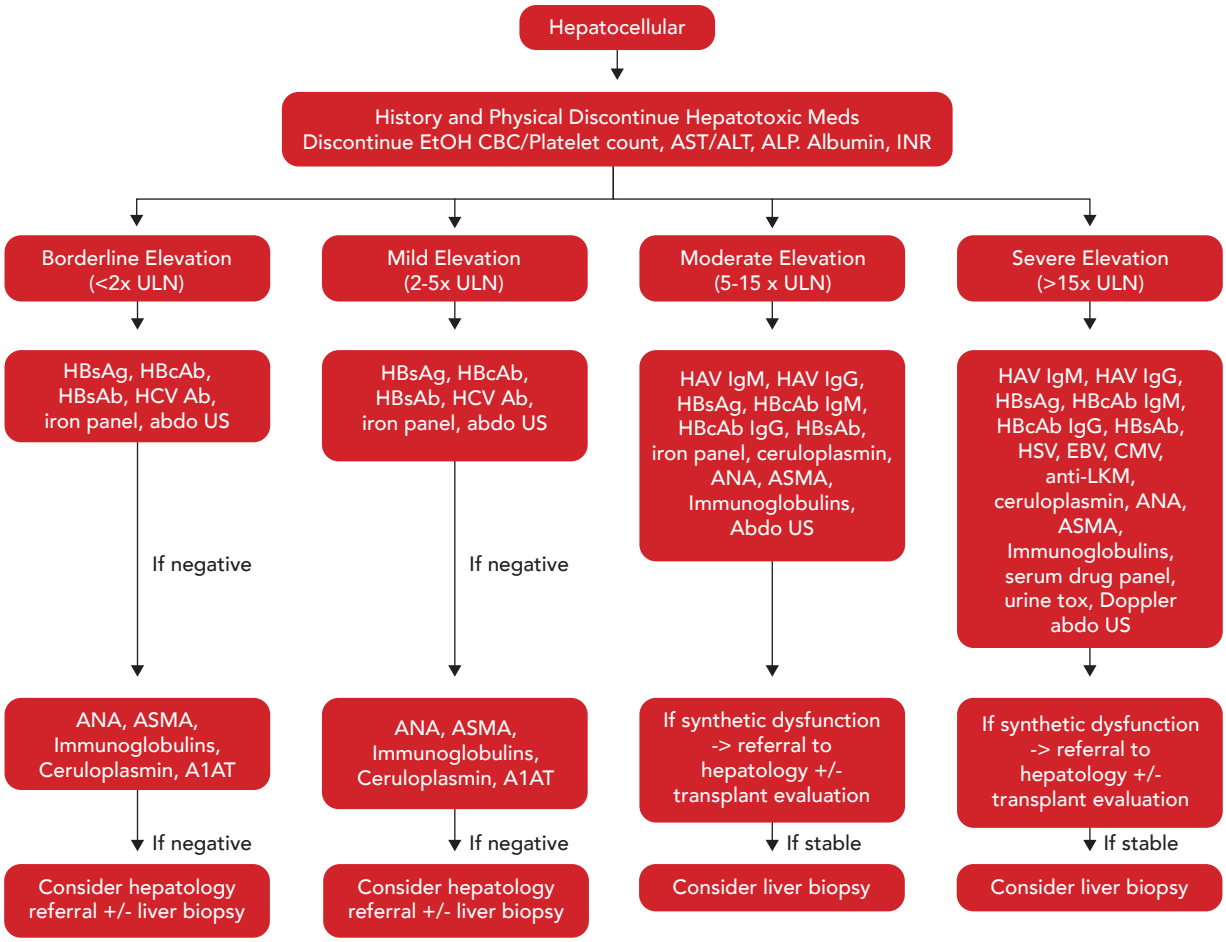

Figure 2. *Approach to Patients with Hepatocellular Injury: Adapted from 2017 AGA guidelines*[5]
A1AT: Alpha-1-antitrypsin, ALT: Alanine Transaminase, AMA: Antimitochondrial antibody, ANA: Antinuclear antibody, anti-LKM: anti-Liver-Kidney Microsomal, ASMA: Anti-smooth muscle antibody, AST: Aspartate aminotransferase, CMV: Cytomegalovirus, EBV: Epstein Barr Virus, EtOH: Alcohol, HAV: Hepatitis A Virus, HBcAb: Hepatitis B core antibody, HBsAb: Hepatitis B surface antibody, HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C Virus, HSV: Herpes Simplex Virus, ULN: Upper Limit of Normal US: Ultrasound.

and response to therapy using validated scoring systems.[23,24] Patients with AIH can experience a range of liver disease presentations, from asymptomatic hepatocellular injury to fulminant liver failure or decompensated cirrhosis. Overlap with AIH-PSC should be suspected in patients with AIH and pruritus, cholestatic injury, and typical bile duct abnormalities on imaging. Although no clear mechanism has been established, current evidence points to a key role for the composition of the gut microbiome in the inflammation that is seen in both AIH and IBD.[22,23] Infliximab is also known to cause a specific drug induced liver injury (DILI) that can mimic AIH.[25] First line treatment for patients with AIH is glucocorticoids combined with a steroid sparing agent, such as azathioprine.[22]

Portal Vein Thrombosis

Patients with IBD are in a hypercoagulable state and are 3.4 times more likely to develop venous thromboembolisms (VTE) than the general population, which further increases to 8.4 times during disease flares.[26] While portal vein thrombosis (PVT) is a rare complication of IBD, it is frequently observed in the post-operative period with a prevalence ranging from 39% to 45%.[27,28] Patients with PVT can be identified incidentally during routine imaging, or with abdominal pain and even mesenteric ischemia if mesenteric vessels are involved.[29] Diagnosis is established using doppler ultrasound or cross-sectional imaging with intravenous contrast. Management takes place in collaboration with thrombosis experts and includes anticoagulation therapy and, if no cause is identified, investigation for underlying thrombophilia and malignancy.[30]

Cholelithiasis

The relationship of IBD with gallstones is well established. In a systematic review and meta-analysis of 53,543 patients with IBD, the prevalence of cholelithiasis was 2.16% compared with 0.78% in the general population.[31] Further subgroup analysis revealed a prevalence of cholelithiasis of 1.84% in patients with UC, and 2.89% in patients with CD.[31] This association is particularly pronounced in patients with CD following ileal resection or with ileal disease, because these conditions disrupt bile reabsorption and lead to the development of cholesterol-supersaturated bile. Another proposed mechanism to account for the presence of cholelithiasis involves the colonization of anaerobic bacteria in the ileum following ileal resection, which impairs mucosal absorption. Additionally, patients with IBD often experience reduced gallbladder motility

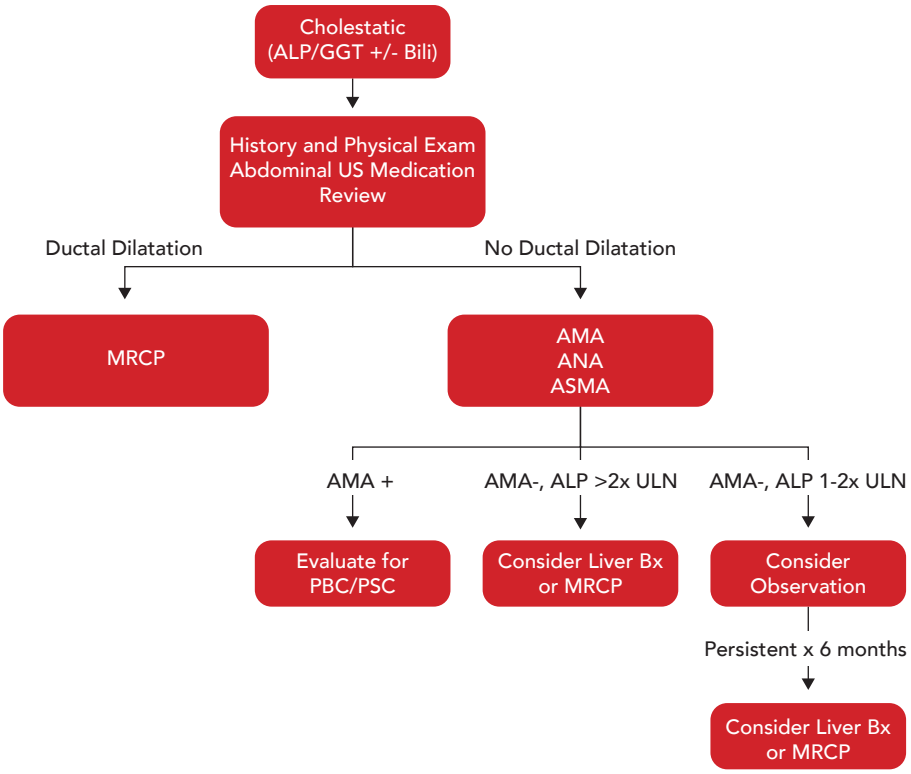

Figure 3. *Approach to Patients with chronic Cholestatic Liver Enzymes: Adapted from 2017 AGA guidelines*[5]
ALP: Alkaline Phosphatase, AMA: Antimitochondrial antibody, ANA: Antinuclear antibody, ASMA: Anti-Smooth Antibody, GGT: Gamma-Glutamyl Transferase, MRCP: Magnetic Resonance Cholangiopancreatography, PBC: Primary Biliary Cholangitis , PSC: Primary Sclerosing Cholangitis.

during prolonged fasting states, including total parenteral nutrition.[32,33] Evaluation with abdominal ultrasound is needed in patients experiencing biliary-type pain, and for those with cholestatic liver injury. Among patients with IBD who develop cholelithiasis, approximately 20% are symptomatic and require surgical intervention.[33]

Medication-related hepatotoxicity

Medications used to treat IBD are potentially hepatotoxic and can cause reactivation of viral hepatitis. All patients with IBD should undergo screening for hepatitis B surface antigen (HBsAg), hepatitis B antibody (HBsAb), and hepatitis B core antigen (HBcAg) before initiating treatment with immunosuppression therapies to prevent hepatitis B reactivation (HBVr). Those with negative serology test results should receive vaccination as recommended by the National Advisory Committee on Immunizations (NACI) and Canadian Association for the Study of the Liver (CASL) guidelines.[34]

Those with HBcAg-positive findings, with or without the presence of HBsAg, should be referred to hepatology for expert opinion. Depending on the serology pattern, antiviral therapy might be required.[34-36] Screening for hepatitis C antibodies should also be routinely obtained before biologic therapy.[37]

DILI can occur within days to months and can be seen in hepatocellular, cholestatic or mixed patterns and range from asymptomatic to fulminant liver failure.[35] When DILI is suspected, physicians should exclude other potential aetiologies and withdraw the offending agent. If the agent is not a well-known hepatotoxic medication, physicians may refer to LiverTox, a web-based compendium of DILI.[38,39] In addition, validated scales such as the Roussel Uclaf Causality Assessment Method (RUCAM) can be used to quantitatively assess causality in suspected cases of DILI.[40] Commonly used medications in the treatment of IBD and their potential hepatotoxicity are described below.

Thiopurine therapy is a well known cause of DILI, which is reported to occur in 3.7 to 13.3% of patients, with adverse effects ranging from hepatocellular, cholestatic, or mixed hepatitis to vascular endothelial lesions such as nodular regenerative hyperplasia.[41-44] Thiopurine S-methyltransferase (TPMT) enzyme plays an important role in the metabolism of 6-methyl-mercatopurine (6-MMP), which has been associated with hepatotoxicity when present at higher levels. ELEs usually occur in the first 3 months of therapy with thiopurines. These ELE are often asymptomatic; thus, liver enzymes should be regularly monitored.[35] After the occurrence of ELE, thiopurines can be restarted at a lower dose under close monitoring and after discussion with carefully selected patients.

Treatment with sulfasalazine and its therapeutically active derivative 5-Aminosalicylic Acid (5-ASA) is a rare cause of DILI with an incidence of 3.1 cases per million prescriptions and between 0% and 4% incidence of DILI respectively.[35,45,46] DILI due to sulfasalazine can be identified as hepatocellular, cholestatic or mixed injury, and

by fever, rash, lymphadenopathy or hepatomegaly. The mechanism is likely related to a hypersensitivity reaction. Patients who experience a DILI to these medications should not be rechallenged.

Methotrexate therapy has well-known hepatotoxic effects. DILI as a result of methotrexate therapy can be identified as hepatocellular injury, which is mild and self-limiting. Chronic use of methotrexate can lead to hepatic steatosis, fibrosis, and cirrhosis. A meta-analysis that included patients with IBD reported an incidence of hepatotoxicity of 0.9 per 100 person-months, with a discontinuation rate of 0.8 per 100 person-months.[47] Patients treated with methotrexate should be screened every 2 weeks for the first 2 months and every 3 months thereafter.[35]

The use of anti-TNF inhibitors, especially infliximab, can cause different types of liver injury which are often mild and transient. Infliximab also induces autoantibodies which can remain asymptomatic except in rare instances of a lupus-like syndrome or drug-induced AIH.[35] Adalimumab is less commonly associated with hepatotoxicity.[35]

Biologic agents such as vedolizumab, ustekinumab, and tofacitinib, are uncommon causes of clinically apparent liver injury. ELEs are typically mild and transient. Persistent ELE might require drug discontinuation, though quite rare.[35,48,49]

Conclusion

ELEs are often seen in patients with IBD at a higher prevalence than in the general population. These liver abnormalities may occur at any stage of their disease and can be either transient or persistent in nature. Being able to identify and diagnose these associations between ELEs and IBD early in their clinical course has important prognostic implications.

Correspondence:

Dr. Amine Benmassaoud,
Email: amine.benmassaoud@mcgill.ca

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Contraindications:

- Patients with known hypersensitivity or any components to STELARA®/STELARA® I.V.
- Severe infections such as sepsis, tuberculosis and opportunistic infections

Relevant warnings and precautions:

- Potential to increase the risk of infections and reactivate latent infections
- STELARA®/STELARA® I.V. should not be given to patients with any clinically important active infection. Patients should be evaluated for tuberculosis infection prior to therapy and monitored for active tuberculosis during and after treatment
- Potential to increase the risk of malignancy
- All patients, in particular those greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy or those with a history of PUVA treatment, should be closely monitored for skin cancer
- Hypersensitivity reactions including serious allergic reactions (anaphylaxis and angioedema), allergic alveolitis and eosinophilic pneumonia
- May cause allergic reactions in individuals sensitive to latex
- Concurrent use with live viral or bacterial vaccines is not recommended
- Caution should be exercised when considering concomitant use of immunosuppressive agents and STELARA®/STELARA® I.V.
- May affect allergy immunotherapy
- If reversible posterior leukoencephalopathy syndrome is suspected, administer appropriate treatment and discontinue STELARA®/STELARA® I.V.
- Should be given to a pregnant woman only if the benefit clearly outweighs the risk
- Women of childbearing potential should use contraception and should receive preconception counselling before planning a pregnancy as STELARA®/STELARA® I.V. remains in circulation for approximately 15 weeks after treatment
- Pediatric studies of STELARA® I.V. have not been conducted. No studies have been conducted in pediatric patients with psoriatic arthritis, Crohn's disease or ulcerative colitis.

For more information

Please consult the Product Monograph at www.janssen.com/canada/our-medicines for important information relating to adverse reactions, drug interactions, and dosing that has not been discussed in this piece. The Product Monograph is also available by calling 1-800-567-3331.

Reference

1. STELARA/STELARA I.V. Product Monograph. Janssen Canada Inc., September 9, 2021.