

Hepatic manifestations of non-steroidal inflammatory bowel disease therapy

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Author contributions: Hirten R, Sultan K and Bernstein DE contributed to conception and design; Hirten R, Sultan K and Thomas A contributed to drafting of the article; Hirten R, Sultan K, Thomas A and Bernstein DE contributed to critical revision of the article for important intellectual content; Hirten R, Sultan K, Thomas A and Bernstein DE contributed to final approval of the article.

Conflict-of-interest statement: The authors declare that no conflicts of interest exist.

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Received: June 28, 2015

Peer-review started: June 29, 2015

First decision: July 28, 2015

Revised: October 25, 2015

Accepted: November 13, 2015

Article in press: November 17, 2015

Published online: November 28, 2015

Abstract

Inflammatory bowel disease (IBD) is composed of Crohn's disease and ulcerative colitis and is manifested by both bowel-related and extraintestinal manifestations. Recently the number of therapeutic options available to treat IBD has dramatically increased, with each new medication having its own mechanism of action and side effect profile. A complete understanding of the hepatotoxicity of these medications is important in order to distinguish these complications from the hepatic manifestations of IBD. This review seeks to evaluate the hepatobiliary complications of non-steroid based IBD medications and aide providers in the recognition and management of these side-effects.

Key words: Hepatotoxicity; Adverse drug reactions; Drug induced liver injury; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

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Core tip: Recently the number of medical therapies for inflammatory bowel disease (IBD) has greatly increased. Each medication has its own mechanism of action and side effect profile. This review article discusses the hepatic side effects of medications used to treat IBD enabling physicians to better recognize and manage these complications.

Hirten R, Sultan K, Thomas A, Bernstein DE. Hepatic manifestations of non-steroidal inflammatory bowel disease therapy. *World J Hepatol* 2015; 7(27): 2716-2728 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v7/i27/2716.htm> DOI: <http://dx.doi.org/10.4254/wjh.v7.i27.2716>

INTRODUCTION

Inflammatory bowel disease (IBD) is primarily composed of Crohn's disease (CD) and ulcerative colitis (UC). The North American incidence is 19.2 cases per 100000 person years and 20.2 cases per 100000 person years for UC and CD, respectively^[1]. Through a combination of genetic and environmental factors, IBD appears to be caused by an inappropriate and overactive response of the body's immune system directed primarily at the gastrointestinal tract. Though most disease manifestations are bowel-related, multiple extraintestinal manifestations including dermatologic (pyoderma gangrenosum, erythema nodosum), ophthalmic (uveitis and episcleritis), joint (large and small joint arthritis and sacroiliitis) as well hepatobiliary complications may occur. Additionally, biliary and hepatic manifestations are common, with up to 29% of IBD patients developing abnormal liver tests^[2].

Recently the number of therapeutic options available to treat IBD has increased dramatically. Current guidelines emphasize a move away from short term corticosteroid based treatment and towards IBD targeted medications proven to either induce and/or maintain clinical remission. Each new class of medication has its own mechanism of action and side effect profile. While multiple reviews have evaluated the hepatobiliary manifestations of IBD, few have focused in detail on the hepatic side effects of these medications. A complete understanding of the prevalence, characteristics and management of the hepatotoxicity of these medications is important to distinguish these effects from IBD itself, limit their toxicity and maximize their therapeutic benefit. This review evaluates the hepatobiliary complications, mainly drug induced liver injury (DILI), of currently available non-steroid based IBD therapies.

SULFASALAZINE AND 5-AMINOSALICYLATES

Sulfasalazine is a pro-drug composed of 5-aminosalicylic acid (5-ASA) linked to sulfapyridine by an azo bond, and has been used in the treatment of IBD for over 70 years^[3]. The primary efficacy of sulfasalazine in IBD is through the 5-ASA moiety and although the exact mechanism of action is not known, 5-ASA has been shown to have an array of anti-inflammatory properties including effects on reactive oxygen species, nuclear factor kappa B, and cytokines^[4-6]. Though mainly demonstrating benefit for UC, it is commonly used for CD. Common side effects include headache, nausea, dyspepsia, or allergic reactions, and are generally attributed to the sulfa component. The overall incidence of liver toxicity has been estimated to be between 0.4%-2.9%, depending upon the study group and underlying disease^[7,8]. Though most liver test abnormalities are minor and reversible with drug discontinuation, previous studies have described severe hepatotoxicity to sulfasalazine

due to a systemic hypersensitivity reaction characterized by high fevers, generalized lymphadenopathy, a maculopapular rash, elevated liver enzymes, eosinophilia and immune complexes^[9]. Granulomatous hepatitis has been described in patients on sulfasalazine presenting with an elevated alkaline phosphatase and bilirubin along with the presence of granulomas on liver biopsy. This has been described in patients without CD and appears to be medication rather than disease related^[10-12]. Also reported are rare cases of fatal fulminant hepatic necrosis from drug rash with eosinophilia and systemic symptoms, a devastating complication with an estimated mortality of 10% if not appropriately diagnosed and treated with high dose corticosteroids^[13-20].

Due to adverse effects of the sulfapyridine moiety, 5-ASA formulations without sulfa, the mesalamine derivatives, were developed in the 1970s, and are now more widely used than sulfasalazine. A systematic review of the short-term adverse effects of mesalamine show that this class of medication is generally well tolerated, with rates of adverse events similar to placebo controls^[21]. The most common side effects associated with mesalamine include flatulence, nausea, headache, dyspepsia, and diarrhea. Despite the absence of the sulfa moiety and limited systemic absorption of mesalamine, a randomized trial comparing mesalamine to sulfasalazine showed rates of DILI to be similar between the two medications, with 2.6% of patients taking mesalamine experiencing liver injury^[8]. One case report described possible drug-induced autoimmune hepatitis in a patient with CD treated with mesalamine. This patient developed chronic hepatitis with evidence of fibrosis on liver biopsy, as well as an elevated anti-nuclear antibody and anti-smooth muscle antibody, which resolved with discontinuation of the medication^[22]. Other case reports have linked mesalamine to systemic hypersensitivity reactions similar to sulfasalazine as well as to the development of hepatocellular cholestasis^[23,24].

When signs of liver injury develop secondary to sulfasalazine or mesalamine, the dosage should be decreased or the medication stopped completely depending upon the severity of the liver test elevation and the patient's condition. While no formal guidelines exist specifically for sulfasalazine or mesalamine, cases suspicious for DILI should be evaluated and managed according to currently accepted guidelines^[25].

AZATHIOPRINE AND 6-MERCAPTOPURINE

The thiopurine immunomodulators azathioprine (AZA) and its principle metabolite, 6-mercaptopurine (6-MP), have shown efficacy in the maintenance of steroid induced remission for both CD and UC^[26]. AZA is converted to its active metabolite 6-MP through non-enzymatic reactions by compounds such as glutathione. Intracellular metabolism of 6-MP is dictated by the activity of several enzymatic pathways resulting in both the

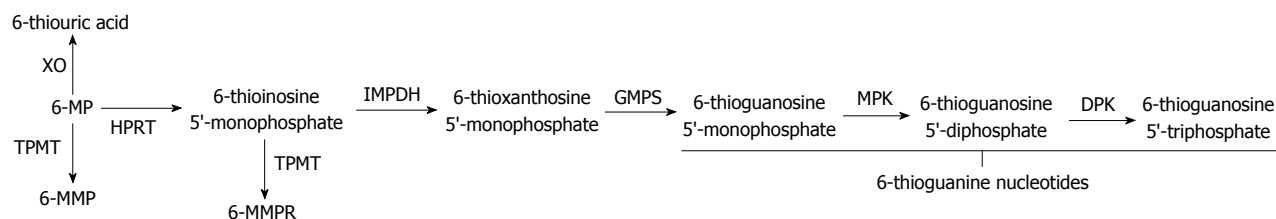


Figure 1 Azathioprine/6-mercaptopurine metabolism. Azathioprine is converted to 6-MP via nonenzymatic reactions. IMPDH and GMPS generate active 6-thioguanine nucleotides. TPMT results in the production of hepatotoxic 6-MMP and 6-MMPR metabolites. 6-MP: 6-mercaptopurine; TPMT: Thiopurine methyltransferase; XO: Xanthine oxidase; HPRT: Hypoxanthineguanine-phosphoribosyl-transferase; 6-MMP: 6-methylmercaptopurine; 6-MMPR: 6-methylmercaptopurine ribonucleotide; IMPDH: Inosine monophosphate dehydrogenase; GMPS: Guanosine monophosphate synthetase; MPK: Monophosphate kinase; DPK: Diphosphate kinase. Adapted from Cuffari C, Theoret Y, Latour S, Seidman G. 6-Mercaptopurine metabolism in Crohn's disease: Correlation with efficacy and toxicity. *Gut* 1996; 39: 401-406.

therapeutically active metabolite 6-thioguanine (6-TG), which is associated with myelosuppression, as well as the non-therapeutic metabolites 6-methylmercaptopurine (6-MMP) and 6-methylmercaptopurine ribonucleotide (6-MMPR) which have been associated with hepatotoxicity (Figure 1)^[27].

AZA and 6-MP have been shown to result in both a hepatocellular and cholestatic hepatitis, with a number of studies evaluating the incidence of liver test abnormalities occurring in IBD patients treated with these medications. A large study of 3931 patients from the prospective Spanish nationwide database found that 4% of patients on thiopurines developed hepatotoxicity^[28]. Another study that followed 786 patients with IBD, of whom 138 received either AZA or 6-MP, found that 7.1% of those treated per patient year developed elevated liver tests that were 1-2 times the upper limit of normal. Approximately 2.6% of those treated per patient year developed liver tests greater than twice the upper limit of normal^[29]. A large systematic review of 3485 patients from 2007 evaluating the incidence of liver injury in patients with IBD exposed to AZA or 6-MP showed an overall prevalence of abnormal liver tests of 3.3%. When follow-up time was included, 2992 patients received treatment during a total of 6952 years of follow-up, with the average rate of drug-induced liver test elevation being 1.4% per patient year. These liver test abnormalities were generally noted to occur within the first few months of drug initiation^[30].

The primary hepatic manifestations include hypersensitivity reactions, cholestasis, peliosis hepatitis, Disse space fibrosis, veno-occlusive disease and nodular regenerative hyperplasia (NRH)^[31]. In hypersensitivity syndromes, symptoms usually develop within 2-3 wk of initiation with an elevated bilirubin and alkaline phosphatase, as well as with moderate elevations of aminotransferases. At the histologic level, parenchymal cell necrosis is noted^[30,31]. NRH, peliosis hepatitis, fibrosis, and veno-occlusive disease have been shown to be dose-dependent injuries and likely secondary to damage to the endothelial cells lining the sinusoids and terminal hepatic venules^[30,32]. This is often noted between 3 mo and 3 years of initiating treatment^[30].

Thiopurine methyltransferase (TPMT) activity plays an important role in determining AZA and 6-MP metabolism

and the development of side effects. Approximately 0.3% of the population has low or absent activity, 11% of the population has intermediate activity as they are heterozygotes, and 89% of the population possess the wild type with normal activity^[33]. In general, 6-TG levels greater than 230-260 pmol/8 × 10⁸ erythrocytes are associated with clinical efficacy, while levels over 450 pmol/8 × 10⁸ erythrocytes are associated with bone marrow toxicity. Though high levels of 6-TG can also result in liver damage, particularly the development of NRH, most liver toxicity is believed to be related to 6-MMP and 6-MMPR, particularly at levels over 5700 pmol/8 × 10⁸ erythrocytes^[27,30,34].

Though no commercial testing is available for high TPMT activity, this appears to occur in up to 15% of the population with a preferential formation of the hepatotoxic 6-MMP and 6-MMPR metabolites^[35]. Despite this association, routine monitoring for 6-MMP and 6-MMPR is not widely recommended. In patients who develop abnormal liver tests associated with the overproduction of 6-MMP and 6-MMPR the thiopurine may be stopped, the dose reduced or allopurinol may be used to inhibit xanthine oxidase. While an examination of the metabolic pathways involved would suggest this approach to result in an increase of both 6-TG and 6-MMP/6-MMPR levels, in fact, the effect is one of preferentially increased 6-TG over 6-MMP/6-MMPR. Typically AZA or 6-MP dosing is cut to one third or half the prior dose when used in conjunction with allopurinol, and the patient's blood work monitored closely.

As no formal guidelines exist, and most cases of liver toxicity occur within the first few months of therapy, we recommend following the protocol outlined by the United States Food and Drug Administration (FDA) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205919s000lbl.pdf), which suggests checking serum transaminase levels, alkaline phosphatase, and bilirubin levels weekly for the first month^[30]. Following this initial therapy we agree with repeat testing monthly for the next 3 mo, then every three months thereafter, following along with the currently recommended monitoring of white blood cell counts. This sequence should be repeated with any dose increase. It is common for patients to have a slight elevation of liver enzymes with normalization on repeat testing. However, if elevations

become persistent or marked, the dose of AZA or 6-MP may be reduced in half with continued close monitoring, or by finer dose adjustments guided by metabolite levels. With normalization, careful resumption of the previous dose can be reattempted^[30]. In one prospective study that evaluated this method, slightly less than half of patients were able to resume their previous dosage^[36]. Patients whose liver tests fail to normalize should have the medication discontinued. If severe cholestatic jaundice occurs, the medication should be withdrawn with continued close monitoring of the liver tests for improvement. Patients should consider undergoing liver biopsy if liver tests remain persistently elevated after medication withdrawal^[30].

METHOTREXATE

Methotrexate (MTX) was discovered in the 1940's and was first used to treat leukemia in 1948. It is a structural analogue of folate which competitively inhibits the enzyme dihydrofolate reductase and thereby the production of the intracellular metabolite folinic acid and the synthesis of purines and pyrimidines. Clinically, it has demonstrated effectiveness in the treatment of CD but not UC^[37,38]. Generally, it is given intramuscularly at a dose of 25 mg weekly in combination with another medication used to induce remission, such as steroids or a biologic agent. Once a clinical response is observed, patients are switched to subcutaneous or intramuscular injections at a dose of 15 mg weekly. Multiple side effects have been reported including infections, pneumonitis, bone marrow suppression and liver test abnormalities.

There is extensive literature relating to MTX's effects on the liver with significant variability in reports of liver tests abnormalities and histologic changes on biopsy. While the mechanism resulting in hepatotoxicity is not fully understood, it is likely related to MTX induced folate deficiency, as supplementation has been shown to reduce hepatic adverse events^[39,40]. Much of the evidence relating to its hepatotoxicity comes from its use in rheumatoid arthritis and psoriatic arthritis, where it has been shown to have a variety of effects on the liver ranging from hepatic steatosis to fibrosis. The CORRONA database is a large cohort of patients which followed 2104 patients with rheumatoid arthritis and psoriatic arthritis exposed to methotrexate. Overall, approximately 22% of patients exposed to MTX with rheumatoid arthritis developed an elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT), while 35% of patients with psoriatic arthritis exposed to MTX had an AST/ALT $> 1 \times$ the upper limit of normal^[41].

Similar results were found in patients with IBD on chronic low dose MTX. A retrospective study evaluating 87 subjects with a mean duration of therapy of 81 wk and an average dose of 1813 mg found that 24% of patients developed elevated liver tests. Of these patients, 44% had underlying risk factors for liver disease. While 23% of patients in the study had abnormal liver tests at baseline, 45% had normalization while on MTX, while

45% experienced a worsening of their liver tests^[42]. A meta-analysis evaluating 12 studies of 457 children with IBD exposed to MTX found that 10.2% of patients developed abnormal liver biochemistry with 6.4% of patients requiring dose reduction and 4.5% of patients requiring discontinuation of the medication^[43].

Beyond elevated liver tests, long term MTX use may lead to the development of fibrosis and cirrhosis. The histologic feature of methotrexate-induced liver toxicity tends to resemble nonalcoholic steatohepatitis^[44]. Earlier studies reported up to a 50% chance of developing fibrosis, though there is concern that this may be an overestimation secondary to confounding factors^[45-47]. A more recent meta-analysis of 15 studies examined the relationship between long term low-dose MTX and biopsy evidence of liver fibrosis. It showed that patients have a 6.7% chance of progressing at least one histologic grade of fibrosis for every gram of MTX taken and that the rate of progression of liver disease was associated with the cumulative dose of the medication. In addition, it revealed a 5.0% chance of having advanced pathologic changes on biopsy^[48].

In general, measures to prevent or identify hepatotoxic effects should be employed prior to chronic use and risk factors for the development of hepatotoxicity identified. These risk factors, created by the American Academy of Dermatology, allow for stratification and guidance in how aggressive liver enzymes should be monitored and whether a patient should be considered for liver biopsy^[44]. Patients should be ruled out for chronic viral infections such as hepatitis B and hepatitis C, and educated to avoid hepatotoxic agents. In addition, all patients should undergo periodic monitoring of their liver tests. While there are no formal recommendations for laboratory monitoring by gastrointestinal societies, the American College of Rheumatology recommends monitoring liver tests every 2-4 wk for the first 3 mo, then every 8-12 wk for the next 3 mo. After 6 mo of therapy liver tests should be checked every 12 wk^[49].

With regards to liver biopsy, the most recent set of American College of Gastroenterology guidelines recommend consideration of a biopsy prior to initiation of MTX in patients with elevated liver tests at baseline, patients with one or more risk factor for hepatotoxicity and in patients who are suspected to have chronic liver disease^[26]. Given the lack of biopsy data in patients with CD, current guidelines defer to the American Rheumatology Associations guidelines which recommend a liver biopsy for patients who develop elevations in AST in 5 of 9 blood samples in a 12-mo period, 6 of 12 samples if performed monthly, or if there is a decrease in serum albumin below the normal range^[26,50]. The role for current noninvasive technologies such as transient or MRI elastography, or serum non-invasive markers of fibrosis remains unclear.

ANTI TUMOR NECROSIS FACTOR-ALPHA

Tumor necrosis factor-alpha (TNF- α) is a pro-inflamma-

tory cytokine that plays a role in the immunopathology of IBD^[51]. Infliximab (REMICADE®) is a chimeric monoclonal anti-TNF- α antibody which was first approved to treat CD in 1998 and UC in 2005^[52]. Its most common side effects are headache, rash and cough, while infusion reactions have been seen in 5% of patients^[53]. In addition, through its immunosuppressive properties, it has been associated with an increased risk of infection based on large cohort studies^[54].

Infliximab has been associated with several forms of DILI. A large, prospective cohort study found that 6.7% of patients treated with infliximab experienced hepatocellular cytolytic injury, with mild elevations in AST/ALT $> 1 \times$ the upper limit of normal, but discontinuation rates were not significant compared to those who did not have liver enzyme elevations^[55]. In another retrospective cohort study, 6% of patients, the vast majority who were on low-dose infliximab, developed mild idiopathic liver enzyme elevations. In up to 50% of these patients, other possible causes (medication, alcohol, metabolic, viral) were identified. The mean time to ALT elevation was 29 wk, and resolution occurred after a median of 17 wk in 82% of patients despite continuation of therapy^[56]. In this study, a small subset of patients were found to have positive autoimmune markers, and underwent liver biopsies which demonstrated features of autoimmune hepatitis, requiring cessation of the initial anti-TNF- α treatment.

Although infliximab has been used in several studies to treat refractory autoimmune hepatitis, autoimmune hepatitis due to infliximab is becoming an increasingly recognized form of hepatocellular injury^[57-59]. In a review of 34 cases of DILI secondary to TNF- α antagonists, 16/26 patients treated with infliximab had autoimmune antibodies or liver biopsies suggestive of autoimmune hepatitis, with interface hepatitis, piecemeal necrosis, and portal lymphocytic inflammation with plasma cells^[60]. Patients with autoimmune features had a latency period of 16 wk before liver injury was apparent and higher peak ALT values. In the reported cases, patients often recovered with discontinuation of infliximab and corticosteroid therapy.

Cholestatic liver injury has been described in several case reports of patients treated with infliximab. Patients developed jaundice after infliximab infusions, with markedly elevated alkaline phosphatase and bilirubin. One patient who underwent liver biopsy demonstrated bland cholestasis. Cholestatic liver injury resolved in most cases within 6-8 wk with supportive therapy and withdrawal of infliximab^[61,62]. In a severe case of acute cholestatic hepatitis after eight months of treatment with infliximab for rheumatoid arthritis, one patient progressed to liver failure requiring liver transplant. This patient's liver biopsy showed ductal proliferation with collapse and enucleation of the hepatocytes^[63].

Apart from DILI, infliximab has also been shown to cause reactivation of hepatitis B, in patients with a positive surface antigen (HBsAg) and patients with anti-core antibodies (HBcAb) without HBsAg. In a systematic

review of HBsAg-positive patients, 2/14 patients treated with infliximab experienced hepatitis B reactivation, characterized by jaundice with elevated liver enzymes and a positive HBV DNA^[64]. The outcomes for patients with reactivation range from recovery with lamivudine treatment to fatal fulminant hepatitis^[65]. Patients with HBsAg-positive or anti-HBc positive serology are considered to be at moderate risk (1%-10%) for reactivation (Table 1)^[66]. Given the poor outcomes associated with hepatitis B and the availability of prophylactic antivirals, both the AGA and AASLD recommend screening for hepatitis B with HBsAg and anti-HBcAb prior to initiating therapy^[66,67]. If a positive result is obtained, HBV DNA should be checked before initiating prophylaxis. Antiviral prophylaxis has been associated with an 87% relative risk reduction of reactivation and an 84% relative risk reduction of HBV-associated hepatitis flares. Tenofovir or entecavir is recommended for long-term antiviral prophylaxis given high resistance rates with lamivudine. In contrast to the experience with hepatitis B, hepatitis C has not been shown to be affected by infliximab usage, and screening for hepatitis C is not currently recommended.

Adalimumab (HUMIRA®) is a fully human monoclonal anti-TNF- α antibody, and was FDA-approved for use in CD in 2007 and UC in 2012. It has also been associated with DILI, though less seldom than infliximab. In a population-based study from Iceland, the absolute risk of DILI with adalimumab was reported to be 1/270 patients, compared to 1/120 infliximab users^[68]. Idiosyncratic liver enzyme elevations can be seen with adalimumab, albeit at a lower incidence than infliximab. In a study of 1753 IBD patients treated with anti-TNF therapy, 33% of patients were initiated on adalimumab; however, only 6% of the 102 patients with elevated liver enzymes were adalimumab users (three times the number on infliximab)^[56]. Resolution of mild liver enzyme elevations generally occurred despite continued use of adalimumab.

Two cases of drug-induced autoimmune hepatitis have been reported in patients being treated with adalimumab, including one patient with CD^[69,70]. Liver enzyme elevations and autoantibodies were seen after 10-12 wk of treatment. Liver biopsies in both patients showed typical morphologic features of autoimmune hepatitis. Both patients recovered with cessation of the medication and initiation of corticosteroids. Interestingly, two cases of patients who developed autoimmune hepatitis with infliximab with subsequent treatment with adalimumab have also been described in the literature. In both cases, autoimmune hepatitis resolved after infliximab was discontinued, with no evidence of recurrence after adalimumab was initiated, suggesting that DILI from one anti-TNF- α treatment does not preclude therapy with another drug in the same class^[71,72].

One case of severe cholestatic injury due to adalimumab has been reported^[73]. A female patient with CD being treated with adalimumab developed severe jaundice after seven months. Bilirubin and alkaline phosphatase

Table 1 Risk of hepatitis B viral DNA associated with medication use and hepatitis B status

Risk group	Medication	Hepatitis B virus status
High risk (> 10%)	Corticosteroids > 4 wk (moderate-high dose)	HBsAg+/HBcAb+
Moderate risk (1%-10%)	TNF- α inhibitors	HBsAg+/HBcAb+ (1%-10%)
	Ustekinumab	HBsAg-/HBcAb+ (1%)
	Vedolizumab	
	Natalizumab	
Low-risk (< 1%)	Corticosteroids > 4 wk	HBsAg+/HBcAb+ (1%-10%) (low dose)
		HBsAg-/HBcAb+ (1%) (moderate-high dose)
	Azathioprine	HBsAg+/HBcAb+
	6-mercaptopurine	HBsAg-/HBcAb+
	Methotrexate	

Adapted from American Gastroenterological Association Institute Technical Review on Prevention and Treatment of Hepatitis B Virus Reactivation During Immunosuppressive Drug Therapy^[66]. Corticosteroids (prednisone equivalent): Low dose: < 10 mg; Moderate dose: 10-20 mg; High dose: > 20 mg. HBsAg: Hepatitis B surface antigen; HBcAb: Anti-hepatitis B core antibody; TNF- α : Tumor necrosis factor- α .

were elevated, and liver biopsy demonstrated canalicular cholestasis associated with large intracannicular bile thrombi throughout the parenchyma without other significant inflammation. Spontaneous recovery was seen 5 wk after discontinuation of adalimumab.

As with infliximab, adalimumab has been implicated in hepatitis B reactivation, including fatal hepatic failure in a patient with clinically resolved hepatitis B infection^[74,75]. Consequently, hepatitis B screening and prophylaxis is recommended prior to starting patients on adalimumab. Certolizumab and golimumab are the remaining anti-TNF- α treatments which have been FDA-approved for use in CD and UC, respectively. Due to limited use, data on hepatotoxicity is scarce, though the same recommendations for hepatitis B screening apply.

In addition to direct drug-related injury or injury by viral reactivation, there is evidence of an increased risk of malignancy affecting the liver in patients on TNF- α treatment. Nineteen cases of hepatosplenic T-cell lymphoma (HSTCL) have been associated with infliximab use^[76]. This rare but aggressive malignancy is an extranodal form of non-Hodgkin's lymphoma that predominantly affects young males, and often has a poor prognosis. Presenting symptoms include hepatomegaly, splenomegaly, systemic B-type symptoms, elevated liver enzymes and signs of hepatitis. The exact causal relationship between infliximab and HSTCL is unclear, as patients were also treated with azathioprine, 6-mercaptopurine, or steroids. More long-term studies are needed to delineate the relationship between infliximab and HSTCL.

ANTI-INTEGRIN THERAPIES

The use of anti-integrin therapy for moderate to severe UC or CD that is refractory to anti-TNF agents or

immunomodulators has increased with the approval of vedolizumab in May 2014. Integrins modulate the adhesion of leukocytes to endothelial cells and are responsible for a key step in the inflammatory cascade whereby activated leukocytes anchor to the endothelial wall prior to transmigration. Two anti-integrin therapies are currently approved to treat IBD, natalizumab and vedolizumab, while a third, ertolizumab, is currently in phase 3 testing.

Natalizumab (TYSABRI®) is a monoclonal antibody directed to the α -4 integrin. Initially used for multiple sclerosis, it was subsequently approved to induce and maintain clinical remission in patients with moderate to severe active CD in patients who failed conventional therapies and anti-TNF- α agents^[77,78]. Its use has been significantly limited in CD due to morbidity and mortality in postmarketing cases of progressive multifocal leukoencephalopathy that developed secondary to the JC virus. Initial trials examining natalizumab's efficacy in treating IBD did not mention hepatotoxicity^[77,79-82]. Generally elevation of aminotransferases have occurred in approximately 5% of patients on natalizumab compared with 3%-4% of controls^[83,84]. In the post marketing setting, clinically significant liver injury, including liver failure, has been reported with at least 59 cases of hepatic injury reported to the FDA's Adverse Event Reporting System. In a report of 6 cases of liver injury, there was a significant hepatocellular component with ALT's reaching 2212 IU/L in one patient. Serum bilirubins ranged from 4.5-16 g/dL and occurred as early as 6 d after treatment. In addition, there were varying degrees of autoantibodies that were positive^[85]. The etiology of the liver injury that occurs is unclear but is likely immunologically mediated.

Vedolizumab (ENTYVIO®) and ertolizumab are newer anti-integrin therapies with less data relating to their hepatotoxic effects. Vedolizumab is a monoclonal antibody to the α 4 β 7 integrin that modulates lymphocyte migration into the gut. In the phase 3 trials examining its efficacy, three patients developed elevated transaminases with or without bilirubin elevation after 2-5 doses of vedolizumab. One further case was reported in the open labeled trial. Some patients developed autoantibodies and were treated with systemic steroids^[86-90]. Currently, screening for hepatitis B prior to treatment is not routinely recommended.

Ertolizumab is a monoclonal antibody that binds the β 7 subunit of α 4 β 7 and α E β 7 integrins. Phase 1 and phase 2 studies in UC have been performed while phase 3 studies are underway. No reported adverse events related to the liver have been reported^[91,92].

USTEKINUMAB

Ustekinumab (STELARA®) is a human IgG1 κ monoclonal antibody that targets interleukin (IL)-12 and IL-23 activity by blocking its receptors^[93]. It was approved in 2009 for use in moderate to severe psoriasis and psoriatic arthritis. While it has demonstrated benefit in

patients with CD, it currently does not have FDA approval for this indication. In the two published trials evaluating its efficacy in CD, there were two hepatobiliary disorders reported as biliary colic and cirrhosis, which did not differ significantly in number from the control group^[94,95]. Elevated liver enzymes were a relatively rare occurrence, occurring in up to 1.4% of patients through 64 wk of follow up in one study. In patients treated for up to 5 years with ustekinumab for moderate-severe psoriasis, hepatobiliary disorders were rare, representing only 0.2 events per 100 patient-years for up to 5 years of follow up^[96-98].

IL-12 plays an important role in controlling hepatitis B viral infections through its facilitation of type 1 T helper lymphocytes and by inhibiting HBV replication through interferon-gamma production^[99-101]. Given its mechanism of action, reactivation rates between 1%-10% would be expected (Table 1)^[66]. There is therefore a theoretical risk of reactivation of hepatitis B with the use of ustekinumab. One retrospective study in patients with psoriasis reported 11 patients who were hepatitis B surface antigen positive and surface antibody negative who were started on ustekinumab. Out of the 7 patients in whom prophylaxis was not given, two experienced reactivation. Of the 4 patients in whom prophylaxis was initiated, no cases of reactivation were observed^[101]. Assuming a 5% rate of reactivation of hepatitis B in patients exposed to ustekinumab, prophylaxis would result in 44 fewer reactivation events per 1000 patients treated and should be considered^[66].

CYCLOSPORINE

Cyclosporine prevents the activation of T-lymphocytes by inhibiting the production and release of IL- II. It is used to induce remission in refractory UC and serve as a bridge to medications such as AZA or 6-MP for maintenance therapy. Traditionally given as an intravenous infusion at a rate of 4 mg/kg, the lower 2 mg/kg dose has been shown to be equally effective with fewer reported side effects^[102-104]. Over 80% of steroid refractory patients will respond to therapy and in many cases, cyclosporine provides an alternative to colectomy^[105]. While side effects such as nephrotoxicity, hypertension and infections are more prevalent, hepatotoxicity is rare.

Animal studies evaluating its effects on the liver reveal increased bile acid and bilirubin concentrations when given at high doses, with a corresponding reduction of the biliary secretion of bile acids, cholesterol and phospholipids. Cholestasis was secondary to a decrease in bile acid dependent and independent bile flow fractions^[106,107]. Case series that evaluated dosages ranging from 2-10 mg/kg per day found mild abnormalities in liver tests consistent with mild increases in alkaline phosphatase levels as well as slight increases in bilirubin and aminotransferases^[108]. In addition, cyclosporine has been reported to increase the incidence of cholelithiasis^[109]. Earlier studies evaluating cyclosporine use in post-renal transplant patients reported evidence

of hepatotoxicity in 20%-82% of patients, characterized by transaminase elevations as well as elevations in bilirubin and alkaline phosphatase, which were dose responsive^[110-112]. In IBD patients, the rate of liver tests abnormalities is closer to 1%-4% of patients, with a recent systematic review of the literature reporting only 11 cases of elevated liver tests in IBD patients treated with cyclosporine^[113,114].

ANTIBIOTICS

Though their benefits are not well defined in prospective randomized trials, antimicrobials have long been used as either adjunctive therapy for IBD complications such as CD related abscesses, or as the primary therapy in pouchitis, an IBD like condition occurring in surgically constructed continent jejunal or "J-pouch" reservoirs following total colectomy for UC. Since current IBD models suggest that even normal bowel bacteria may play a role in initiating and propagating the aberrant immune response typical of IBD, the appeal of antibiotics is straight forward; that decreasing bacterial concentrations may lessen this immune stimulation and thus decrease the inflammatory response. Though there is some evidence of benefit to this approach in fistulizing peri-anal and colonic CD, a clearer benefit in UC is lacking. Currently, antibiotic therapy for UC is only recommended for end-stage cases of toxic megacolon, when bacteremia is common.

The two most commonly used antibiotics are metronidazole and ciprofloxacin, either individually or in combination. Metronidazole is a synthetic nitroimidazole derivative used to treat both anaerobic bacteria and protozoa, generally dosed orally at 10 to 20 mg/kg per day. Ornidazole, another nitroimidazole derivative not currently available in the United States, has also been studied for the treatment of CD. Though metronidazole is often given intravenously when utilized for inpatients with CD related abscesses, most clinical experience in CD is with oral use. While dose adjustment is recommended in patients with severe liver impairment, primary hepatotoxicity is extremely rare. Cases of DILI have been reported, typically presenting with a hepatocellular injury pattern several weeks after the initiation of therapy^[115,116]. Small prospective trials of metronidazole and ornidazole in CD have reported elevations of liver enzymes, that did not significantly differ from the placebo group^[117,118].

Ciprofloxacin is a member of the fluoroquinolone class of antibiotics whose mechanism involves inhibition of DNA gyrase within sensitive bacteria, preventing the relaxation of supercoiled DNA and subsequent breakage of double stranded DNA. Minor elevations of serum AST and ALT related to ciprofloxacin use is quite common, affecting approximately 1% of users. A recent large study of a Veterans Administration population of 7862 patients with fluoroquinolone exposure matched against 45512 controls, each group excluding underlying liver disease, showed an increased risk of hepatotoxicity in exposed compared to unexposed patients, odds ratio

Table 2 Summary of medication side effects and management options

Medication	Prevalence of liver injury	Manifestation	Management ¹
Sulfasalazine	0.4%-2.9%	Mild liver test abnormalities Severe systemic hypersensitivity Granulomatous hepatitis DRESS syndrome	
5-ASA	Approximately 2.6%	Mild liver test abnormalities Drug induced autoimmune hepatitis Systemic hypersensitivity reaction	
AZA/6-MP	1.4%-7.1%	Hypersensitivity reaction Cholestasis Peliosis hepatitis Disse space fibrosis Veno-occlusive disease Nodular regenerative hyperplasia Hepatosplenic T-cell lymphoma	Slight liver test elevation → Monitor Persistent elevation → Consider stopping medication/reducing dose Marked elevation → Stop medication
Methotrexate	Approximately 10.2%	Elevated liver tests Fibrosis	
Anti-TNF- α agents	0.37%-6.7%	Hepatocellular injury Cholestasis Hepatosplenic T-cell lymphoma Autoimmune hepatitis	
Anti-integrin therapy	< 5%	Hepatocellular injury Cholestasis Autoimmune hepatitis Liver failure	
Ustekinumab	1.4%	Elevated liver tests	
Cyclosporine	1%-4%	Increased bile acids Cholestasis Hepatocellular injury	

¹For general management of elevated liver tests. For specific recommendations see text. ASA: Aminosalicic acid; AZA: Azathioprine; 6-MP: 6-Mercaptopurine; TNF: Tumor necrosis factor; DRESS: Drug reaction with eosinophilia and systemic symptoms.

(OR) = 1.20; 95%CI: 1.04-1.38^[119]. Much rarer cases of severe hepatocellular, cholestatic or a mixed pattern of injury have been reported with fluoroquinolones, which are among the group of antibiotics most commonly associated with this complication. Clinical trials of ciprofloxacin for the treatment of CD have not shown any significant rates of liver injury, but given the small size of these studies it is not possible to determine whether there is any disease specific associated liver risk^[120,121].

Finally, though CD is not widely considered to be caused by a specific infection, there is a possible association of CD with the organism *Mycobacterium avium* paratuberculosis (MAP), which has been found in the serum and tissue of some CD patients. Though there has been modest success with antimicrobial treatment regimens directed at MAP, it is unclear whether this success is related to its effect on MAP or a general alteration of the bowel flora. While isoniazid (INH) has an anti-mycobacterial effect, and has been used as part of MAP directed therapy, the common usage of INH in individuals with IBD is not as a direct therapy, but as a co-therapy to prevent reactivation of mycobacterium tuberculosis (TB) in individuals with suspected latent infection treated with anti-TNF- α therapy^[122,123]. In the United States population the risk of latent TB has been estimated at 4%, with significant variations depending upon the region and socioeconomic status^[124]. Current prescribing guidelines recommend testing for latent

TB prior to initiation of biologic therapy with anti-TNF- α agents^[125]. In patients at risk for latent TB, at least one month of INH therapy is suggested prior to the initiation of biologic therapy^[126].

INH inhibits the synthesis of mycolic acid, an essential component of the bacterial cell wall, and is commonly associated with DILI. Mild elevations of serum transaminases occur in up to 20% of INH treated patients, and usually requires close monitoring without discontinuation of therapy. Traditionally more severe, and potentially fatal INH hepatitis has been directly associated with increasing patient age, ranging from a rate of 0.3% in individuals 20 to 34 years of age, and as high as 4.6% in those over age 65 years manifesting as an acute hepatocellular pattern. Though, more recent studies have suggested that rates may be as low as 0.1%^[127,128]. Fatality rates once hepatitis develops have been reported as high as 10%, and are worse with increasing age, though overall fatality rates in those treated and monitored following current American Thoracic Society guidelines appear to be very low^[129,130]. Current guidelines recommend routine monitoring of patients treated with INH prophylaxis who are at higher risk of underlying liver disease such as those with chronic viral hepatitis, recent pregnancy, and regular alcohol consumption. However, monitoring may be considered for anyone greater than 35 years of age. Suggested intervals of AST, ALT, and bilirubin testing are at baseline, then as often as every 4 wk while on

therapy. Discontinuation of therapy should be considered for an ALT $> 5 \times$ the upper limit of normal, or $> 3 \times$ the upper limit of normal with associated nausea, vomiting, abdominal pain, jaundice, or unexplained fatigue^[131].

CONCLUSION

While both patients and physicians alike may look forward to a true "cure" for illness, the management of chronic medical conditions typically requires the use of medications, often for an indefinite length of time. This is certainly true for the management of IBD. The fact that IBD is itself an immune related disease, requiring immune suppressing or modifying therapies, for long periods of time, further increases the side effect potential of these treatments. IBD medications are prominent on the list of well described agents causing DILI, as well as other hepatobiliary manifestations, each with their own prevalence and management strategy (Table 2)^[25]. While the data on newer therapies appears encouraging with regard to DILI specifically, further post marketing experience will be needed to determine the exact nature of this risk and appropriate prophylactic and management strategies.

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