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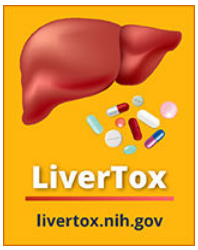


Mercaptopurine

Updated: August 17, 2017.

OVERVIEW

Introduction

Mercaptopurine (also referred to as 6-mercaptopurine or 6-MP) is a purine analogue that is effective both as an anticancer and an immunosuppressive agent, and is used to treat leukemia and autoimmune diseases as a corticosteroid-sparing agent. Mercaptopurine therapy is associated with a high rate of serum aminotransferase elevations which can be accompanied by jaundice. In addition, mercaptopurine has been linked to instances of clinically apparent acute liver injury and long term therapy to nodular regenerative hyperplasia.

Background

Mercaptopurine (mer kap" toe pure' een) is a purine analogue that acts as an antimetabolite by antagonism of purine metabolism which results in a general inhibition of DNA, RNA and subsequent protein synthesis. Mercaptopurine also has antiinflammatory and immunosuppressive activity, inhibiting the maturation of T cells and blocking delayed hypersensitivity reactions. Mercaptopurine was introduced into use in the 1950s for the therapy of leukemia and lymphoma and was formally approved for use in the United States in 1953. It is still used in therapy of acute lymphocytic leukemia and off-label for autoimmune conditions such as Crohn's disease. Mercaptopurine is available generically and under the brand name of Purinethol as tablets of 50 mg. The usual dose is 1 to 3 mg per kilogram or 50 to 150 mg daily, and it is typically given long term. Common side effects include nausea, abdominal upset, rash, aphthous ulcers and dose related bone marrow suppression.

Hepatotoxicity

Mercaptopurine has been associated with several forms of hepatotoxicity. Patients receiving mercaptopurine for leukemia often have transient and asymptomatic rises in serum aminotransferase or alkaline phosphatase levels and a proportion of these patients develop jaundice, particularly when it is given in high doses. In case series of patients with autoimmune diseases (such as inflammatory bowel disease) treated with mercaptopurine, up to 30% developed serum aminotransferase elevations and these can be persistent as long as therapy is continued, resolving either with dose reduction or discontinuation. Liver biopsy usually demonstrates steatosis and centrolobular injury with scant inflammation.

Mercaptopurine can also lead to a distinctive acute, clinically apparent liver injury that usually presents with fatigue and jaundice and a cholestatic or mixed pattern of serum enzyme elevations 1 to 6 months after starting therapy, but sometimes later, particularly following an increase in dose. Serum enzyme levels are often not very high, certainly not in the range that occurs with acute viral hepatiits. Rash, fever and eosinophilia are uncommon and autoantibodies are generally not found. Liver biopsy typically shows a mixed hepatocellular-cholestatic injury with cholestasis, focal hepatocellular necrosis, bile duct injury and variable amounts of

inflammation. The injury is idiosyncratic and similar to the cholestatic hepatitis associated with azathioprine. The liver injury usually resolves upon stopping, but prolonged cholestasis has been reported and some cases have been fatal. In large case series and registries, mercaptopurine usually ranks among the top 20 causes of drug induced liver injury, and if combined with cases due to azathioprine [a prodrug of mercaptopurine] would rank among the top 10 more frequent causes.

Chronic therapy with mercaptopurine and other thiopurines can lead to nodular regeneration and symptomatic portal hypertension. This chronic hepatotoxicity typically presents with fatigue and signs and symptoms of portal hypertension (ascites, varices), with mild liver enzyme abnormalities and minimal jaundice arising 6 months to many years after starting mercaptopurine. Liver biopsy shows nodular regenerative hyperplasia without significant fibrosis and varying amounts of sinusoidal dilation and central vein injury. This syndrome can progress to hepatic failure, particularly if mercaptopurine is continued, but gradual improvement on stopping therapy is typical. Rarely, the onset of this syndrome can be acute with abdominal pain and ascites in which situation liver biopsy usually shows sinusoidal dilation, central congestion and injury to sinusoidal endothelial cells suggestive of veno-occlusive disease, which is currently referred to as sinusoidal obstructive syndrome. Typically, serum aminotransferase levels and alkaline phosphatase levels are minimally elevated, even in the presence of hyperbilirubinemia and other manifestations of hepatic dysfunction and portal hypertension. Many cases present initially with unexplained thrombocytopenia, and progressive decreases in platelet counts may be the most sensitive marker for the development of the non-cirrhotic portal hypertension.

Finally long-term therapy with mercaptopurine and other thiopurines has been implicated in leading to the development of malignancies, including hepatocellular carcinoma (HCC) and hepatosplenic T cell lymphoma (HSTCL). Both of these complications are rare but have been reported in several dozen case reports and small case series. In neither instance, has the role of thiopurine therapy in causing the malignacies been proven, and similar cases have been described in patients with autoimmune conditions or after solid organ transplantation who have not received thiopurines. Hepatocellular carcinoma typically arises after years of azathioprine or mercaptopurine therapy and in the absence of accompanying liver disease (although sometimes with focal hepatic glycogenosis). The HCC is most frequently found on an imaging study done of an unrelated condition. The prognosis is more favorable than that of HCC associated with cirrhosis. Hepatosplenic T cell lymphoma has been reported largely among young men with inflammatory bowel disease and long term immunosuppression with a thiopurine with or without anti-tumor necrosis factor therapy. The typical presentation is with fatigue, fever, hepatosplenomegaly and pancytopenia. The diagnosis is made by bone marrow or liver biopsy showing marked infiltration with malignant T cells. HSTCL is poorly responsive to antineoplastic therapy and has a high mortality rate.

Likelihood score: A (well known cause of clinically apparent liver injury).

Mechanism of Injury

Mercaptopurine is believed to have a direct, dose related hepatotoxic effect and similar types of injury can be reproduced in animal models. The toxic effects of mercaptopurine, and particularly the myelotoxicity, have been linked to higher levels of methyl-mercaptopurine, a product of one of the metabolic pathways of mercaptopurine metabolism. Mercaptopurine undergoes extensive hepatic metabolism to other thiopurines via three different pathways. Patients with low levels or a deficiency in thiopurine methyltransferase, which mediates one of these metabolic pathways, have a higher rate of complications of mercaptopurine use, particularly bone marrow suppression, but may not be at a higher risk for liver injury. The acute cholestatic hepatitis associated with mercaptopurine, on the other hand, is more likely due to idiosyncratic reaction, although it is also more common with higher doses of the thiopurine.

Outcome and Management

The acute liver injury caused by mercaptopurine usually begins to improve rapidly upon stopping the medication, but instances of progression to hepatic failure despite discontinuation of mercaptopurine have been reported. There are no known specific treatments for mercaptopurine hepatotoxicity. Rechallenge with mercaptopurine usually results in recurrence of the injury (within days to weeks) and should be avoided. Some, but not all, patients have tolerated switching therapy to azathioprine or thioguanine or with use of lower doses in combination with allopurinol. In cases of severe hepatic injury from mercaptopurine, however, substitution with a structurally unrelated antimetabolite or immunosuppressive agent is more appropriate.

Drug Class: Antineoplastic Agents, Antimetabolites; Gastrointestinal Agents

Other Drugs in the Subclass, Purine Analogues: Azathioprine, Cladribine, Clofarabine, Fludarabine, Nelarabine, Pentostatin, Thioguanine

See also: Transplant Drugs

Other Drugs in the Subclass, Purine Analogues/Thiopurines: Azathioprine, Thioguanine

CASE REPORT

Case 1. Acute cholestatic hepatitis due to mercaptopurine.

[Modified from: Shorey J, Schenker S, Suki WN, Combes B. Hepatotoxicity of mercaptopurine. Arch Intern Med 1968; 122: 54-8. PubMed Citation]

A 45 year old man with membranous glomerulonephritis developed nausea and fatigue followed by jaundice 4 months after adding mercaptopurine (150 to 200 mg/day) to chronic prednisolone therapy. He had no previous history of liver disease, alcohol abuse or risk factors for viral hepatitis. Physical examination revealed jaundice, enlargement of the liver and spleen and peripheral edema. He also had Cushingoid features. Laboratory testing showed total bilirubin of 9.9 mg/dL (direct 5.9 mg/dL), AST 112 and alkaline phosphatase 11.3 Bodansky units (2.5 times ULN). Mercaptopurine was stopped and he improved clinically within a week, while laboratory abnormalities decreased more slowly (Table). Two months later all liver tests were normal.

Key Points

Medication:	Mercaptopurine (200 mg daily)
Pattern:	Cholestatic (R=1.1)
Severity:	3+ (jaundice, hospitalization)
Latency:	4 months
Recovery:	2 months
Other medications:	Prednisolone, furosemide which were continued

Laboratory Values

Time After Starting	Time After Stopping	AST (U/L)	Alk P (BU/L)	Bilirubin (mg/dL)	Other
0	Pre	14	3.5		
18 weeks	0	112	11.3	9.9	Admission
	4 days	86	14.4	11.6	
19 weeks	1 week		19.2	7.0	

Table continued from previous page.

Time After Starting	Time After Stopping	AST (U/L)	Alk P (BU/L)	Bilirubin (mg/dL)	Other
23 weeks	5 weeks	22	11.9	0.2	
6 months	9 weeks		4.6		
Normal Values		**<40**	**<4.5**	**<1.2**	

Comment

A typical cholestatic hepatitis due to mercaptopurine arising after 4 months of therapy with mild symptoms, prominent jaundice, and only mild-to-moderate elevations in serum enzymes. Jaundice resolved within a month, while the serum alkaline phosphatase elevations persisted for longer.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Mercaptopurine – Generic, Purinethol®

DRUG CLASS

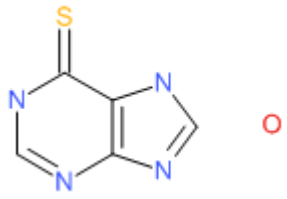
Antineoplastic Agents

Antirheumatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Mercaptopurine	6112-76-1	C5-H4-N4-S.H2-O	

ANNOTATED BIBLIOGRAPHY

References updated: 17 August 2017

Zimmerman HJ. Antipurines. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 687-9.

(Expert review of hepatotoxicity of thiopurines published in 1999).

DeLeve LD. Thiopurines. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 555-6.

(Review of hepatotoxicity of thiopurines).

Chabner BA, Bertino J, Cleary J, Ortiz T, Lane A, Supko JG, Ryan D. Purine analogues. Cytotoxic agents. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1701-5.

(Textbook of pharmacology and therapeutics; mercaptopurine nucleotides inhibit de novo purine synthesis and become incorporated into nucleic acids).

Farber S. Summary of experience with 6-mercaptopurine. Ann N Y Acad Sci 1954; 60: 412-4. PubMed PMID: 14350545.

(Initial experience in treating 80 children with malignancies using mercaptopurine; 6 cases of jaundice; "Liver function tests inconclusive. Icterus cleared when 6-MP omitted").

Philips FS, Sternberg SS, Hamilton S, Clarke DA. The toxic effects of 6-mercaptopurine and related compounds. Ann N Y Acad Sci 1954; 60: 283-96. PubMed PMID: 14350534.

(Toxicity studies in laboratory animals).

Ellison RR, Silver RT, Engle RL Jr. Comparative study of 6-chloropurine and 6-mercaptopurine in acute leukemia in adults. Ann Intern Med 1959: 322-38. PubMed PMID: 13820065.

(Among 18 patients with leukemia treated with mercaptopurine and 16 with chloropurine, jaundice occurred in 6 in each group, arising 18-153 days after starting drug, but few details given and most had septicemia and hepatic leukemic infiltrates).

McIlvanie SK, MacCarthy JD. Hepatitis in association with prolonged 6-mercaptopurine therapy. Blood 1959; 14: 80-90. PubMed PMID: 13607581.

(Four cases of acute "toxic" liver injury during mercaptopurine therapy of leukemia in children, ages 4-13 years, arising 2-6 months after starting drug [bilirubin 4.5-8.7 mg/dL, Alk P mildly elevated]).

Clark PA, Hsia YE, Huntsman RG. Toxic complications of treatment with 6-mercaptopurine: two cases with hepatic necrosis and intestinal ulceration. Br Med J 1960; 1: 393-5. PubMed PMID: 13810473.

(Two cases; 5 year old boy with acute leukemia developed jaundice 7 weeks after starting mercaptopurine [bilirubin 6.6 mg/dL, minimal Alk P elevations], on autopsy liver showed severe centrolobular hepatic necrosis; 40 year old man with acute leukemia developed jaundice 4 weeks after starting mercaptopurine [bilirubin 9.5 mg/mL, ALT 140 U/L, Alk P 2 times ULN], with rapid progress and death, autopsy showing centrilobular necrosis).

Einhorn M, Davidsohn I. Hepatotoxicity of mercaptopurine. JAMA 1964; 188: 802-6. PubMed PMID: 14132534.

(Among 38 patients with leukemia treated with mercaptopurine, 16 developed jaundice, resolving with stopping in half and recurring in two with rechallenge; onset in 4-8 weeks [bilirubin 3.6-14.8 mg/dL, ALT 21-140 U/L, Alk P 1-6 times ULN]).

Mackay IR, Weiden S, Ungar B. Treatment of chronic active hepatitis and lupoid hepatitis with 6-mercaptopurine and azathioprine. Lancet 1964; 1: 899-902. PubMed PMID: 14124080.

(Experience in using mercaptopurine and azathioprine in 5 patients with autoimmune hepatitis, mentions that hyperbilirubinemia was a side effect of higher doses, resolving with dose modification).

Corley CC Jr, Lessner HE, Larsen WE. Azathioprine therapy of "autoimmune" diseases. Am J Med 1966; 41: 404-12. PubMed PMID: 5330635.

(Experience in using azathioprine in 46 patients with various autoimmune diseases, mostly an idiopathic thrombocytopenic purpura and lupus erythematosus; side effects including nausea and vomiting occurred with

higher doses, mild cytopenias were common, and one patient had jaundice after 6 months [350 mg/day] [bilirubin 3.8 mg/L, mild Alk P and ALT elevations], biopsy showing cholestasis).

Krawitt EL, Stein JH, Kirkendall WM, Clifton JA. Mercaptopurine hepatotoxicity in a patient with chronic active hepatitis. Arch Intern Med. 1967; 120: 729-34. PubMed PMID: 4168362.

(18 year old girl with autoimmune hepatitis poorly controlled on prednisone developed fatigue and jaundice within 2-3 weeks of starting mercaptopurine, with worsening hepatic function, multiorgan failure and death).

Shorey J, Schenker S, Suki WN, Combes B. Hepatotoxicity of mercaptopurine. Arch Intern Med 1968; 122: 54-8. PubMed PMID: 5659378.

(Two cases; 45 year old man developed malaise and jaundice 4 months after starting mercaptopurine for glomerulonephritis [bilirubin 9.9 mg/dL, AST 112 U/L, Alk P 3 times ULN], resolving within 6 weeks of stopping; 39 year old woman developed jaundice 2-3 months after starting mercaptopurine [bilirubin 16.4 mg/dL, AST 314 U/L, Alk P 4 times ULN], with sudden unexplained death shortly after, autopsy showing intrahepatic cholestasis with scant necrosis).

Lascari AD, Givier RL, Saper RT, Hill LF. Portal hypertension in a case of acute leukemia treated with antimetabolites for 10 years. N Engl J Med 1968; 279: 303-6. PubMed PMID: 5301748.

(6 year old girl with acute leukemia and long term chemotherapy including mercaptopurine developed splenomegaly after 3 years, with subsequent recurrent variceal hemorrhage; splenectomy and porto-caval shunt yielded excellent outcome; biopsy showing fibrosis without cirrhosis).

Robert J, Barbier P, Manaster J, Jacobs E. Hepatotoxicity of cytostatic drugs evaluated by liver function tests and appearance of jaundice. Digestion 1968; 1: 229-32. PubMed PMID: 5696244.

(Analysis of 417 courses of cytostatic therapy with various agents; half of patients receiving mercaptopurine developed elevations in serum bilirubin, but no specifics given).

Sparberg M, Simon N, Del Greco F. Intrahepatic cholestasis due to azathioprine. Gastroenterology 1969; 57: 439-41. PubMed PMID: 4951148.

(44 year old man developed jaundice 13 months after renal transplant [bilirubin 21 mg/dL, ALT 94 U/L, Alk P normal], biopsy showing cholestasis without hepatocyte necrosis; patient died after withdrawal of azathioprine and increase in corticosteroids).

Lehmann GW. [Intrahepatic cholestasis caused by 6-mercaptopurine]. Kinderarztl Prax 1969; 37: 506-11. German. PubMed PMID: 5379242.

(15 year old girl with acute leukemia developed nausea followed by jaundice 2 months after starting mercaptopurine [bilirubin 10.6 rising to 38.1 mg/dL, ALT 42 U/L, Alk P ~2 times ULN, eosinophils 15%], ultimately responding to prednisolone, but subsequent relapse of leukemia).

Drinkard JP, Stanley TM, Dornfeld L, Austin RC, Barnett EV, Pearson CM, Vernier RL, et al. Azathioprine and prednisone in the treatment of adults with lupus nephritis. Medicine (Baltimore) 1970; 49: 411-32. PubMed PMID: 4924695.

(Report on 20 patients with lupus nephritis treated with combination of prednisone and azathioprine; hepatotoxicity occurred in one patient developing jaundice at 11 months [bilirubin 11.4 mg/dL, ALT 80 U/L and Alk P ~1.5 times ULN], resolving with stopping).

Malekzadeh MH, Grushkin CM, Wright HT Jr, Fine RN. Hepatic dysfunction after renal transplantation in children. J Pediatr 1972; 81: 279-85. PubMed PMID: 4339534.

(Nine of 63 children with renal transplants had evidence of liver disease, 8 considered due to azathioprine, arising 3 to 30 months after transplant [bilirubin 1.2-24 mg/dL, ALT 116-500 U/L, Alk P 1-10 times elevated], improving on stopping).

Zarday A, Veith FJ, Gliedman ML, Soberman R. Irreversible liver damage after azathioprine. JAMA 1972; 222: 690-1. PubMed PMID: 4562099.

(27 year old woman developed chronic liver disease after renal transplantation, improving on stopping azathioprine but then progressing to end stage liver disease; in retrospect, possibly due to hepatitis C).

Millard PR, Herbertson BM, Evans DB, Calne RY. Azathioprine hepatotoxicity in renal transplantation. Transplantation 1973; 16: 527-30. Not in PubMed

(Complex analysis of patients after renal transplantation finding no correlation between changes in azathioprine dose and changes in ALT levels).

Briggs WA, Lazarus JM, Birtch AG, Hampers CL, Hager EB, Merrill JP. Hepatitis affecting hemodialysis and transplant patients. Arch Intern Med 1973; 132: 21-8. PubMed PMID: 4577389.

(Analysis of 14 patients who developed hepatitis B while on renal dialysis and 14 after renal transplant; reinstitution of azathioprine was often associated with exacerbation of the hepatitis).

Ireland P, Rashid A, von Lichtenberg F, Cavallo T, Merrill JP. Liver disease in kidney transplant patients receiving azathioprine. Arch Intern Med 1973; 132: 29-37. PubMed PMID: 4577390.

(Analysis of course of liver disease in 24 kidney transplant patients suggested that azathioprine had little or no effect on course of what was likely chronic viral hepatitis in transplant patients).

Koretz RL. Azathioprine in liver disease. Arch Intern Med 1974; 133: 870-1. Replies by authors. PubMed PMID: 4595401.

(Letter in response to Briggs [1973] and Ireland [1973] pointing out that the patients were from the same institution and may have been the same in the two studies, but that conclusions regarding safety of azathioprine were different).

Du Vivier A, Munro DD, Verbov J. Treatment of psoriasis with azathioprine. Br Med J 1974; 1: 49-51. PubMed PMID: 4812392.

(Among 29 patients with psoriasis treated with azathioprine, 2 developed cholestasis and 8 portal fibrosis as shown by liver biopsies performed before, at 6 months and then annually).

Berne TV, Chatterjee SN, Craig JR, Payne JE. Hepatic dysfunction in recipients of renal allografts. Surg Gynecol Obstet 1975; 141: 171-5. PubMed PMID: 168654.

(Among 142 patients undergoing renal transplantation, 18 developed liver disease, all while on azathioprine; in 10 patients there was improvement with stopping).

Ware AJ, Luby JP, Eigenbrodt EH, Long DL, Hull AR. Spectrum of liver disease in renal transplant recipients. Gastroenterology 1975; 68: 755-64. PubMed PMID: 164401.

(Liver disease developed in 31 of 82 [38%] patients undergoing renal transplantation, 8 with acute self-limited disease, 2 with acute liver failure [1 due to HBV] and 21 with chronic liver injury; all received azathioprine, but no consistent effect of stopping or modifying dose in chronic cases, possibly being due to chronic hepatitis C which could not be serologically identified in 1975).

Marubbio AT, Danielson B. Hepatic veno-occlusive disease in a renal transplant patient receiving azathioprine. Gastroenterology 1975; 69: 739-43. PubMed PMID: 1098955.

(54 year old man developed jaundice 14 months after renal transplant [bilirubin 5.1 mg/dL, AST 125 U/L, Alk P 1.5 times ULN], progressing to liver failure and death despite stopping azathioprine promptly; biopsies and autopsy showing veno-occlusive disease; patient also had hepatitis B).

Griner PF, Elbadawi A, Packman CH. Veno-occlusive disease of the liver after chemotherapy of acute leukemia. Report of two cases. Ann Intern Med 1976; 85: 578-82. PubMed PMID: 1068643.

(Two men with leukemia, ages 17 and 72 years, developed abdominal pain, ascites and progressive liver failure 3-4 months after starting cyclic cytotoxic therapy with multiple agents including thioguanine [initial bilirubin 1.3 and 2.5 mg/dL, AST 348 and 48 U/L, Alk P 92 and 276 U/L]; autopsies showed acute sinusoidal obstruction syndrome [veno-occlusive disease]).

Minow RA, Stern MH, Casey JH, Rodriguez V, Luna MA. Clinico-pathologic correlation of liver damage in patients treated with 6-mercaptopurine and adriamycin. Cancer 1976; 38: 1524-8. PubMed PMID: 1068739.

(Combination of adriamycin [50 mg/m^2/day] and mercaptopurine [500 mg/m^2/day] with vincristine and prednisone for acute leukemia was associated with high rate of hepatotoxicity; in 11 cases, bilirubin rising with each course with mild elevations in ALT and Alk P; liver tissue showing central cholestasis with mild hepatocellular necrosis and fatty change).

Degott C, Rueff B, Kreis H, DuBoust A, Potet F, Benhamou JP. Peliosis hepatis in recipients of renal transplants. Gut 1978; 19: 748-53. PubMed PMID: 355072.

(Among 500 patients undergoing renal transplantation between 1965-75, 55 had liver biopsy, 12 of which showed peliosis hepatis [6 major; 6 minor changes], often in association with chronic hepatitis B; in major forms there was hepatomegaly and portal hypertension; hypothesized possible role of azathioprine).

Nataf C, Feldmann G, Lebrec D, Degott C, Descamps JM, Rueff B, Benhamou JP. Idiopathic portal hypertension(perisinusoidal fibrosis) after renal transplantation. Gut 1979; 20: 531-7. PubMed PMID: 381128.

(Two cases of young men developing esophageal varices 1.5 and 7 years after renal transplantation and azathioprine therapy with normal liver tests and liver biopsy, but perisinusoidal fibrosis found on electron microscopy, seemingly improving once azathioprine was stopped).

Topley JM, Benson J, Squier MV, Chessells JM. Hepatotoxicity in the treatment of acute lymphoblastic leukaemia. Med Pediatr Oncol 1979; 7: 393-9. PubMed PMID: 296787.

(Among 21 children receiving mercaptopurine for acute leukemia, most had transient ALT elevations, but liver biopsies were often normal or showed minimal changes).

Ware AJ, Luby JP, Hollinger B, Eigenbrodt EH, Cuthbert JA, Atkins CR, Shorey J, et al. Etiology of liver disease in renal-transplant patients. Ann Intern Med 1979; 91: 364-71. PubMed PMID: 224742.

(Analysis of 72 episodes of liver disease occurring in 62 of 120 renal transplant recipients; 4 episodes of acute cholestasis were attributed to azathioprine, resolving with stopping or dose reduction; azathioprine did not seem to account for cases of chronic liver injury, responses to stopping being equivocal).

Stromeyer FU, Ishak KG. Nodular transformation(nodular regenerative hyperplasia) of the liver. A clinicopathological study of 30 cases. Hum Pathol 1981; 1: 60-71. PubMed PMID: 7203455.

(30 cases of nodular regenerative hyperplasia from the files of the Armed Forces Institute of Pathology; ages 14-80 years, half males, 18 discovered incidentally, 84% splenomegaly, 58% ascites, half died, 3 with liver failure, mild elevations in AST and Alk P levels were typical; 6 had rheumatologic disorder, 7 hematologic disease; 10 on corticosteroids, several on azathioprine, but mercaptopurine not specifically mentioned).

Whisnant JK, Pelkey J. Rheumatoid arthritis: treatment with azathioprine>(IMURAN(R)). Clinical side-effects and laboratory abnormalities. Ann Rheum Dis 1982; 41 Suppl 1: 44-7. PubMed PMID: 7065742.

(Review of literature on 542 patients in 24 studies given azathioprine for up to 4 years; leucopenia in 26%, gastrointestinal complaints in 19%; only two reports of hepatotoxicity).

Weitz H, Gokel SM, Loeschke K, Possinger K, Eder M. Venoocclusive disease of the liver in patients receiving immunosuppressive therapy. Virchows Arch [1] 1982; 395: 245-56. PubMed PMID: 7051531.

(Four cases of sinusoidal obstruction syndrome in 34-41 year old men who developed mild jaundice 9-21 months after renal transplantation [bilirubin 2.8-3.7 mg/dL, ALT 17-60 U/L, Alk P 108-673 U/L], ultimately with fatal outcomes).

D'Cruz CA, Wimmer RS, Harcke HT, Huff DS, Naiman JL. Veno-occlusive disease of the liver in children following chemotherapy for acute myelocytic leukemia. Cancer 1983; 52: 1803-7. PubMed PMID: 6578867.

(Three children [2 girls and 1 boy, ages 4, 8 and 14] developed sinusoidal obstruction syndrome 5-6 months after starting chemotherapy for leukemia, presenting with abdominal pain and hepatomegaly [bilirubin 1.2-2.0 mg/dL, ALT and Alk P normal], improving on decreasing dose of chemotherapy).

Harvey C, Dixon JS, Bird HA. Serum IgA concentration and hepatotoxicity in rheumatoid arthritis treated with azathioprine. Br Med J (Clin Res Ed) 1983; 287: 534. PubMed PMID: 6411213.

(Among 27 patients with rheumatoid arthritis treated with azathioprine [1.5 mg/kg/day], 4 developed ALT elevations 2-8 weeks after starting, all 4 had low levels of IgA before starting [mean=109 mg/dL]).

DePinho RA, Goldberg CS, Lefkowitch JH. Azathioprine and the liver: evidence favoring idiosyncratic, mixed cholestatic-hepatocellular injury in man. Gastroenterology 1984; 86: 162-5. PubMed PMID: 6689657.

(22 year old man with lupus erythematosus developed jaundice 3 weeks after starting azathioprine [peak direct bilirubin ~4.9 mg/dL, ALT ~710 U/L, Alk P ~560 U/L], resolving within 6 weeks of stopping; biopsy showed intrahepatic cholestasis with scant inflammation and necrosis: Azathioprine Case 1).

Eisenhauer T, Hartmann H, Rumpf KW, Helmchen U, Scheler F, Creutzfeldt W. Favorable outcome of hepatic veno-occlusive disease in a renal transplant patient receiving azathioprine, treated by portacaval shunt: report of a case and review of the literature. Digestion 1984; 30: 185-90. PubMed PMID: 6389237.

(45 year old man developed ascites and abdominal pain 2 years after renal transplant while on azathioprine, biopsy showing veno-occlusive disease and ascites, responding to stopping azathioprine and portacaval shunt).

Watanabe A, Obata T, Nagashima H, Sakagami K, Orita K. Nonicteric liver damage with a gamma-glutamyl transpeptidase level of 5,609 units/l in a renal-transplant recipient receiving azathioprine. Acta Med Okayama 1984; 38: 533-9. PubMed PMID: 6151783.

Pappas SC, Holone DG, Rabin L, Hoofnagle JH, Jones EA. Hepatic veno-occlusive disease in a patient with systemic lupus erythematosus. Arthr Rheum 1984; 27: 104-8. PubMed PMID: 6691850.

(26 year old woman with lupus erythematosus developed abdominal pain and hepatomegaly [bilirubin 0.5 mg/dL, ALT 21 U/L, Alk P 185 U/L], later developing ascites; biopsies showed sinusoidal obstruction syndrome; only medications had been aspirin and hydroxychloroquine).

Zimm S, Ettinger LJ, Holcenberg JS, Kamen BA, Vietti TJ, Belasco J, Cogliano-Shutta N, et al. Phase I and clinical pharmacological study of mercaptopurine administered as a prolonged intravenous infusion. Cancer Res 1985; 45: 1869-73. PubMed PMID: 4038917.

(Among 38 children with acute leukemia treated with cycles of intravenous mercaptopurine, ALT elevations were common, but were transient, asymptomatic and resolved in 5-7 days).

Gerlag PG, Labatty S, Driessen WM, Deckers PFL, Van Hooff JP, Schroder E, Assmann KM, et al. Hepatic sinusoidal dilatation with portal hypertension during azathioprine treatment after kidney transplantation. J Hepatol 1986; 1: 339-48. PubMed PMID: 3902952.

(3 patients developed evidence of portal hypertension 16-24 months after renal transplant on azathioprine therapy without portal fibrosis, improvement on stopping, but residual changes found during follow up).

Read AE, Wiesner RH, La Brecque DR, Tifft JG, Mullen KD, Sheer RL, Petrelle M, et al. Hepatic veno-occlusive disease associated with renal transplantation and azathioprine therapy. Ann Intern Med 1986; 104: 651-6. PubMed PMID: 3008617.

(Four patients developed sinusoidal obstruction syndrome and signs of portal hypertension 0.5 to 9 years after renal transplantation while on azathioprine; one improved, 3 had progressive problems with portal hypertension and hepatic failure).

Lemarchand P, Desrumeaux B, Bercoff E, Manchon ND, Chassagne P, Deshayes P, Hémet J, Bourreille J. [Cholestasis and sinusoidal dilatation following treatment with azathioprine]. Gastroenterol Clin Biol 1986; 10: 853-4. French. PubMed PMID: 3803830.

(53 year old woman with rheumatoid arthritis developed jaundice 6 months after starting azathioprine [bilirubin 12.9 mg/dL, ALT 75 U/L, Alk P 1150 U/L], resolving within 1 month of stopping and relapsing 3 days after rechallenge, biopsy showed sinusoidal dilatation and intrahepatic cholestasis with minimal inflammation).

Kissel JT, Levy RJ, Mendell JR, Griggs RC. Azathioprine toxicity in neuromuscular disease. Neurology 1986; 36: 35-9. PubMed PMID: 3941781.

(Retrospective review of 64 patients with autoimmune neuromuscular disease treated with azathioprine for 0.5 to 16 years; dose modification for toxicity was done in 42%, most commonly for leucopenia, hepatotoxicity occurred in 9%, arising within 1-8 weeks, resolving within 1-2 months in all; recurrence on rechallenge within days).

Katzka DA, Saul SH, Jorkasky D, Sigal H, Reynolds JC, Soloway RD. Azathioprine and hepatic venoocclusive disease in renal transplant patients. Gastroenterology 1986; 90: 446-54. PubMed PMID: 3510146.

(3 men, ages 37-59 years, developed liver test abnormalities [bilirubin 1.5-3.5 mg/dL, ALT 44-86 U/L, Alk P 505-648 U/L] 12-32 months after starting azathioprine, 2 dying and one surviving with improvement after stopping azathioprine; all had nodular regenerative hyperplasia and sinusoidal obstructive changes on biopsy or autopsy).

Cooper C, Cotton DW, Minihane N, Cawley MI. Azathioprine hypersensitivity manifesting as acute focal hepatocellular necrosis. J R Soc Med 1986; 79: 171-3. PubMed PMID: 3701755.

(58 year old man with rheumatoid arthritis developed jaundice 2 weeks after starting azathioprine [bilirubin 2.3 mg/dL, ALT >300 U/L, Alk P 898 U/L], liver biopsy showing nonspecific changes and symptoms resolving within 1 week and laboratory abnormalities within 1 month of stopping).

Barrowman JA, Kutty PK, Mu RA, Huang SN. Sclerosing hepatitis and azathioprine. Dig Dis Sci 1986; 31: 221-2. PubMed PMID: 3943451.

(35 year old man treated with azathioprine for 8 years developed jaundice [bilirubin 10 mg/dL, AST 350 U/L, Alk P 287 U/L], which progressed to end-stage liver disease and death 5 months later despite stopping azathioprine; clinical course possibly representing vanishing bile duct syndrome).

Adler M, Delhaye M, Deprez C, Hardy N, Gelin M, DePauw L, Vererstraeten P, et al. Hepatic vascular disease after kidney transplantation: report of two cases and review of the literature. Nephrol Dialysis Transplant 1987; 2: 183-8. PubMed PMID: 3114679.

(Two men, ages 31 and 40 years, developed portal hypertension due to azathioprine 9 and 4 years after kidney transplant, presenting with fatigue and abdominal distension with mild jaundice and minimal elevations in Alk P and ALT, biopsy showed changes of peliosis and sinusoidal obstruction syndrome; subsequently, both had hepatic decompensation and one died).

Fonseca V, Havard CW. Portal hypertension secondary to azathioprine in myasthenia gravis. Postgrad med J 1988; 64: 950-2. PubMed PMID: 2112245.

(52 year old man with myasthenia was found to have splenomegaly 3 years after starting azathioprine [150 mg/day] [bilirubin 4.1 mg/dL, AST 40 U/L, Alk P 107 U/L, platelets 103,000/μL], biopsy showing nodular regenerative hyperplasia with improvement in liver tests [bilirubin 1.2 mg/dL] upon stopping).

Haboubi MB, Hiam H, Whitwell HL, Ackrill P. Role of endothelial cell injury in the spectrum of azathioprine-induced liver disease after renal transplant: light microscopy and ultrastructural observations. Am J Gastroenterol 1988; 83: 256-61. PubMed PMID: 3278593.

(3 cases, men, ages 26-44 developing hepatomegaly and signs of portal hypertension 1-5 years after renal transplant while on azathioprine; biopsies showed peliosis and nodular regenerative hyperplasia, 1 died of hepatic failure, 2 improved on stopping azathioprine; suggestive of endothelial cell injury from the thiopurine).

Buffet C, Cantarovitch M, Pelletier G, Fabre M, Martin E, Charpentier B, Etienne JP, et al. Three cases of nodular regenerative hyperplasia of the liver following renal transplantation. Nephrol Dial Transplant 1988; 3: 327-30. PubMed PMID: 3140108.

(Three men, ages 22, 29 and 50 years, developed nodular regenerative hyperplasia with hepato-splenomegaly 24-30 months after renal transplant while on azathioprine, two had peliosis and one sinusoidal obstruction syndrome; minimal liver test abnormalities were found in two; jaundice in the third who had a fatal outcome [initial bilirubin 5.8 mg/dL, AST 35 U/L, Alk P 80 U/L]).

Jones MC, Best PV, Catto GRD. Is nodular regenerative hyperplasia of the liver associated with azathioprine therapy after renal transplantation. Nephrol Dial Transplant 1988; 3: 330-3. PubMed PMID: 3140109.

(33 year old man developed minor elevations in liver tests starting 15 months after renal transplantation while on azathioprine [bilirubin 1.0 mg/dL, AST 42 U/L, Alk P 185 U/L], later developing hepatomegaly and ascites; biopsy showed nodular regenerative hyperplasia).

Lemley DE, Delacy LM, Seeff LB, Ishak KG, Nashel DJ. Azathioprine induced hepatic veno-occlusive disease in rheumatoid arthritis. Ann Rheum Dis 1989; 48: 342-6. PubMed PMID: 2712618.

(59 year old man with rheumatoid arthritis developed abdominal pain 3 months after starting azathioprine with bilirubin 0.2 mg/dL, with minimal elevations in ALT and Alk P; azathioprine was continued and signs of portal hypertension arose 4 months later, biopsy showing sinusoidal obstruction syndrome).

Small P, Lichter M. Probable azathioprine hepatotoxicity: a case report. Ann Allergy 1989; 62: 518-20. PubMed PMID: 2735558.

(57 year old woman with rheumatoid arthritis and polymyositis developed AST and Alk P elevations 3 weeks after starting azathioprine, resolving with stopping and recurring with rechallenge, biopsies showed minimal nonspecific changes).

Ramalho HJ, Terra EG, Cartapatti E, Barberato JB, Alves VA, Gayotto LC, Abbud-Filho M. Hepatotoxicity of azathioprine in renal transplant recipients. Transplant Proc 1989; 21 (1 Pt 2): 1716-7. PubMed PMID: 2652562.

(2 women and 2 men, ages 28-49 years, developed cholestasis 2-18 months after renal transplant while on azathioprine [bilirubin 9.3-44 mg/dL, ALT 62-842 U/L, Alk P 1-3 times ULN], improving on stopping and reappearing within weeks on restarting azathioprine).

Adamson PC, Zimm S, Ragab AH, Steinberg SM, Balis F, Kamen BA, Vietti TJ, et al. A phase II trial of continuous-infusion 6-mercaptopurine for childhood solid tumors. Cancer Chemother Pharmacol 1990; 26: 343-4. PubMed PMID: 2208575.

(Open label trial of cyclic infusions of mercaptopurine in 40 children with leukemia; reversible hepatotoxicity was dose-limiting and occurred in 50% [peak bilirubin 15.8 mg/dL, ALT 1,194 U/L], details not provided).

Tolman KG. Hepatotoxicity of antirheumatic drugs. J Rheumatol Suppl 1990; 22: 6-11. PubMed PMID: 2192059.

(Review of hepatotoxicity of drugs used in rheumatology; mentioning acute mixed hepatocellular-cholestatic injury from azathioprine).

Jeurissen ME, Boerbooms AM, van de Putte LB, Kruijsen MW. Azathioprine induced fever, chills, rash, and hepatotoxicity in rheumatoid arthritis. Ann Rheum Dis 1990; 49: 25-7. PubMed PMID: 2138007.

(Among 25 patients with rheumatoid arthritis, 3 developed fever and rash within 2 weeks of starting azathioprine; one had cholestasis [bilirubin 1.6 mg/dL, ALT 150 U/L, Alk P 810 U/L], resolving slowly after stopping and fever recurring upon rechallenge).

Singh G, Fries JF, Williams CA, Zatarain E, Spitz P, Bloch DA. Toxicity profiles of disease modifying antirheumatic drugs in rheumatoid arthritis. J Rheumatol 1991; 18: 188-94. PubMed PMID: 1673721.

(Analysis of side effects of 7 agents from the ARAMIS database including 2,479 patients [153 on azathioprine, mercaptopurine not mentioned] with rheumatoid arthritis reported 5 instances of liver abnormalities, but no jaundice during ~228 patient years of exposure to azathioprine).

Horsmans Y, Rahier J, Geubel AP. Reversible cholestasis with bile duct injury following azathioprine therapy. A case report. Liver 1991; 11: 89-93. PubMed PMID: 2051906.

(67 year old man with polymyositis developed jaundice 3 months after starting azathioprine [bilirubin ~5.0 mg/dL, ALT ~120 U/L, Alk P 550 U/L], liver biopsy showing intrahepatic cholestasis and bile duct injury, resolving within 2 months of stopping).

Sterneck M, Wiesner R, Ascher N, Roberts J, Ferrell L, Ludwig J, Lake J. Azathioprine hepatotoxicity after liver transplantation. Hepatology 1991; 14: 806-10. PubMed PMID: 1937385.

(Two patients [58 year old woman and 41 year old man] developed jaundice 2 and 8 weeks after liver transplantation [bilirubin 33.8 and 7.1 mg/dL, AST 456 and 2965 U/L, Alk P not given and 349 U/L], liver biopsies showing centrilobular congestion, sinusoidal dilation and hemorrhagic necrosis suggesting vascular outflow obstruction, both improved on stopping azathioprine, one worsened on rechallenge).

Mion F, Napoleon B, Berger F, Chevallier M, Bonvoisin S, Descos L. Azathioprine induced liver disease: nodular regenerative hyperplasia of the liver and perivenous fibrosis in a patient treated for multiple sclerosis. Gut 1991; 32: 715-7. PubMed PMID: 2060883.

(37 year old man with multiple sclerosis developed variceal hemorrhage 7 years after starting azathioprine [100-150 mg/day] with biopsy showing nodular regeneration and perivascular fibrosis without inflammation).

Gross R, Scapa E. Hepatotoxicity of 6-mercaptopurine in Crohn's disease. Am J Gastroenterol 1992; 87: 1885-6. PubMed PMID: 1449165.

(27 year old man developed fatigue and jaundice ~3 months after starting mercaptopurine [bilirubin 6.2 mg/dL, ALT 247 U/L, Alk P 120 U/L], improving rapidly on stopping).

Wagoner LE, Olsen SL, Bristow MR, O'Connell JB, Taylor DO, Lappe DL, Renlund DG. Cyclophosphamide as an alternative to azathioprine in cardiac transplant recipients with suspected azathioprine-induced hepatotoxicity. Transplantation 1993; 56: 1415-8. PubMed PMID: 8279012.

(29 of 320 cardiac transplant patients developed elevated liver enzymes while on azathioprine which improved when they were switched to cyclophosphamide 30 to 2014 days after transplant [mean bilirubin falling from 4.3 to 1.8 mg/dL, ALT 84 to 44 U/L, Alk P 184 to 149 U/L]; no patient developed rejection and all except one tolerated cyclophosphamide long term).

Gane E, Portmann B, Saxena R, Wong P, Ramage J, Williams R. Nodular regenerative hyperplasia of the liver graft after liver transplantation. Hepatology. 1994; 20: 88-94. PubMed PMID: 8020909.

(Nine cases of biopsy proven nodular regenerative hyperplasia in liver transplant recipients arising after 0.5 to 12 years; 6 presenting with ascites or varices and 3 without symptoms [bilirubin 0.5-5.1 mg/dL, AST 36-192 U/L, Alk P 159-1182 U/L], 5 improving on stopping azathioprine and 4 developing progressive hepatic failure; several had earlier biopsies showing venous outflow obstruction).

Dhillon AP, Burroughs AK, Hudson M, Shah N, Rolles K, Scheuer PJ. Hepatic venular stenosis after orthotopic liver transplantation. Hepatology 1994; 19: 106-11. PubMed PMID: 8276346.

(Retrospective review of 49 liver biopsies taken after liver transplantation identified 7 patients with venous outflow obstruction usually within 30 days of transplant, associated with endothelitis, only 5 on azathioprine suggesting that changes were due to rejection rather than drug).

Stetter M, Schmidl M, Krapf R. Azathioprine hypersensitivity mimicking Goodpasture's syndrome. Am J Kidney Dis 1994; 23: 874-7. PubMed Citation

(Patient with renal transplant developed fever, arthralgias, diarrhea and pulmonary infiltrates within 7 days of starting azathioprine on three occasions, but later tolerated mercaptopurine suggesting hypersensitivity to nitroimidazole component of azathioprine).

Gross R. Hepatotoxicity of 6-mercaptopurine and azathioprine. Mayo Clin Proc 1994; 69: 498. PubMed PMID: 8170206.

(Letter in response to a review article by Stark and Tremaine on use of thiopurines to treat Crohn disease mentioning the problem of hepatotoxicity of mercaptopurine and importance of monitoring for liver test abnormalities).

Laidlaw ST, Reilly JT, Suvarna SK. Fatal hepatotoxicity associated with 6-mercaptopurine therapy. Postgrad Med J 1995; 71: 639. PubMed PMID: 8545299.

(68 year old man developed jaundice [bilirubin 9.1 mg/dL, ALT 149 U/L, Alk P 143 U/L] after 5th cycle of chemotherapy for leukemia including mercaptopurine, with progressive hepatic failure and death).

Kowdley KV, Keeffe EB. Hepatotoxicity of transplant immunosuppressive agents. Gastroenterol Clin North Am 1995; 24: 991-1001. PubMed PMID: 8749908.

(Review of hepatotoxicity of agents used in solid organ transplantation including azathioprine, [but not specifically mercaptopurine] which causes a broad range of hepatic injuries including transient ALT elevations, cholestasis, sinusoidal dilatation, sinusoidal obstruction syndrome, peliosis and nodular regenerative hyperplasia with portal hypertension).

Knowles SR, Gupta AK, Shear NH, Sauder D. Azathioprine hypersensitivity-like reactions - a case report and a review of the literature. Clin Exp Dermatol 1995; 20: 353-6. PubMed PMID: 8549000.

(17 year old girl with vasculitis developed fever and leucopenia 15 days after starting azathioprine with recurrence of fever within 24 hours of restarting; liver tests were normal).

Romagnuolo J, Sadowski DC, Lalor E, Jewell L, Thomson AB. Cholestatic hepatocellular injury with azathioprine: a case report and review of the mechanisms of hepatotoxicity. Can J Gastroenterol 1998; 12: 479-83. PubMed PMID: 9812167.

(63 year old man with Crohn disease developed jaundice 9 weeks after starting azathioprine [bilirubin 8.0 mg/dL, AST 65 U/L, Alk P 896 U/L], liver biopsy showed intrahepatic cholestasis, resolved with stopping).

Griger DR, Higgs JB, Roane DW. Azathioprine hepatotoxicity is uncommon in patients with rheumatic diseases. J Clin Rheumatol 1999; 5: 60-4. PubMed PMID: 19078358.

(Retrospective review of 56 patients with rheumatic diseases treated with azathioprine, 41% had at least transient elevation in Alk P [146-302 U/L] or AST [39-234 U/L], but levels fell to normal despite continuation in 80% of patients and none were "clinically significant").

Mahadevan U, Tremaine WJ, Johnson T, Pike MG, Mays DC, Lipsky JJ, Sandborn WJ. Intravenous azathioprine in severe ulcerative colitis: a pilot study. Am J Gastroenterol 2000; 95: 3463-8. PubMed PMID: 11151878.

(9 hospitalized patients with refractory ulcerative colitis received 36 hour infusions of azathioprine; 5 had a clinical response and only one had hepatotoxicity [bilirubin not given, ALT 695 U/L, Alk P 474 U/L], resolving within a week of stopping).

Mok MY, Ng WL, Yuen MF, Wong RW, Lau CS. Safety of disease modifying anti-rheumatic agents in rheumatoid arthritis patients with chronic viral hepatitis. Clin Exp Rheumatol 2000; 18: 363-8. PubMed PMID: 10895374.

(Retrospective review of 29 Chinese patients with rheumatoid arthritis and chronic hepatitis B [n=23] or C [n=6] receiving disease modifying agents; one patient on azathioprine for 2.7 years developed reactivation of hepatitis B).

Evans WE, Hon YY, Bomgaars L, Coutre S, Holdsworth M, Janco R, Kalwinsky D, et al. Preponderance of thiopurine S-methyltransferase deficiency and heterozygosity among patients intolerant to mercaptopurine or azathioprine. J Clin Oncol 2001; 19: 2293-301. PubMed PMID: 11304783.

(Thiopurine S methyltransferase [TPMT] activity was low or deficient in 71% of patients with azathioprine hematologic toxicity, but among 6 patients with hepatoxicity none were deficient, 3 had intermediate and 3 normal levels of TPMT activity).

Schwab M, Schaeffeler E, Marx C, Fischer C, Lang T, Behrens C, Gregor M, et al. Azathioprine therapy and adverse drug reactions in patients with inflammatory bowel disease: impact of thiopurine S-methyltransferase polymorphism. Pharmacogenetics 2002; 12: 429-36. PubMed PMID: 12172211.

(Among 93 adults treated with azathioprine, thiopurine S-methyl transferase [TPMT] activities were normal in those with gastrointestinal [n=9] and liver toxicities [n=3], but were low in those with hematological toxicities).

Sinico RA, Sabadini E, Borlandelli S, Cosci P, Di Toma L, Imbasciati E. Azathioprine hypersensitivity: report of two cases and review of the literature. J Nephrol 2003; 16: 272-6. PubMed PMID: 12768076.

(Two patients with systemic vasculitis developed fever, rash and malaise 10 and 20 days after starting azathioprine with prompt improvement on stopping and rapid relapse on restarting; no mention of liver test results as being abnormal).

Rulyak SJ, Saunders MD, Lee SD. Hepatotoxicity associated with 6-thioguanine therapy for Crohn's disease. J Clin Gastroenterol 2003; 36: 234-7. PubMed PMID: 12590235.

(27 year old with Crohn disease developed asymptomatic rise in ALT to 191 U/L 2 weeks after starting thioguanine, ALT then rising to 803 U/L at 4 weeks with normal Alk P and minimal increase in bilirubin [1.5 mg/dL], resolving within 1 month of stopping).

Stoneham S, Lennard L, Coen P, Lilleyman J, Saha V. Veno-occlusive disease in patients receiving thiopurines during maintenance therapy for childhood acute lymphoblastic leukaemia. Br J Haematol 2003; 123: 100-2. PubMed PMID: 14510948.

(Retrospective analysis of sinusoidal obstruction syndrome (SOS) among 99 children who received thioguanine or mercaptopurine for acute leukemia; 12 developed SOS all of whom received thioguanine and were male; no correlation with dose or thiopurine methyltransferase levels).

Piel B, Vaidya S, Lancaster D, Taj M, Pritchard-Jones K. Chronic hepatotoxicity following 6-thioguanine therapy for childhood acute lymphoblastic leukaemia. Br J Haematol 2004; 125: 410-1; author reply 412. PubMed PMID: 15086428.

(Letter in response to Stoneham [2003] reporting SOS in 7 of 59 children receiving thioguanine [12%], with chronic liver injury in 7 [suspected to be nodular regenerative hyperplasia]; patients tolerated being switched to mercaptopurine).

de Abajo FJ, Montero D, Madurga M, Garcia Rodriguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004; 58: 71-80. PubMed PMID: 15206996.

(Analysis of UK General Practice Research Database found 128 cases of suspected drug induced liver injury [2.4 per 100,000 person-years], 2 anicteric cases were attributed to azathioprine, yielding an odds ratio of 10.5: mercaptopurine not discussed).

Kontorinis N, Agarwal K, Gondolesi G, Fiel MI, O'Rourke M, Schiano TD. Diagnosis of 6 mercaptopurine hepatotoxicity post liver transplantation utilizing metabolite assays. Am J Transplant 2004; 4: 1539-42. PubMed PMID: 15307844.

(Two women, ages 46 and 53 years, with liver transplants developed jaundice 5 and 3 months after starting mercaptopurine [bilirubin 11.7 and 8.0 mg/dL, ALT 108 and 392 U/L, Alk P 464 and 395 U/L], resolving within 1-2 months of stopping; neither had TPMT deficiency).

Nygaard U, Toft N, Schmiegelow K. Methylated metabolites of 6-mercaptopurine are associated with hepatotoxicity. Clin Pharmacol Ther 2004; 75: 274-81. PubMed PMID: 15060506.

(High frequency of ALT elevations occurred in children with acute leukemia treated with mercaptopurine, usually resolving with stopping or lowering the dose; ALT elevations were associated with higher doses and higher levels of methylated metabolites of mercaptopurine).

Reuther LO, Vainer B, Sonne J, Larsen NE. Thiopurine methyltransferase(TPMT) genotype distribution in azathioprine-tolerant and -intolerant patients with various disorders. The impact of TPMT genotyping in predicting toxicity. Eur J Clin Pharmacol 2004; 59: 797-801. PubMed PMID: 14634700.

(Weak correlation found between azathioprine intolerance and TPMT mutations).

de Boer NK, Mulder CJ, van Bodegraven AA. Myelotoxicity and hepatotoxicity during azathioprine therapy. Neth J Med 2005; 63: 444-6. PubMed PMID: 16397313.

(38 year old man with Crohn disease was found to have abnormal liver tests and portal hypertension 3 years after starting azathioprine [bilirubin 2.1 mg/dL, ALT 53 U/L, Alk P 141 U/L], improving upon stopping).

de Boer NK, De Graaf P, Wilhelm AJ, Mulder CJ, van Bodegraven AA. On the limitation of 6-tioguaninenucleotide monitoring during thioguanine treatment. Aliment Pharmacol Ther 2005; 22: 447-51. PubMed PMID: 16128683.

(Analysis of drug levels in 25 patients switched from azathioprine to thioguanine found no correlation with myelotoxicity; hepatotoxicity not mentioned).

Bastida G, Nos P, Aguas M, Beltrán B, Rubín A, Dasí F, Ponce J. Incidence, risk factors and clinical course of thiopurine-induced liver injury in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2005; 22: 775-82. PubMed PMID: 16225485.

(Prospective analysis of 161 patients treated with azathioprine for inflammatory bowel disease; 16 [10%] developed elevations in liver tests at least twice normal after 2 days to 3 years [bilirubin normal, ALT 85-240 U/L, Alk P 48-526 U/L], resolving in all 16 patients including 11 who continued therapy).

Heckmann JM, Lambson EM, Little F, Owen EP. Thiopurine methyltransferase(TPMT) heterozygosity and enzyme activity as predictive tests for the development of azathioprine-related adverse events. J Neurol Sci 2005; 231: 71-80. PubMed PMID: 15792824.

(7 of 129 neurological patients on azathioprine developed hepatotoxicity; testing for TPMT activity or mutations had low predictive value).

Sparrow MP, Hande SA, Friedman S, Lim WC, Reddy SI, Cao D, Hanauer SB. Allopurinol safely and effectively optimizes thioguanine metabolites in inflammatory bowel disease patients not responding to azathioprine and mercaptopurine. Aliment Pharmacol Ther 2005; 22: 441-6. PubMed PMID: 16128682.

(Adding allopurinol to azathioprine therapy led to higher thioguanine and methyl-mercaptopurine levels, thus allowing for reduction in azathioprine dose, and theoretically better efficacy, lower toxicity).

Daniel F, Cadranel JF, Seksik P, Cazier A, Duong Van Huyen JP, Ziol M, Coutarel P, et al. Azathioprine induced nodular regenerative hyperplasia in IBD patients. Gastroenterol Clin Biol 2005; 29: 600-34. PubMed PMID: 15980758.

(Four men, ages 26-46 years, with inflammatory bowel disease developed nodular regenerative hyperplasia 6-12 months after starting azathioprine, presenting with liver test abnormalities and decrease in platelet counts, improving with stopping including slight increase in platelet count: Azathioprine Case 3).

Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish Registry over a 10-year period. Gastroenterology 2005; 129: 512-21. PubMed PMID: 16083708.

(Among 446 cases of drug induced liver injury collected in Spain between 1984-2004, azathioprine accounted for 6 cases, ranking 14th; injury usually cholestatic, no fatalities).

De Bruyne R, Portmann B, Samyn M, Bansal S, Knisely A, Mieli-Vergani G, Dhawan A. Chronic liver disease related to 6-thoguanine in children with acute lymphoblastic leukaemia. J Hepatol 2006; 44: 407-10. PubMed PMID: 16226335.

(Evaluation of 6 children with acute leukemia who developed sinusoidal obstructive syndrome during thioguanine therapy; disease progressed despite switching to mercaptopurine biopsies showing nodular regeneration; platelet counts 74-181,000/μL).

Derijks LJ, Gilissen LP, de Boer NK, Mulder CJ. 6-Thioguanine-related hepatotoxicity in patients with inflammatory bowel disease: dose or level dependent? J Hepatol 2006; 44: 821-2. PubMed PMID: 16487623.

(Letter in response to De Bruyne [2006] suggesting that use of lower doses and monitoring for metabolites may help avoid hepatotoxicity).

Seiderer J, Zech CJ, Diebold J, Schoenberg SO, Brand S, Tillack C, Göke B, Ochsenkühn T. Nodular regenerative hyperplasia: a reversible entity associated with azathioprine therapy. Eur J Gastroenterol Hepatol 2006; 18: 553-5. PubMed PMID: 16607155.

(54 year old developed jaundice 5 months after starting azathioprine for Crohn disease [bilirubin 7.5 mg/dL, but normal serum enzymes]; biopsy showing nodular regenerative hyperplasia, improvement on stopping).

Heneghan MA, Allan ML, Bornstein JD, Muir AJ, Tendler DA. Utility of thiopurine methyltransferase genotyping and phenotyping, and measurement of azathioprine metabolites in the management of patients with autoimmune hepatitis. J Hepatol 2006; 45: 584-91. PubMed PMID: 16876902.

(Among 86 patients with autoimmune hepatitis treated with azathioprine, TPMT mutations did not predict toxicities; one patient developed hepatotoxicity with rise in ALT to 3 times ULN that improved with dose reduction).

Teml A, Schwab M, Hommes DW, Almer S, Lukas M, Feichtenschlager T, Florin T, et al. A systematic survey evaluating 6-thioguanine-related hepatotoxicity in patients with inflammatory bowel disease. Wien Klin Wochenschr 2007; 119: 519-26. PubMed PMID: 17943403.

(Among 296 patients with inflammatory bowel disease treated with thioguanine for 1 month to 4 years at 15 medical centers, liver enzyme elevations occurred in 43 [15%] and nodular regenerative hyperplasia was found in 16 of 60 patients undergoing liver biopsy; older age was the only risk factor identified).

Shaye OA, Yadegari M, Abreu MT, Poordad F, Simon K, Martin P, Papadakis KA, et al. Hepatotoxicity of 6-mercaptopurine (6-MP) and azathioprine (AZA) in adult IBD patients. Am J Gastroenterol 2007; 102: 2488-94. PubMed PMID: 17764490.

(Among 173 adult patients with inflammatory bowel disease treated with azathioprine or mercaptopurine, 8 developed ALT elevations greater than twice ULN [bilirubin 0.3-2.4 mg/dL, ALT 58-434 U/L, Alk P 54-130 U/L], resolving with stopping or lowering dose; toxicity had weak association with higher methyl metabolites in serum).

Gisbert JP, Luna M, González-Lama Y, Pousa ID, Velasco M, Moreno-Otero R, Maté J. Liver injury in inflammatory bowel disease: long-term follow-up study of 786 patients. Inflamm Bowel Dis 2007; 13: 1106-14. PubMed PMID: 17455203.

(Long term follow up of 138 patients treated with azathioprine or mercaptopurine; incidence of any abnormal liver test was 7.1% per year, values above twice ULN occurred in only 2.6% and often resolved spontaneously; 5 of 49 required discontinuation).

Gisbert JP, González-Lama Y, Maté J. Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. Am J Gastroenterol 2007; 102: 1518-27. PubMed PMID: 17391318.

(Systematic review of the literature on hepatotoxicity of thiopurines in patients with inflammatory bowel disease; rates of hepatotoxicity have ranged from 0% to 13% [averaging 1.4% per year], depending upon definition of injury and degree of monitoring; these agents can also cause syndromes of acute hypersensitivity reactions, acute cholestasis and chronic injury of endothelial cell injury and nodular regenerative hyperplasia).

Gilissen LP, Derijks LJ, Driessen A, Bos LP, Hooymans PM, Stockbrügger RW, Engels LG. Toxicity of 6-thioguanine: no hepatotoxicity in a series of IBD patients treated with long-term, low dose 6-thioguanine. Some evidence for dose or metabolite level dependent effects? Dig Liver Dis 2007; 39: 156-9. PubMed PMID: 17188950.

(Among 13 patients with inflammatory bowel disease treated with thioguanine for at least 2 years, none had evidence of nodular regeneration by either liver biopsy [n=11] or imaging studies [n=11]).

de Boer NK, van Bodegraven AA, Jharap B, de Graaf P, Mulder CJ. Drug Insight: pharmacology and toxicity of thiopurine therapy in patients with IBD. Nat Clin Pract Gastroenterol Hepatol 2007; 4: 686-94. PubMed PMID: 18043678.

(Review of pharmacokinetics and metabolism of thiopurines and management of intolerance using genetic tests for TPMT and measurements of metabolites).

Contreras AM, Monteón FJ, Flores MR, Mendoza-Sánchez F, Ruiz I. Drug-related hepatotoxicity in a renal transplant recipient with long-term survival and hepatitis C. Ann Hepatol 2007; 6: 70-3. PubMed PMID: 17297434.

(53 year old man with renal transplant developed ALT elevations during long term azathioprine therapy, but was subsequently found to have acquired chronic hepatitis C as a possible reason for the liver injury).

Gardiner SJ, Gearry RB, Burt MJ, Ding SL, Barclay ML. Severe hepatotoxicity with high 6-methylmercaptopurine nucleotide concentrations after thiopurine dose escalation due to low 6-thioguanine nucleotides. Eur J Gastroenterol Hepatol 2008; 20: 1238-42. PubMed PMID: 18989148.

(3 patients with autoimmune disorders developed hepatotoxicity 1-4 months after the dose of mercaptopurine or azathioprine was increased [bilirubin 6.9, 37 and 21.2 mg/dL, ALT 195, 200 and 79 U/L, Alk P 123, 109 and 194 U/L]; two progressed to hepatic failure and died; methyl-metabolites of mercaptopurine were elevated in all 3).

Leong RW, Gearry RB, Sparrow MP. Thiopurine hepatotoxicity in inflammatory bowel disease: the role for adding allopurinol. Expert Opin Drug Saf 2008; 7: 607-16. PubMed PMID: 18759713.

(Allopurinol can increase levels of mercaptopurine and allow for dose reductions as well as shift its metabolism towards the active [6-thioguanine nucleotides] and away from toxic metabolites [methyl-mercaptopurine ribonucleotide], but requires monitoring).

Lees CW, Maan AK, Hansoti B, Satsangi J, Arnott DR. Tolerability and safety of mercaptopurine in azathioprine-intolerant patients with inflammatory bowel disease. Aliment Pharmacol Ther 2008; 27: 220-7. PubMed PMID: 17988235.

(Retrospective analysis of 61 patients with inflammatory bowel disease who were intolerant to azathioprine; 36 [59%] were able to tolerate mercaptopurine, including 3 of 9 with hepatotoxicity).

Ehmsen L, Marko C, Breidert M. [Portal vein hypertension during azathioprine therapy in patients with Crohn's disease - a frequent phenomenon?]. Dtsch Med Wochenschr 2008; 133: 950-3. German. PubMed PMID: 18431703.

(45 year old man with Crohn disease on azathioprine for 4 years developed variceal hemorrhage [bilirubin 4.1 mg/dL, normal ALT, platelets 84,000/.L] and was found to have nodular regenerative hyperplasia on liver biopsy, and subsequently improved on stopping azathioprine).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, 3 were attributed to mercaptopurine, but none to azathioprine or thioguanine).

Rahhal RM, Bishop WP. Initial clinical experience with allopurinol-thiopurine combination therapy in pediatric inflammatory bowel disease. Inflamm Bowel Dis 2008; 14: 1678-82. PubMed PMID: 18521913.

(Description of 13 children with inflammatory bowel disease who were treated with allopurinol and had dose reduction of azathioprine [by ~60%] with overall increase in serum 6-thioguanine levels and decrease in methyl-metabolites; ALT elevations improved in all).

Ansari A, Elliott T, Baburajan B, Mayhead P, O'Donohue J, Chocair P, Sanderson J, et al. Long-term outcome of using allopurinol co-therapy as a strategy for overcoming thiopurine hepatotoxicity in treating inflammatory bowel disease. Aliment Pharmacol Ther 2008; 28: 734-41. PubMed PMID: 19145729.

(11 patients with inflammatory bowel disease who developed hepatotoxicity within 1-8 weeks of starting azathioprine [n=10] or mercaptopurine [n=1] were treated with allopurinol and low doses of the thiopurine; 9 tolerated long term therapy without recurrence).

Xin HW, Xiong H, Wu XC, Li Q, Xiong L, Yu AR. Relationships between thiopurine S-methyltransferase polymorphism and azathioprine-related adverse drug reactions in Chinese renal transplant recipients. Eur J Clin Pharmacol 2009; 65: 249-55. PubMed PMID: 19048245.

(Association found between TPMP activity and hemato- but not hepato-toxicity; only 2 of 16 patients with hepatotoxicity were heterozygous for TPMT mutations, none were homozygous).

Hindorf U, Johansson M, Eriksson A, Kvifors E, Almer SH. Mercaptopurine treatment should be considered in azathioprine intolerant patients with inflammatory bowel disease. Aliment Pharmacol Ther 2009; 29: 654-61. PubMed PMID: 19183142.

(Analysis of usefulness of measuring thiopurine metabolites in management of 238 patients with autoimmune hepatitis on azathioprine, finding it useful only in managing patients with a poor response; patients with hepatotoxicity were not able to tolerate switch to mercaptopurine).

Murakami A, Tanaka Y, Ueda M, Nagano Y, Kunisaki R, Morimoto M, Enaka M, et al. Hepatocellular carcinoma occurring in a young Crohn's disease patient. Pathol Int 2009; 59: 492-6. PubMed PMID: 19563414.

(25 year old man with 12 year history of Crohn disease presented with hepatocellular carcinoma approximately one year after starting infliximab; no other risk factors identified; review of literature identified 7 cases of liver cancer in patients with Crohn disease, mean age 20 years, all had received azathioprine and two infliximab).

Moran G, Dillon J, Green J. Crohn's disease, hepatosplenic T-cell lymphoma and no biological therapy: are we barking up the wrong tree? Inflamm Bowel Dis 2009; 15 (9): 1281-2. PubMed PMID: 19067412.

(Although fewer than 200 cases of hepatospenic T cell lymphoma [HSTCL] have been described in the literature, 23 have occurred in patients with inflammatory bowel disease, all of whom were on thiopurines and 16 also on anti-tumor necrosis factor antagonists [anti-TNF]; the authors describe a 23 year old man with ulcerative colitis treated with azathioprine for 7 years without anti-TNF who developed HSTCL).

Beigel F, Jürgens M, Tillack C, Subklewe M, Mayr D, Göke B, Brand S, et al. Hepatosplenic T-cell lymphoma in a patient with Crohn's disease. Nat Rev Gastroenterol Hepatol 2009; 6: 433-6. PubMed PMID: 19575026.

(58 year old man with 35 year history of Crohn disease on azathioprine for 5 years developed HSTCL).

Murakami A, Tanaka Y, Ueda M, Nagano Y, Kunisaki R, Morimoto M, Enaka M, et al. Hepatocellular carcinoma occurring in a young Crohn's disease patient. Pathol Int 2009; 59: 492-6. PubMed PMID: 19563414.

(25 year old Japanese man with 12 year history of Crohn diseaes on azathioprine and infliximab presented with abdominal pain and 8 cm HCC without cirrhosis in the non-tumorous liver).

Miura H, Kawaguchi T, Takazoe M, Kitamura S, Yamada H. Hepatocellular carcinoma and Crohn's disease: a case report and review. Intern Med 2009; 48: 815-9. PubMed PMID: 19443977.

(52 year old Japanese man with 36 year history of Crohn disease, but never treated with thiopurines presented with hepatic mass, found to be HCC with chronic hepatitis in non-tumorous liver tissue).

Ishida M, Naka S, Shiomi H, Tsujikawa T, Andoh A, Nakahara T, Saito Y, et al. Hepatocellular carcinoma occurring in a Crohn's disease patient. World J Gastroenterol 2010; 16: 3215-8. PubMed PMID: 20593510.

(37 year old Japanese man with 7 year history of Crohn disease developed 3 to 4 cm HCC, with focal hepatic glycogenosis without cirrhosis in the non-tumorous liver and with successful resection).

Ochenrider MG, Patterson DJ, Aboulafia DM. Hepatosplenic T-cell lymphoma in a young man with Crohn's disease: case report and literature review. Clin Lymphoma Myeloma Leuk 2010; 10: 144-8. PubMed PMID: 20371449.

(18 year old man with 5 year history of Crohn disease treated with mercaptopurine developed HSTCL [bilirubin and ALT levels normal]).

Thai A, Prindiville T. Hepatosplenic T-cell lymphoma and inflammatory bowel disease. J Crohns Colitis 2010; 4: 511-22. PubMed PMID: 21122554.

(Review of the association of HSTCL and inflammatory bowel disease).

Bermejo F, López-Sanromán A, Algaba A, Van-Domselaar M, Gisbert JP, García-Garzón S, Garrido E, et al. Mercaptopurine rescue after azathioprine-induced liver injury in inflammatory bowel disease. Aliment Pharmacol Ther 2010; 31: 120-4. PubMed PMID: 19709096.

(Retrospective analysis of 31 patients with inflammatory bowel disease who were switched from azathioprine to mercaptopurine because of liver toxicity; in 87% mercaptopurine was tolerated without evidence of further toxicity).

Leung Y, Sparrow MP, Schwartz M, Hanauer SB. Long term efficacy and safety of allopurinol and azathioprine or 6-mercaptopurine in patients with inflammatory bowel disease. J Crohns Colitis 2009; 3: 162-7. PubMed PMID: 21172265.

(Among 25 patients with inflammatory bowel disease switched from thiopurines to thioguanine and allopurinol for up to two years, none developed abnormal liver tests or thrombocytopenia).

Takatsu N, Matsui T, Murakami Y, Ishihara H, Hisabe T, Nagahama T, Maki S, et al. Adverse reactions to azathioprine cannot be predicted by thiopurine S-methyltransferase genotype in Japanese patients with inflammatory bowel disease. J Gastroenterol Hepatol 2009; 24: 1258-64. PubMed PMID: 19682195.

(TPMT deficiency variants were rare [~2%] in Japanese subjects and were not increased among those with azathioprine intolerance due to toxicity; 2 cases had hepatotoxicity).

Germani G, Pleguezuelo M, Villamil F, Vaghjiani S, Tsochatzis E, Andreana L, Burroughs AK. Azathioprine in liver transplantation: a reevaluation of its use and a comparison with mycophenolate mofetil. Am J Transplant. 2009; 9: 1725-31. PubMed PMID: 19538488.

(Review of literature suggests that there is no evidence for added benefit of mycophenolate over azathioprine for prevention of rejection or graft survival after liver transplantation; no discussion of hepatotoxicity).

Hunt CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: a systematic review. Hepatology 2010; 52: 2216-22. PubMed PMID: 21105110.

(Systematic review of literature on drug rechallenge after acute injury; positive rechallenge after azathioprine hepatotoxicity is common and can be severe).

Andrejic J, Rojas-Balcazar J, Dennis M, Berkelhammer C. Azathioprine-induced hypersensitivity hepatitis: tolerance to 6-mercaptopurine. Inflamm Bowel Dis. 2010; 16: 1828-9. PubMed PMID: 20196148.

(50 year old man with ulcerative colitis developed jaundice 4 weeks after starting azathioprine [bilirubin 4.6 mg/dL, ALT 1077 U/L, Alk P 361 U/L], resolving upon stopping and not recurring when treated with mercaptopurine [for up to 6 years]).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to azathioprine or mercaptopurine).

Ishida M, Naka S, Shiomi H, Tsujikawa T, Andoh A, Nakahara T, Saito Y, et al. Hepatocellular carcinoma occurring in a Crohn's disease patient. World J Gastroenterol 2010; 16: 3215-8. PubMed PMID: 20593510.

(37 year old Japanese man with Crohn disease treated with azathioprine for 8 years developed liver cancer without cirrhosis, but with glycogenosis present; review of 10 reported cases, all without cirrhosis).

Bryant DL, Miles CJ, Gearry RB. Nodular regenerative hyperplasia of the liver secondary to azathioprine in a patient with inflammatory bowel disease. N Z Med J 2010; 123: 74-6. PubMed PMID: 20581898.

(54 year old man developed ascites and splenomegaly 18 months after starting azathioprine for Crohn's disease, biopsy showing nodular regenerative hyperplasia, improving upon stopping).

Okan G, Vural P, Peker O, Colakoglu E, Saruc M. Azathioprine-induced liver injury in a patient with multiple autoimmune syndrome. J Dermatolog Treat 2010; 21: 357-60. PubMed PMID: 20443662.

(39 year old man with autoimmune disease developed abnormal liver tests 3 weeks after starting azathioprine [bilirubin normal, GGT 2768 U/L, Alk P 306 U/L], resolving within 2 months of stopping).

López-Martín C, de la Fuente-Fernández E, Corbatón P, Sánchez MC, Gisbert JP. [Nodular regenerative hyperplasia: azathioprine-induced hepatotoxicity in a patient with Crohn's disease]. Gastroenterol Hepatol 2011; 34: 16-9. Spanish. PubMed PMID: 21168244.

(53 year old man developed abnormal liver tests after 5 years of azathioprine therapy [7 months after dose increase] for Crohn disease [bilirubin 2.2 mg/dL, ALT 61 U/L, Alk P 284 U/L], with esophageal varices and biopsy showing nodular regenerative hyperplasia; slow improvement upon stopping).

Blogowski W, Marlicz W, Smereczynski A, Lawniczak M, Lewosiuk A, Starzynska T. Nodular regenerative liver hyperplasia as a complication of azathioprine-containing immunosuppressive treatment for Crohn's disease. Immunopharmacol Immunotoxicol 2011; 33: 398-402. PubMed PMID: 20726808.

(40 year old woman with Crohn disease developed nodular regenerative hyperplasia [splenomegaly and varices] 3 years after starting azathioprine).

van Asseldonk DP, Jharap B, Kuik DJ, de Boer NK, Westerveld BD, Russel MG, Kubben FJ, et al. Prolonged thioguanine therapy is well tolerated and safe in the treatment of ulcerative colitis. Dig Liver Dis 2011; 43: 110-5. PubMed PMID: 20739231.

(Among 46 patients switched from other thiopurines to thioguanine and treated for an average of two years, none developed hepatotoxicity and liver biopsies done in 12 showed no evidence of nodular regeneration).

Seksik P, Mary JY, Beaugerie L, Lémann M, Colombel JF, Vernier-Massouille G, Cosnes J. Incidence of nodular regenerative hyperplasia in inflammatory bowel disease patients treated with azathioprine. Inflamm Bowel Dis 2011; 17: 565-72. PubMed PMID: 20848502.

(Among 1888 patients with inflammatory bowel disease treated with azathioprine for median of 2.5 years, 15 developed nodular regenerative hyperplasia, 0.6% at 5 and 1.3% at 10 years; predictive factors were male gender and history of small bowel resection).

Aithal GP. Hepatotoxicity related to antirheumatic drugs. Nat Rev Rheumatol 2011; 7: 139-50. PubMed PMID: 21263458.

(Review of the hepatotoxicity of antirheumatic drugs including azathioprine; acute cholestatic injury occurs in 1:1000 treated subjects, mechanism may be immunologic, metabolic, and/or genetic).

Adam de Beaumais T, Fakhoury M, Medard Y, Azougagh S, Zhang D, Yakouben K, Jacqz-Aigrain E. Determinants of mercaptopurine toxicity in paediatric acute lymphoblastic leukemia maintenance therapy. Br J Clin Pharmacol 2011;71: 575-84. PubMed PMID: 21395650.

(66 children with acute leukemia treated with mercaptopurine were tested for thiopurine methyltransferase [TPMT] and inosine pyrophosphatase (ITPA) polymorphisms and for serum levels of mercaptopurine and metabolites; those with higher levels of methyl metabolites [which varied by ITPA genotype] were more likely to have hepatotoxicity, present in 84% of participants).

Calabrese E, Hanauer SB. Assessment of non-cirrhotic portal hypertension associated with thiopurine therapy in inflammatory bowel disease. J Crohns Colitis 2011; 5: 48-53. PubMed PMID: 21272804.

(Review of thiopurine toxicity and its management, highlighting a case of nodular regenerative hyperplasia in a patient with Crohn colitis treated with mercaptopurine).

Tuyama AC, Krakauer M, Alzaabi M, Fiel MI, Legnani P, Schiano TD. Mercaptopurine-induced hepatoportal sclerosis in a patient with Crohn's disease. J Crohns Colitis 2013; 7 (7): 590-3. PubMed PMID: 22841133.

(23 year old man with Crohn disease treated with mercaptopurine for 6 years developed thrombocytopenia, splenomegaly and abnormal liver tests [bilirubin 0.5 mg/dL, ALT 62 U/L, Alk P 164 U/L, platelets 141,000/μL], with ascites and esophageal varices, liver biopsy showing "hepatoportal sclerosis" without cirrhosis).

Masia R, Pratt DS, Misdraji J. A histopathologic pattern of centrilobular hepatocyte injury suggests 6-mercaptopurine-induced hepatotoxicity in patients with inflammatory bowel disease. Arch Pathol Lab Med 2012; 136: 618-22. PubMed PMID: 22646267.

(Histological review of 3 cases of mercaptopurine hepatotoxicity [aminotransferase elevations only] showed minimal lobular inflammation and fibrosis, and prominent centrilobular injury, steatosis and ceroid laden macrophages).

Laish I, Pomeranz I, Kitay-Cohen Y, Konikof F. [Thiopurine-induced hyperammonaemic encephalopathy in a patient with Crohn's disease]. Harefuah 2012; 151: 692-5, 720. Hebrew. PubMed PMID: 23330262.

(Patient with Crohn disease developed noncirrhotic portal hypertension complicated by hyperammonemic coma during mercaptopurine therapy).

Cohen-Ezra O, Avni Y, Morgenstern S, Ben-Ari Z. [Nodular regenerative hyperplasia as a complication of thiopurine treatment in a patient with inflammatory bowel disease]. Harefuah 2012; 151: 675-8, 721. Hebrew. PubMed PMID: 23330258.

(40 year old man developed thrombocytopenia and liver enzyme elevations during therapy with thiopurine, later developing variceal hemorrhage despite stopping therapy).

Choudhary NS, Gupta S, Chawla YK, Duseja A, Dhiman RK, Das A. Azathioprine induced liver injury: a case report. Dig Dis Sci 2012; 57: 1717-8. PubMed PMID: 22526581.

(61 year old man developed jaundice 16 days after starting azathioprine [bilirubin 9.2 rising to 21.6 mg/dL, ALT 138 U/L, Alk P 3 times ULN], resolving within 6 months of stopping).

van Asseldonk DP, Seinen ML, de Boer NK, van Bodegraven AA, Mulder CJ. Hepatotoxicity associated with 6-methyl mercaptopurine formation during azathioprine and 6-mercaptopurine therapy does not occur on the short-term during 6-thioguanine therapy in IBD treatment. J Crohns Colitis 2012; 6: 95-101. PubMed PMID: 22261533.

(Among 19 patients with inflammatory bowel disease who developed serum enzyme elevations during azathioprine or mercaptopurine therapy, none developed liver injury during thioguanine therapy and mean ALT values decreased [64 to 20 U/L]).

Hoentjen F, Seinen ML, Hanauer SB, de Boer NK, Rubin DT, Bouma G, Harrell LE, van Bodegraven AA. Safety and effectiveness of long-term allopurinol-thiopurine maintenance treatment in inflammatory bowel disease. Inflamm Bowel Dis 2013; 19: 363-9. PubMed PMID: 22605661.

(Among 36 patients with inflammatory bowel disease who developed ALT elevations during thiopurine therapy and were treated with low doses of thiopurines and allopurinol, ALT levels became normal in 24 and mean values decreased from 38 [range 21-84] to 21 [range 15-26] U/L).

Selvaraj SA, Chairez E, Wilson LM, Lazarev M, Bass EB, Hutfless S. Use of case reports and the Adverse Event Reporting System in systematic reviews: overcoming barriers to assess the link between Crohn's disease medications and hepatosplenic T-cell lymphoma. Syst Rev 2013; 2: 53. PubMed PMID: 23826928.

(Review of the literature and spontaneous reports made to the FDA of HSTCL and medication use, identified 37 cases, ages 12 to 79 [mean 30] years; 86% male; disease duration 4 to 35 [mean 10] years; 96% having received thiopurines, 76% biologics; survival poor [8%]).

Bašić Kinda S, Duraković N, Dotlić S, Serventi Seiwerth R, Davidović Mrsić S, Dubravčić K, Aurer I. Hepatosplenic αβ T-cell lymphoma arising after long-term azathioprine therapy successfully treated with allogeneic bone marrow transplant. Leuk Lymphoma 2013; 54: 1334-5. PubMed PMID: 23083012.

(Report of a patient with Crohn disease who developed HSTCL after 7 years of azathioprine therapy, few details provided).

Björnsson ES. Epidemiology and risk factors for idiosyncratic drug-induced liver injury. Semin Liver Dis 2014; 34: 115-22. PubMed PMID: 24879977.

(Review of the epidemiology of drug induced liver injury mentions that the estimated crude risk of hepatotoxicity from azathioprine is 1 per 1,103 exposed patients).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to azathioprine or mercaptopurine).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 10 [1.3%] cases were attributed to azathioprine and 9 [1.2%] to mercaptopurine, thus representing the 13th and 14th most frequent prescription drugs implicated).

Botros Y, Mathews M, Patel H, Shah N, Baddoura W, de la Torre A. Recurrent hepatocellular carcinoma in patient with Crohn's disease: incidental or expected outcome of azathioprine? Case Rep Gastrointest Med 2015; 2015: 939136. PubMed PMID: 26788381.

(62 year old man with Crohn disease and azathioprine therapy for 21 years, developed HCC with recurrence after resection; no mention of cirrhosis).

Brinkert F, Arrenberg P, Krech T, Grabhorn E, Lohse A, Schramm C. Two cases of hepatosplenic T-cell lymphoma in adolescents treated for autoimmune hepatitis. Pediatrics 2016; 138. pii: e20154245. PubMed PMID: 27516526.

(Two patients who developed HSTCL during azathioprine therapy of autoimmune hepatitis: 21 year old man treated for 5 years and an 18 year old female treated for 4 years, both presenting with hepatosplenomegaly, fever and pancytopenia).

Suárez Ferrer C, Llop Herrera E, Calvo Moya M, Vera Mendoza MI, González Partida I, González Lama Y, Matallana Royo V, et al. Idiopathic portal hypertension regarding thiopurine treatment in patients with inflammatory bowel disease. Rev Esp Enferm Dig 2016; 108: 79-83. PubMed PMID: 26838489.

(Among 1419 patients with inflammatory bowel disease followed at a referral center in Spain, 927 were treated with thiopurines, of whom 63 [7%] developed liver injury, mostly hepatotoxicity that resolved with dose modification or discontinuation, but 4 had portal hypetension and probable nodular regenerative hyperplasia [ages 42-72 years, treated for 2.5-10 years, bilirubin 0.4-2.2 mg/dL, ALT 21-65 U/L, platelet counts 60,000-100,000]).

van de Meeberg MM, Derikx LA, Sinnige HA, Nooijen P, Schipper DL, Nissen LH. Hepatosplenic T-cell lymphoma in a 47-year-old Crohn's disease patient on thiopurine monotherapy. World J Gastroenterol 2016; 22: 10465-10470. PubMed PMID: 28058028.

(47 year old man with Crohn disease on azathioprine therapy developed HSTCL, few details provided).

Heron V, Fortinsky KJ, Spiegle G, Hilzenrat N, Szilagyi A. Resected hepatocellular carcinoma in a patient with Crohn's disease on azathioprine. Case Rep Gastroenterol 2016; 10: 50-6. PubMed PMID: 27403102.

(61 year old woman with 30 year history of Crohn disease and 10 years of azathioprine therapy presented with liver mass with HCC on biopsy without cirrhosis, but no malignancy at time of resection several months later).

Björnsson ES, Gu J, Kleiner DE, Chalasani N, Hayashi PH, Hoofnagle JH; DILIN Investigators. Azathioprine and 6-mercaptopurine-induced liver injury: clinical features and outcomes. J Clin Gastroenterol 2017; 51: 63-9. PubMed PMID: 27648552.

(Among 10 cases of mercaptopurine induced liver injury enrolled in a prospetctive US database, 9l patients were adults being treated for autoimmune conditions and one a child with leukemia; latency ranged from a 2 months to several years, but usually was within 3 months of starting therapy or a major dose escalation, the disease being anicteric in 2, icteric in 8, severe in 5, with inital bilirubin 0.7-21.9 [mean=10.6] mg/dL, ALT 64-539 [mean=121] U/L, Alk P 35-187 [mean=143] U/L and liver biopsy showing cholestatic hepatitis and mild-to-moderate bile duct injury but no duct loss; cases due to azathioprine [n=12] tended to be similar in clinical characteristics, although somewhat less severe in course and outcome).