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Allopurinol

Updated: February 24, 2015.

OVERVIEW

Introduction

Allopurinol is a xanthine oxidase inhibitor and a widely used medication for gout. Allopurinol is a rare but well known cause of acute liver injury that has features of a hypersensitivity reaction and can be severe and even fatal.

Background

Allopurinol (al' oh pure' i nol) is an analog of hypoxanthine and a potent inhibitor of the enzyme xanthine oxidase that is responsible for converting hypoxanthine to xanthine and xanthine to uric acid in the breakdown pathway of purines. Allopurinol lowers serum and tissue uric acid levels and has potent activity against gout, largely in preventing rather than treating acute attacks of gout. Allopurinol was approved for use in the United States in 1963 and is still widely used. Current indications include therapy and prevention of gout, uric acid nephropathy, and the hyperuricemia caused by malignancy and anticancer therapy. It is not recommended for treatment of asymptomatic hyperuricemia. Allopurinol is available in multiple generic forms and under the brand name of Zyloprim or Aloprim in tablets of 100 and 300 mg. Intravenous formulations are also available. The recommended initial dose for therapy of gout is 100 mg daily, with increases of 100 mg in daily dose weekly until uric acid levels fall to 6 mg/dL or below, but not to exceed 800 mg daily. The average daily dose in therapy of gout is 300 mg. Common side effects include skin rash and hypersensitivity reactions.

Hepatotoxicity

Chronic therapy with allopurinol is associated with transient and minor liver test abnormalities in 2% to 6% of patients, which resolve spontaneously or with drug discontinuation. More importantly, allopurinol has been linked to acute liver injury that is typically associated with immunoallergic manifestations such as fever, rash, eosinophilia, lymphadenopathy, lymphocytosis, arthralgias and facial edema (drug-rash, eosinophilia and systemic symptoms — DRESS syndrome) (Case 1). The typical latency to onset is 2 to 6 weeks and the pattern of liver enzyme elevations tends to be hepatocellular or mixed, but can be cholestatic. Autoantibodies are not common. Allopurinol hepatotoxicity has a high fatality rate, either from acute liver failure or complications of other allergic manifestations such as toxic epidermal necrolysis, vasculitis, pancreatitis and renal dysfunction. African-American race and preexisting renal disease appear to be risk factors for hypersensitivity to allopurinol.

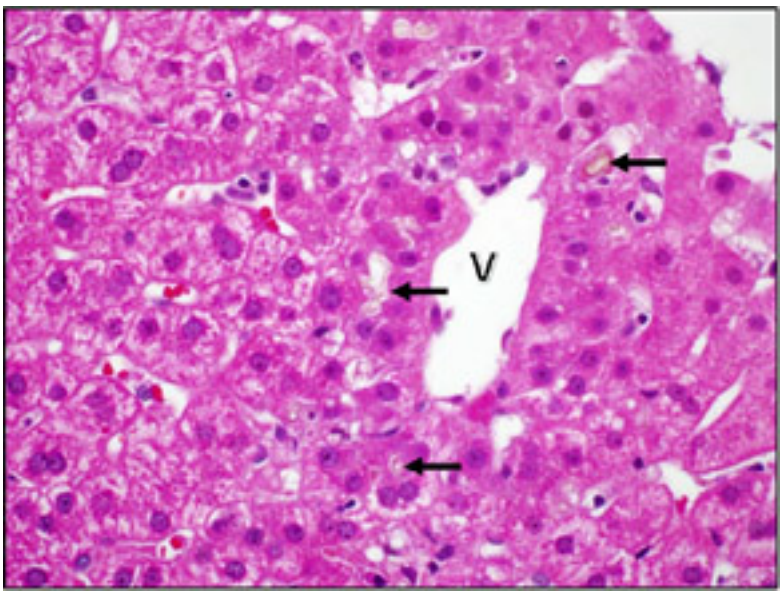
Likelihood score: A (well established cause of clinically apparent liver injury).

Histopathology

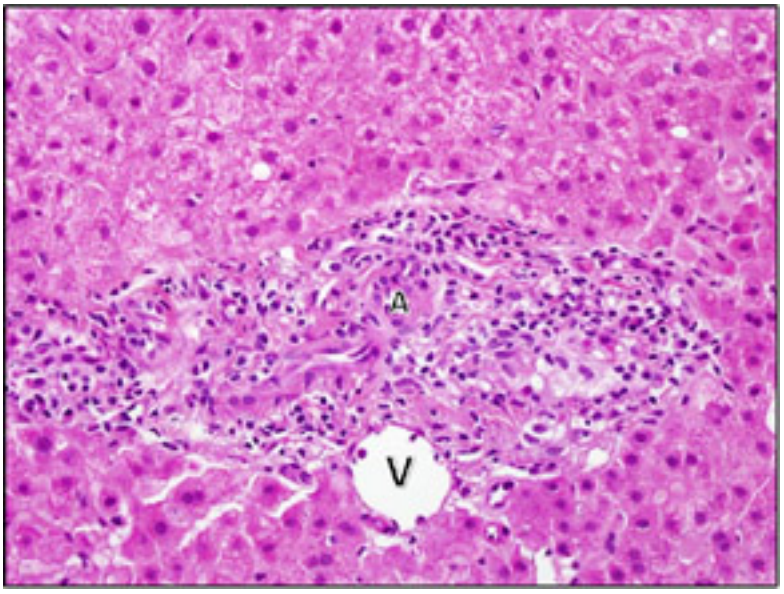
Liver biopsy in allopurinol hepatotoxicity typically shows an acute cholestatic or mixed hepatitis. Bile duct injury may be prominent early and loss of bile ducts later during the course. Histology can also show granulomas

including "ring" granulomas that are typically associated with visceral infections such as Q fever or Kala-azar. Granulomas may be found in other organs as well and represent a typical histological correlate to the immunoallergic response to a medication. Two examples of allopurinol hepatotoxicity are shown: one with a cholestatic hepatitis and another with acute granulomatous changes.

CHOLESTATIC HEPATITIS

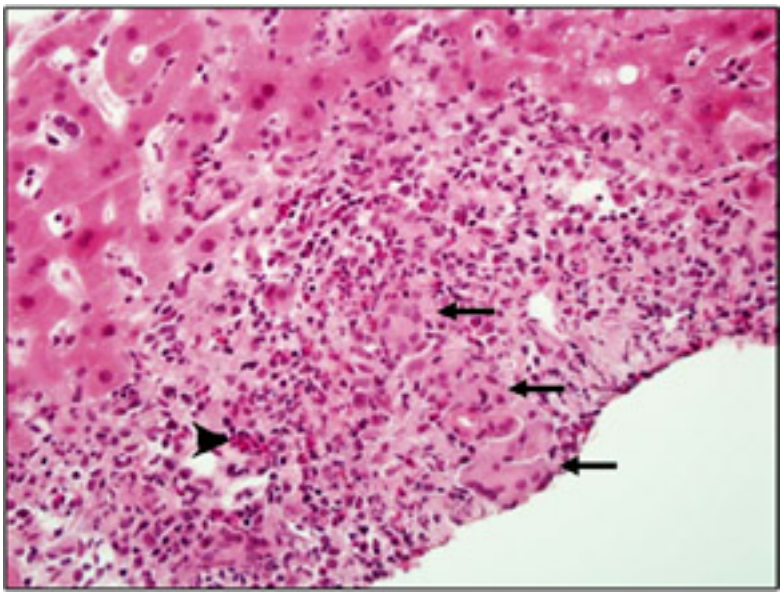


Allopurinol may cause cholestatic hepatitis. This case shows canalicular (arrow) and hepatocellular cholestasis in zone 3. Only very mild inflammation is present in this photo. The central vein (V) is indicated.

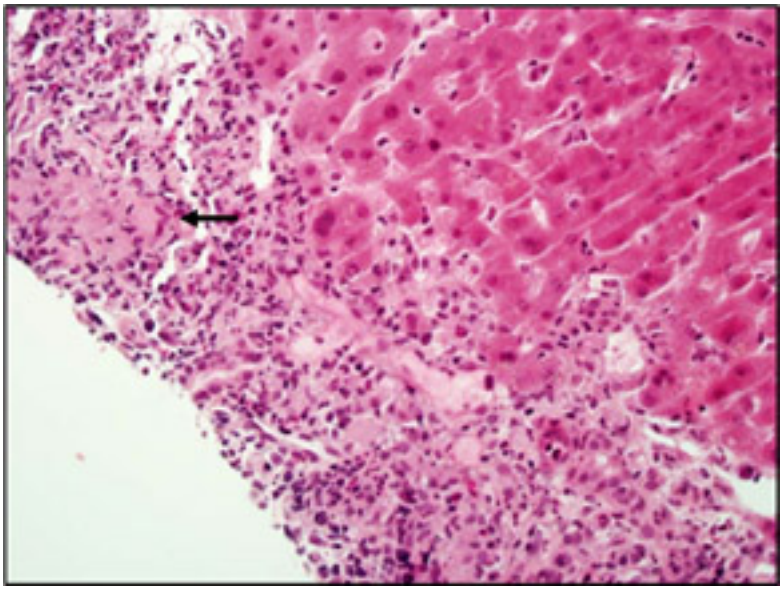


In this case, there was mild portal inflammation, mainly composed of lymphocytes. In over half the portal areas, no duct could be found, consistent with a vanishing bile duct syndrome. This portal area only shows an artery (A) and vein (V).

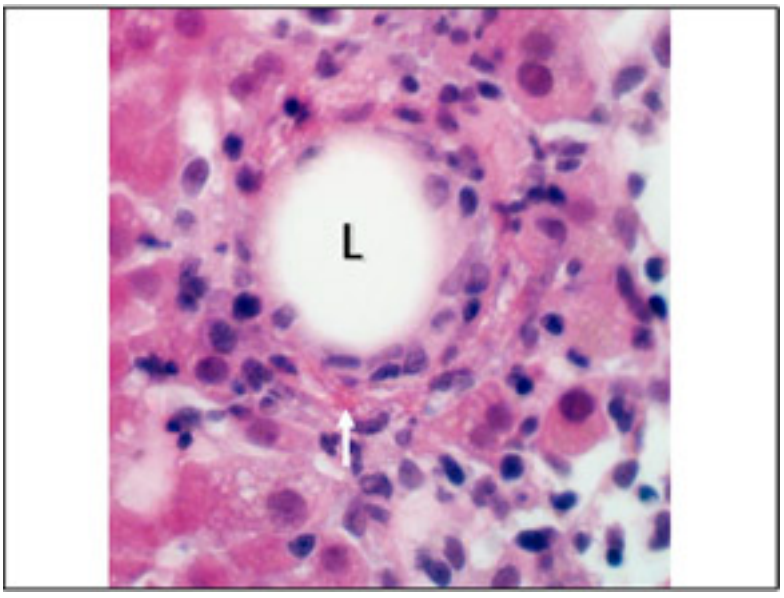
GRANULOMATOUS HEPATITIS



This case had granulomas in almost all of the portal areas. In this portal, the epithelioid macrophages (arrow) of the granulomas are in the center part of the portal area. The granuloma is surrounded by a mixed inflammatory infiltrate of lympocytes, neutrophils and eosinophils. A cluster of eosinophils is indicated by the arrowhead.



Another portal area showing a granuloma (arrow) along with mixed inflammation.



A fibrin-ring granuloma was present in this case. A fibrin-ring granuloma is a granuloma that forms around a lipid droplet (L). A thin, irregular, ring of brightly eosinophilic fibrin can be seen running circumferentially around the lipid drop. It is best seen at the bottom (arrow).

Mechanism of Injury

The mechanism of allopurinol hepatotoxicity is believed to be immunoallergic. Many cases resemble those of anticonvulsant hypersensitivity. Recently, several cases have been linked to concurrent infection with human herpesvirus-6, EBV or CMV infections. Severe allopurinol hypersensitivity skin reactions have been closely linked to HLA B*58:01 particularly in Asian populations but also to a lesser extend in Caucasians.

Outcome and Management

While most cases of acute liver injury attributed to allopurinol are self-limited and start to resolve within 7-10 days of stopping the medication, other cases are protracted, severe and even fatal. Instances of chronic vanishing bile duct syndrome due to allopurinol have been reported. Because of the accompanying allergic manifestations, corticosteroids are often used and usually result in prompt improvements in fever and rash, but their efficacy in ameliorating the liver injury is unproven. Relapse with early discontinuation of corticosteroids is common. There is no known cross reactivity of hypersensitivity to allopurinol with similar reactions to other medications, including the anticonvulsants.

Drug Class: Antigout Agents

CASE REPORTS

Case 1. Acute hepatic failure due to allopurinol.

[Modified from: Raper R, Ibels L, Lauer C, Barnes P, Lunzer M. Fulminant hepatic failure due to allopurinol. Aust NZ J Med 1984; 14: 63-5. PubMed Citation]

A 58 year old woman with diabetes, hypertension, gastric ulcer and gouty arthritis with hyperuricemia and mild renal insufficiency was started on allopurinol (300 mg daily) and developed fever and rash 17 days later. She had undergone resection of a parathyroid adenoma under enflurane anesthesia shortly after starting allopurinol, but she recovered uneventfully and was sent home on doxycycline, in addition to her usual medications including glibenclamide, indomethacin and cimetidine. One week later, she developed fever, fatigue and rash which became generalized and exfoliative. Allopurinol was stopped and she was admitted for observation. She was markedly febrile (39^{o}C) and had a generalized erythematous rash. Blood testing showed leukocyotosis and eosinophilia. Liver tests, which were previously normal, were mildly elevated on admission, but over the next few days worsened with onset of jaundice (Table). Tests for hepatitis A and B were negative. She subsequently developed progressive prolongation of the prothrombin time followed by confusion, encephalopathy and ascites. Corticosteroids were started. She developed gram negative sepsis followed by multiorgan failure and died. Postmortem liver biopsy showed marked centrilobular necrosis, cholestasis, inflammation and small islands of regenerating hepatocytes.

Key Points

Medication:	Allopurinol (300 mg daily)
Pattern:	Mixed (R=2.2)
Severity:	5+ (death from hepatic failure)
Latency:	3 weeks
Recovery:	None
Other medications:	Glibenclamide, indomethacin, and cimetidine chronically. Enflurane 2 weeks before onset, doxycycline for the 6 days before onset.

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Allopurinol started (300 mg daily) for gout					
4 days		25	100	0.5	Pre-operative testing
17 days	0	110	120	0.5	Admission: rash and fever
4 weeks	11 days	1240	1240	12.0	Prothrombin time 9 sec prolonged
6 weeks	25 days	65	390	30.0	Ascities, coma and sepsis
Normal Values		**<40**	**<95**	**<1.2**	

Comment

This patient developed typical allopurinol hypersensitivity syndrome 3 weeks after starting therapy. Risk factors included preexisting renal insufficiency. Several days after being admitted for rash and fever, she developed jaundice and had subsequent worsening with development of hepatic failure. This syndrome is also referred to as DRESS (drug rash with eosinophilia and systemic symptoms) and is usually rapidly reversible with stopping the medication. However, the hypersensitivity reaction can be severe and result in death from acute liver failure or from complications of generalized skin rash (toxic epidermal necrolysis) or renal disease. Corticosteroid therapy is often given and usually results in rapid disappearance of fever and improvement in rash, but relapse with stopping corticosteroids is common and this therapy is of unproven benefit for the hepatic injury and can complicate management of acute liver failure. Severe cutaneous reactions to allopurinol have been linked to HLA B*58:01 and cases of hepatotoxicity with allergic manifestations and skin rash are likely to have a similar linkage.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Allopurinol – Generic, Aloprim®, Zyloprim®

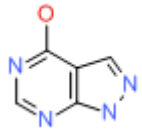
DRUG CLASS

Antigout Agents/Gout Suppressants

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Allopurinol	315-30-0	C5-H4-N4-O	

ANNOTATED BIBLIOGRAPHY

References updated: 24 February 2015

Zimmerman HJ. Drugs used to treat gout. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 543-4.

(Expert review of allopurinol hepatotoxicity published in 1999; mentions that allopurinol has been implicated in 25 cases of liver injury, usually with fever, rash and eosinophilia arsing 3-6 weeks after starting, sometimes with granulomas on liver biopsy).

Grosser T, Smyth E, FitzGerald GA. Pharmacology of gout. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 994-1004.

(Textbook of pharmacology and therapeutics).

Hall AP, Holloway VP, Scott JT. 4-hydroxypyrazolo (3,4-d) pyrimidine (HPP) in the treatment of gout: preliminary observations. Ann Rheum Dis 1964; 23: 439-46. PubMed PMID: 14229577.

(Initial description of allopurinol effects in 4 patients with gout; one developed rash ~6 weeks after starting, resolving on stopping, but not recurring on rechallenge)

Lidsky MD, Sharp JT. Jaundice with the use of 4-hydroxypyrazolo (3,4-d) pyrimidine. Arthritis Rheum 1967; 10: 294. Not in PubMed.

(Abstract: Among 14 patients with gout given allopurinol, 2 developed cholestatic hepatitis and several more had serum enzyme elevations; preexisting renal disease appeared to be a predisposing factor).

Jarzobski J, Ferry J, Wombolt D, Fitch DM, Egan JD. Vasculitis with allopurinol therapy. Am Heart J 1970; 79: 116-21. PubMed PMID: 5410273.

(76 year old man developed fever and severe exfoliative rash 4 weeks after starting allopurinol with 9% eosinophils, but normal AST and bilirubin; subsequently developed renal failure and died; autopsy showed hypersensitivity vasculitis involving kidneys, liver, spleen and lungs).

Kantor GL. Toxic epidermal necrolysis, azotemia, and death after allopurinol therapy. JAMA 1970; 212: 478-9. PubMed PMID: 5467301.

(72 year old man developed fever and severe rash 2 weeks after starting allopurinol [bilirubin and Alk P not given, ALT 65 U/L, 13% eosinophils, creatinine 3.6 mg/dL], treated with corticosteroids, but died of toxic epidermal necrolysis and sepsis; no mention of liver pathology).

Mills RM. Severe hypersensitivity reactions associated with allopurinol. JAMA 1971; 216: 799-802. PubMed PMID: 4252397.

(52 year old man and 59 year old woman developed fever and rash with eosinophilia and renal insufficiency 3 and 5 weeks after starting allopurinol, little documentation of liver involvement, both recovered but required prolonged corticosteroid therapy).

Simmons F, Feldman B, Gerety D. Granulomatous hepatitis in a patient receiving allopurinol. Gastroenterology 1972; 62: 101-4. PubMed PMID: 5059424.

(50 year old man developed fever with eosinophilia and enzyme elevations [ALT 320 U/L, Alk P 240 U/L] without jaundice 3 weeks after starting allopurinol; liver biopsy showed granulomas and focal necrosis, rapid resolution with stopping and no granulomas on two follow up biopsies 1 and 4 months later).

Young JL, Boswell RB, Nies AS. Severe allopurinol hypersensitivity. Association with thiazides and prior renal compromise. Arch Intern Med 1974; 134: 553-8. PubMed PMID: 4546912.

(40 year old man and 67 year old woman developed fever, rash and eosinophilia 4 weeks after starting allopurinol [bilirubin 2.0 and 1.8 mg/dL, AST 1550 and 210 U/L]; one patient dying of liver [bilirubin rising to 15.0 mg/dL] and renal failure, and the other surviving; preexisting renal insufficiency, thiazide use and African-American race were thought to be risk factors).

McMenamin RA, Davies LM, Craswell PW. Drug induced interstitial nephritis, hepatitis and exfoliative dermatitis. Aust N Z J Med 1976; 6: 583-7. PubMed PMID: 139882.

(Among 4 cases of rash, fever, nephritis and hepatitis, one was linked to allopurinol, arising after 6 weeks of therapy [bilirubin 2.5 mg/dL, AST 215 U/L, Alk P 323 U/L, eosinophils 7%], with transient renal failure [creatinine 15 mg/dL], resolving after therapy with prednisone).

Boyer TD, Sun N, Reynolds TB. Allopurinol-hypersensitivity vasculitis and liver damage. West J Med 1977; 126: 143-7. PubMed PMID: 139760.

(29, 59 and 67 year old men developed rash and fever 4 weeks after starting allopurinol [bilirubin 14.4, 1.8 and 3.1 mg/dL, ALT 940, 165 and 150 U/L, Alk P 1-3x ULN], 2 had renal insufficiency, 1 case was fatal, and others recovered with prednisone treatment in 1-3 months; rechallenge with a single dose induced fever and rash without liver abnormalities).

Espiritu CR, Alalu J, Glueckauf LG, Lubin J. Allopurinol-induced granulomatous hepatitis. Am J Dig Dis 1976; 21: 804-6. PubMed PMID: 961676.

(55 year old woman developed fever and arthralgias [but no rash or eosinophilia] 4 weeks after starting allopurinol [bilirubin 0.9 mg/dL, ALT 140 U/L and Alk P 900 U/L] and biopsy showing granulomas; improved with stopping drug and had normal values and liver histology 3 months later during cholecystectomy).

Chawla SK, Patel HD, Parrino GR, Soterakis J, Lopresti PA, D'Angelo WA. Allopurinol hepatotoxicity. Case report and literature review. Arthritis Rheum 1977; 20: 1546-9. PubMed PMID: 921828.

(44 year old man developed abdominal pain a week after starting allopurinol [bilirubin 1.8 mg/dL, AST 50 U/L, Alk P 98 U/L, 8% eosinophils]; biopsy showed noncaseating granulomas; resolved rapidly with stopping therapy).

Butler RC, Shah SM, Grunow WA, Tester EC. Massive hepatic necrosis in a patient receiving allopurinol. JAMA 1977; 237: 473-4. PubMed PMID: 576272.

(48 year old woman developed urticaria, fever and rash 1-2 weeks after starting allopurinol [bilirubin 4.6 rising to 13.1 mg/dL, AST 880 U/L, Alk P 188 U/L], and progressive liver failure: autopsy showed massive hepatic necrosis).

Shah SM, Butler RC, Grunow WA, Texter EC Jr. Massive hepatic necrosis in a patient receiving concomitant medication. JAMA 1977; 237: 2036. PubMed PMID: 576881.

(Follow up of Butler [1977] listing concomitant medications, none of which were implicated because none had been recently changed).

Swank LA, Chejfec G, Nemchausky BA. Allopurinol-induced granulomatous hepatitis with cholangitis and a sarcoid-like reaction. Arch Intern Med 1978; 138: 997-8. PubMed PMID: 646570.

(36 year old man developed fever and polyarthralgias 1 month after starting allopurinol with leukocytosis [bilirubin 4.7 mg/dL, AST 145 U/L, Alk P 875 U/L] and liver biopsy showing multiple noncaseating granulomas and cholangitis, resolved on stopping and follow up liver biopsy was normal).

Male PJ, Schaer B, Posternak R. Reaction d'hypersensibilite a l'allopurinol. Schweiz Med Wochenschr 1978; 108: 661-3. PubMed PMID: 65331.

(71 year old man developed fever, rash, eosinophilia and lymphadenopathy 20 days after starting allopurinol [bilirubin 25 mg/dL, ALT "without perturbation", Alk P 252 U/L, abnormal renal function], who was treated with prednisone and recovered).

Medline A, Cohen LB, Tobe BA, Sellers EM. Liver granulomas and allopurinol. Br Med J 1978; 108: 681-2. PubMed PMID: 647256.

(47 year old man on allopurinol for 6 years developed fever and abdominal pain [bilirubin 1.4 mg/dL, ALT 53 U/L, Alk P 3 times ULN, eosinophilia of 7%, ESR 80], who upon cholecystectomy had no stones, but liver biopsy showed multiple noncaseating granulomas and giant cells, resolved on stopping allopurinol and follow up biopsy showed no granulomas).

Korting HC, Lesch R. Acute cholangitis after allopurinol treatment. Lancet 1978; 1: 275-6. PubMed PMID: 74697.

(48 year old man with renal insufficiency developed rash, fever and abdominal pain 4-5 weeks after starting allopurinol [bilirubin 1.1 rising to 7.7 mg/dL, ALT 134 U/L, Alk P 1317 U/L, 10% eosinophilia], liver biopsy showing cholangitis and cholestasis, died of multiorgan failure).

Haughey DB, Lanse S, Imhoff T, Tobin M, Schentag JJ. Allopurinol sensitivity: report of two cases. Am J Hosp Pharm 1979; 36: 1377-80. PubMed PMID: 159623.

(2 men, ages 72 and 58 years, developed fever, rash and eosinophilia 2 and 4 weeks after starting allopurinol [bilirubin 2.4 and 0.5 mg/dL, AST 510 and 65 U/L, Alk P 198 and 200 U/L], one required prednisone for rash, both recovered).

Lang PG. Severe hypersensitivity reactions to allopurinol. South Med J 1979; 72: 1361-8. PubMed PMID: 159491.

(Retrospective analysis of 20 cases of allopurinol hypersensitivity seen at 3 Atlanta hospitals 1973-78; 13 [65%] African-Americans, mean age 59 years, 11 with preexisting renal disease, 5 on thiazides; onset after 1-6 weeks often with rash, which was macropapular [9], exfoliative [6] or toxic epidermal necrolysis [5]; 6 had liver involvement [bilirubin 1.4-13.8 mg/dL, AST 56-4000 U/L and Alk P 117-450 U/L], 9 had renal involvement, 4 died of complications of skin involvement and sepsis).

Olsen H, Mrland J. [Hepatic damages caused by allopurinol] Tidsskr Nor Laegeforen 1980; 100: 562-3. PubMed PMID: 7385109.

(72 year old woman developed evidence of liver injury 3 months after starting allopurinol [ALT 365 U/L, Alk P 599 U/L] resolving within 1.5 weeks of stopping).

Al-Kawas FH, Seeff LB, Berendson RA, Zimmerman HJ, Ishak KG. Allopurinol hepatotoxicity. Report of two cases and review of literature. Ann Intern Med 1981; 95: 588-90. PubMed PMID: 7294548.

(Two African-American men developed fever and rash 3 and 4 weeks after starting allopurinol [bilirubin 1.5 and 5.4 mg/dL, ALT 650 and 1780 U/L, Alk P 193 and 248 U/L], recovery within 4-8 weeks of stopping, 1 given prednisone).

Shah KA, Levin J, Rosen N, Greenwald E, Zumoff B. Allopurinol hepatotoxicity potentiated by tamoxifen. N Y State J Med 1982; 82: 1745-6. PubMed PMID: 6960280.

(69 year old man on allopurinol for 12 years developed fever and Alk P and LDH elevations 1 day after starting tamoxifen for prostate cancer, fever and enzyme elevations, resolving within 3 days of stopping allopurinol; ALT and AST levels were elevated before tamoxifen therapy and did not change).

Ramond MJ, Nouel O, Degott C, Lebrec D, Benhamou JP. [Allopurinol-induced hepatitis. Report of a case and review of the literature (author's transl)] Gastroenterol Clin Biol 1982; 6: 138-42. PubMed PMID: 7060857.

(74 year old woman developed fever and jaundice one month after starting allopurinol with eosinophilia, [bilirubin 5.1 mg/dL, ALT 261 U/L, Alk P 6 times ULN], biopsy showing necrosis, inflammation and granulomas, resolving within 1-2 months of stopping).

Falco D. An unusual case of hypersensitivity probably due to allopurinol. J Med Soc NJ 1982; 79: 409-12. PubMed PMID: 6954286.

(58 year old African American man with hypertension, congestive heart failure and renal insufficiency developed fatal, progressive vasculitis within days of restarting allopurinol; liver enzymes did not change and there was no eosinophilia).

Raper R, Ibels L, Lauer C, Barnes P, Lunzer M. Fulminant hepatic failure due to allopurinol. Aust NZ J Med 1984; 14: 63-5. PubMed PMID: 6590011.

(58 year old Chinese woman developed fever and exfoliative rash 3 weeks after starting allopurinol with eosinophilia, jaundice and fulminant course [bilirubin 12 rising to 30 mg/dL, ALT 1240 U/L, Alk P 1240 U/L]: Case 1).

Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. Am J Med 1984; 76: 47-56. PubMed PMID: 6691361.

(Description of 6 patients with allopurinol toxicity and review of another 72 in the literature [latency 1-8 weeks in 90%, skin rash in 92%, fever 87%, eosinophilia 73%, hepatitis in 68%, renal worsening 85%, death 21%], also mentions that renal insufficiency was a strong risk factor and most patients were estimated to have high allopurinol levels: findings that led to recommendations for modification of dose based upon renal function).

Ohsawa T, Ohtsubo M. Hepatitis associated with allopurinol. Drug Intell Clin Pharm 1985; 19: 431-3. PubMed PMID: 4006738.

(66 year old woman developed severe hepatitis 10 days after starting allopurinol [peak bilirubin ~18 mg/dL, ALT 822 U/L, Alk P ~6 times ULN], resolving within 1 month, but recurrence of fever, AST elevation [97 U/L] and eosinophilia [16%] within hours of rechallenge with one dose).

Mousson C, Justrabo E, Tanter Y, Chalopin JM, Rifle G. [Acute granulomatous interstitial nephritis and hepatitis caused by drugs. Possible role of an allopurinol-furosemide combination] Nephrologie 1986; 7: 199-203. PubMed PMID: 3822042.

(58 year old woman with renal insufficiency developed fever and rash 6 weeks after starting allopurinol [bilirubin 2.2 mg/dL, ALT 56 U/L, Alk P 780 U/L], and worsening renal function and granulomas in both liver and kidney biopsies).

Vanderstigel M, Zafrani ES, Lejonc JL, Schaeffer A, Portos JL. Allopurinol hypersensitivity syndrome as a cause of hepatic fibrin-ring granulomas. Gastroenterol 1986; 90: 188-90. PubMed PMID: 3940244.

(39 year old man developed fever, rash and eosinophilia 4 weeks after starting allopurinol [bilirubin 1.2 mg/dL, ALT 167 U/L, Alk P 406 U/L], biopsy showed granulomas with central vacuole and fibrin ring, infectious causes ruled out).

Singer JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. Arthritis Rheum 1986; 29: 82-7. PubMed PMID: 3947418.

(Review of 8 cases of allopurinol hypersensitivity and the literature; typically has onset after 2-12 weeks of therapy with fever, rash, eosinophilia and either renal [n=6] or liver [n=6] involvement, 3 died, 7 did not have strong indications for therapy; authors argue against use of allopurinol for asymptomatic hyperuricemia).

Pewsner D, Bachmann C, Müller U. [Allopurinol-induced kidney failure with hepatitis and squamous dermatitis in pre-existing kidney insufficiency] Schweiz Med Wochenschr 1987; 117: 139-41. PubMed PMID: 2950589.

(66 year old woman developed rash 6-8 weeks after starting allopurinol with jaundice and worsening renal function [peak bilirubin ~14.7 mg/dL, ALT 297 U/L, Alk P 855 U/L], resolving within 2 months of stopping).

Olmos M, Guma C, Colombato LO, Lami G, Miyashiro R, Alvarez E. [Hepatic lesions induced by drugs. Report of 26 cases] Acta Gastroenterol Latinoam 1987; 17: 105-11. Spanish. PubMed PMID: 3442185.

(Review of 2671 liver biopsies done in one Argentinian hospital between 1972-85 identified 26 with drug induced liver disease: 14 from birth control pills, 3 methyldopa, 2 carbon tetrachloride, 2 phenylbutazone, and 1 each from allopurinol [cholestatic hepatitis arising after 90 days], penicillin, chlorpromazine, indomethacin and ketoconazole).

Stricker BH, Blok AP, Babany G, Benhamou JP. Fibrin ring granulomas and allopurinol. Gastroenterology 1989; 96: 1199-203. PubMed PMID: 2925064.

(Found 6 cases of granulomas during allopurinol therapy reported to WHO database; onset of fever, rash, arthralgias and eosinophilia within 2-4 weeks of starting drug with biopsies showing ill defined granuloma-like lesions, but not with fibrin rings).

González Ramallo VJ, Rodríguez Gorostiza FJ, Muiño Míguez A, López de la Riva M. [Severe cholestasis caused by allopurinol] Rev Esp Enferm Apar Dig 1989; 75: 317-8. Spanish. PubMed PMID: 2734478.

(74 year old man with mild renal insufficiency developed fever, rash and jaundice 20 days after starting allopurinol [bilirubin 11.1 mg/dL, ALT 107 U/L, Alk P ~3000 U/L]; biopsy showing cholestasis, resolution in 4 weeks of stopping).

Tam S, Carroll W. Allopurinol hepatotoxicity. Am J Med 1989; 86: 357-8. PubMed PMID: 2919623.

(Patient on unknown dose of allopurinol for uncertain period developed acute liver failure [initially, bilirubin 1.3 mg/dL, ALT 535 U/L, Alk P 331 U/L], allopurinol levels were ~25-fold elevated suggesting an inadvertent overdose).

Chong RS, Ng HS, Teh LB, Ho JM. Hepatic granulomas-an experience over the last 8 years. Singapore Med J 1990; 31: 422-6. PubMed PMID: 2259936.

(Retrospective review identified 20 cases of liver biopsies with granulomas seen over 8 year period, 1 was attributed to allopurinol hypersensitivity: abstract only).

de Bayser L, Roblot P, Ramassamy A, Silvain C, Levillain P, Becq-Giraudon B. Hepatic fibrin-ring granulomas in giant cell arteritis. Gastroenterology 1993; 105: 272-3. PubMed PMID: 8514044.

(70 year old man with giant cell arteritis and not on allopurinol had fibrin-ring granulomas in liver with high Alk P, but normal ALT and bilirubin).

Arellano F, Sacristán JA. Allopurinol hypersensitivity syndrome: a review. Ann Pharmacother 1993; 27: 337-43. PubMed PMID: 8453174.

(Review of 101 cases of allopurinol hypersensitivity syndrome reported in literature; mean age 57 years, 2/3rds men, fever 95%, rash 93%, leukocytosis 40%, eosinophilia 60%, AST elevation 88%, renal dysfunction common and may play role in pathogenesis).

Berbegal J, Morera J, Andrada E, Navarro V, Lluch V, López-Benito I. [Syndrome of allopurinol hypersensitivity. Report of a new case and review of the Spanish literature] Med Clin (Barc) 1994; 102: 178-80. Spanish. PubMed PMID: 8127168.

(75 year old man developed rash and fever 2 weeks after starting allopurinol followed by facial edema and neuropathy with eosinophilia [bilirubin 0.7 mg/dL, ALT 51 U/L, Alk P 494 U/L], liver biopsy showing granulomas, and injury resolving within a few weeks of stopping).

Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. J Invest Dermatol 1994; 102: 28S-30S. PubMed PMID: 8006430.

(Consensus of international group of dermatologists on criteria for SJS and TEN based upon patern of erythema multiforme-like lesions and extent of dermal detachment).

Lee SS, Lin HY, Wang SR, Tsai YY. Allopurinol hypersensitivity syndrome. Zhonghua Min Guo Wei Sheng Wu Ji Mian Yi Xue Za Zhi. 1994; 27: 140-7. PubMed PMID: 9747344.

González U, Reyes E, Kershenovich J, Orozco-Topete RL. [Hypersensitivity syndrome caused by allopurinol. A case of massive hepatic necrosis] Rev Invest Clin 1995; 47: 409-13. Spanish. PubMed PMID: 8584813.

(Abstract only: 72 year old woman developed fever and Stevens-Johnson syndrome 2 weeks after starting allopurinol, with subsequent fatal renal and hepatic failure).

Paitel JF, Trechot P, Stockemer V, Dorvaux V, Lederlin P. [Acute liver disease during treatment with pipobroman and allopurinol] Presse Med. 1995; 24: 460. PubMed PMID: 7746823.

(41 year old woman taking allopurinol for 5 years, developed jaundice 2 months after starting pipobroman for polycythemia vera [bilirubin 11.8 mg/dL, ALT 33 times ULN, normal protime] and recovery in 4-6 months; unlikely due to allopurinol).

Urban T, Maquarre E, Housset C, Chouaid C, Devin E, Lebeau B. [Allopurinol hypersensitivity. A possible cause of hepatitis and mucocutaneous eruptions in a patient undergoing antitubercular treatment] Rev Mal Respir 1995; 12: 314-6. PubMed PMID: 7638430.

(39 year old man with tuberculosis developed fever and rash 2 weeks after starting allopurinol; initially with normal liver tests, but then developing lymphadenopathy, eosinophilia [bilirubin normal, ALT 413 U/L, Alk P 143 U/L], resolving rapidly after stopping allopurinol).

Wade B, Klotz F, Debonne JM, Aubert M. [Fatal hepatitis due to allopurinol in Dakar] Med Trop (Mars) 1995; 55: 186-7. PubMed PMID: 7565008.

Andrade RJ, de la Mata M, Lucena MI, López-Rubio F, Corrales MA. [Severe acute hepatitis due to allopurinol in a patient with asymptomatic hyperuricemia and kidney failure. A review of the literature and an analysis of the risk factors] Gastroenterol Hepatol 1997; 20: 353-6. PubMed PMID: 9377233.

(Patient with mild renal failure developed fever, rash and eosinophilia 19 days after starting allopurinol [bilirubin rising from normal to 27.6 mg/dL, ALT 169 U/L, Alk P 472 U/L, with ascites and prothrombin index 47%], with slow but ultimate recovery).

Jappe U, Franke I, Wendekamm U, Gollnick H. [Allopurinol as an inducer of acute graft-versus-host-like drug reaction. Case report with review of the literature] Hautarzt 1998; 49: 126-30. German. PubMed PMID: 9551335.

Pluim HJ, van Deuren M, Wetzels JFM. The allopurinol hypersensitivity syndrome. Neth J Med 1998; 52: 107-10. PubMed PMID: 9599967.

(61 year old man developed fever, rash, eosinophilia, facial edema and lymphadenopathy 5 weeks after starting allopurinol, [bilirubin normal, ALT 115 U/L, Alk P 97 U/L] and renal insufficiency requiring high dose prednisolone; slow recovery).

Kluger E. [Fatal outcome in allopurinol hypersensitivity syndrome] Ugeskr Laeger 1998; 160: 1179-80. Danish. PubMed PMID: 9492630.

Pereira S, Almeida J, Silva AO, Quintas M, Candeias O, Freitas F. [Fatal liver necrosis due to allopurinol] Acta Med Port 1998; 11: 1141-4. Portuguese. PubMed PMID: 10192993.

Khoo BP, Leow YH. A review of inpatients with adverse drug reactions to allopurinol. Singapore Med J 2000; 41: 156-60. PubMed PMID: 11063179.

(13 patients with adverse reactions to allopurinol over 3 years, all with rash arising after 3-54 [mean=21] days, 10 with fever, 7 had elevated ALT [21-289 U/L], but none had jaundice and all recovered).

Hammer B, Link A, Wagner A, Böhm M. [Hypersensitivity syndrome during therapy with allopurinol in asymptomatic hyperuricemia with a fatal outcome] Dtsch Med Wochenschr 2001; 126: 1331-4. German. PubMed PMID: 11719858.

(86 year old woman developed high fever and severe rash progressing to toxic epidermal necrolysis arising 1 week after starting allopurinol for asymptomatic hyperuricemia, liver tests normal, but developed septicemia and multiorgan failure and died).

Descamps V, Valance A, Edlinger C, Fillet AM, Crossin M, Lerun-Vignes B, Belatch S, et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. Arch Dermatol 2001; 137: 301-4. PubMed PMID: 11255328.

(Among 7 patients with drug rash with eosinophilia and systemic symptoms [DRESS] syndrome, all had anti-HHV-6, 2 in rising titers, 4 with IgM, none had HHV-6 DNA; 5 cases from carbamazepine, 1 sulfasalazine and 1 ibuprofen).

Vázquez-Mellado J, Morales EM, Pacheco-Tena C, Burgos-Vargas R. Relation between adverse events associated with allopurinol and renal function in patients with gout. Ann Rheum Dis 2001; 60: 981-3. PubMed PMID: 11557658.

(Among 120 patients with gout treated with allopurinol, adverse events occurred in 5 [rash, hypersensitivity syndrome] including 3 of 52 [6%] receiving a creatinine adjusted dose and 2 of 68 [3%] receiving higher doses).

Tjwa M, De Hertogh G, Neuville B, Roskams T, Nevens F, Van Steenbergen W. Hepatic fibrin-ring granulomas in granulomatous hepatitis: report of four cases and review of the literature. Acta Clin Belg 2001; 56: 341-8. *(4 patients with febrile illnesses found to have fibrin-ring granulomas on liver biopsy; Q fever in 1, EBV in 1, CMV in 2--* PubMed PMID: 11881318.

one of whom was also receiving allopurinol and thiazides chronically).

ten Holder SM, Joy MS, Falk RJ. Cutaneous and systemic manifestations of drug-induced vasculitis. Ann Pharmacother 2002; 36: 130-48. PubMed PMID: 11816242.

(Review of drug induced causes of vasculitis, allopurinol ranking 4th after propylthiouracil, hydralazine and G-CSF; 16 cases reported; 12 men, ages 17-75 with rash, renal, hepatic and other organ involvement; high mortality rate).

Chan YC, Tay YK, Ng SK. Allopurinol hypersensitivity syndrome and acute myocardial infarction-two case reports. Ann Acad Med Singapore 2002; 31: 231-3. PubMed PMID: 11957564.

(Two patients with allopurinol hepatotoxicity treated with corticosteroids had myocardial infarctions several months after recovery; authors suggest a link between the two: abstract only).

Muller P, Dubreil P, Mahé A, Lamaury I, Salzer B, Deloumeaux J, Strobel M. Drug hypersensitivity syndrome in a West-Indian population. Eur J Dermatol 2003; 13: 478-81. PubMed PMID: 14693494.

(7 year prospective study in Guadeloupe of drug hypersensitivity syndrome; 28 cases found ~1/100,000 incidence, onset averaging 4 weeks, 2 deaths; 7 cases due to allopurinol, frequently given inappropriately, with possible racial predisposition).

Descamps V, Mahe E, Houhou N, Abramowitz L, Rozenberg F, Ranger-Rogez S, Crickx B. Drug-induced hypersensitivity syndrome associated with Epstein-Barr virus infection. Br J Dermatol 2003; 148: 1032-4. PubMed PMID: 12786838.

(Patient with rash and fever after 3 weeks of allopurinol with atypical lymphocytosis, eosinophilia, ALT ~250 U/L, Alk P 504 U/L, normal bilirubin and pancreatitis [amylase 1070 U/L], recovery starting 7-10 days after stopping drug; IgM anti-EBV and anti-HHV-6 were present).

Mete N, Yilmaz F, Gulbahar O, Avdin A, Sin A, Kokuludaq A, Yuce G, Sebik F. Allopurinol hypersensitivity syndrome as a cause of hepatic centrilobular hemorrhagic necrosis. J Investig Allergol Clin Immunol 2003; 13: 281-3. PubMed PMID: 14989119.

(41 year old developed fever, rash, jaundice and eosinophilia 3 weeks after starting allopurinol with fatal outcome, autopsy showing severe centrolobular necrosis: abstract only).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants done in the United States between 1990 and 2002, 137 [0.2%] were done for idiosyncratic drug induced acute liver failure, but none were attributed to allopurinol).

Dia D, Ba-Fall K, Bouldouyre M, Chevalier B, Debonne JM. [DRESS syndrome to allopurinol: a case in Dakar] Dakar Med 2004; 49: 114-5. PubMed PMID: 15786619.

(47 year old man developed fever, rash and facial edema 3 months after starting allopurinol with eosinophilia and jaundice; rapid resolution with stopping drug: abstract only).

Russmann S, Lauterburg B. [Life-threatening adverse effects of pharmacologic antihyperuricemic therapy] Ther Umsch 2004; 61: 575-7. PubMed PMID: 15493119.

(Review of safety of allopurinol and newer xanthine oxidase inhibitors such as febuxostat and benzbromarone).

Becker MA, Schumacher HR Jr, Wortmann RL, MacDonald PA, Palo WA, Eustace D, Vernillet L, Joseph-Ridge N. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005; 353: 2450-61. PubMed PMID: 16339094.

(762 patients at 112 North American centers received either allopurinol [300 mg/day] or febuxostat [80, 120 or 240 mg/day] for 52 weeks; reduction of uric acid to <6 mg/dL achieved in 53-62% of febuxostat- vs 21% of allopurinol-treated patients; rates of acute gout were similar; liver test abnormalities in 4-5% of febuxostat vs 4% of allopurinol recipients; most common cause of discontinuation [2.3%]).

Gutiérrez-Macías A, Lizarralde-Palacios E, Martínez-Odriozola P, Miguel-De la Villa F. Fatal allopurinol hypersensitivity syndrome after treatment of asymptomatic hyperuricaemia. BMJ 2005; 331: 623-4. PubMed PMID: 16166134.

(80 year old man developed fever, rash and jaundice with eosinophilia [16%] 6 weeks after starting allopurinol [bilirubin 31.2 mg/dL, ALT 328 U/L, Alk P 6567 U/L], progressing to hepatic failure and death; risk factors were preexisting renal insufficiency and furosemide use).

Saxena R, Loghmanee F. Fatal drug reaction due to allopurinol therapy in a 72-year-old man. Arch Pathol Lab Med 2005; 129: e183-4. PubMed PMID: 16048416.

(72 year old man developed fever and severe rash 3 weeks after starting allopurinol, which progressed to generalized blistering and sloughing of skin and death from multiorgan failure).

Markel A. Allopurinol-induced DRESS syndrome. Isr Med Assoc J 2005; 7: 656-60. PubMed PMID: 16259349.

(Review of the hypersensitivity reactions to allopurinol including nephro- and hepatotoxicity).

Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, Lin YL, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A 2005; 102: 4134-9. PubMed PMID: 15743917.

*(The HLA-B*58:01 allele was present in all 51 [100%] Chinese patients with allopurinol associated severe cutaneous adverse reactions [SJS/TEN/DRESS], but only 15% of 135 allopurinol tolerant patients and 20% of healthy controls).*

Choi SH, Yang SH, Song YB, Kim HJ, Seo YT, Choi DS, Moon KH, et al. Allopurinol therapy and vanishing bile duct syndrome. Korean J Hepatol 2005; 11: 80-5. PubMed PMID: 15788888.

(60 year old man developed fever, rash and eosinophilia 1 week after starting allopurinol, with progressive liver failure and death 7 weeks later [bilirubin 1.7 rising to 37.2 mg/dL, ALT 483 to 175 U/L, Alk P 140 to 579U/L], biopsy showing loss of bile ducts).

Vital Durand D, Durieu I, Rousset H. [Toxic or drug-induced granulomatous reactions] Rev Med Interne 2008; 29: 33-8. French. PubMed PMID: 18054121.

(Review of drug and toxin induced granulomatous reactions in various organs; in four recent case series, granulomas were found in 292 of 7754 biopsies [4%], of which 2-8% were attributable to drugs, but another 10-30% were "idiopathic" and possibly related; most common agent was allopurinol, but others implicated in single cases were chlorpropamide, phenothiazines, carbamazepine, methyldopa, baclofen, glibencamide, quinidine, metronidazole, and nitrofurantoin).

Chiou CC, Yang LC, Hung SI, Chang YC, Kuo TT, Ho HC, Hu S, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. J Eur Acad Dermatol Venereol 2008; 22: 1044-9. PubMed PMID: 18627428.

(Over a 5 year period, 30 cases of DRESS syndrome were seen at a single referral center in Taiwan; 15 men and 15 women, ages 13 to 78 years, on drug for 3 to 60 days (mean = 23 days], attributed to allopurinol in 11 [37%], carbamazepine in 6 [20%] and phenytoin, indomethacin and vancomyin in 2 each [7%]; liver test abnormalities in 87%, jaundice in 17% and 3 died [10%], but none of liver failure).

Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidoroff A, Naldi L, et al; EuroSCAR Study Group. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. J Am Acad Dermatol 2008; 58: 25-32. PubMed PMID: 17919772.

(Among 379 patients with SJS/TEN, allopurinol was the most frequent cause [n=66: 17%], which was taken by only 2% of matched controls without severe cutaneous adverse events).

Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, Sawada J, et al; JSAR research group. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. Pharmacogenomics 2008; 9: 1617-22. PubMed PMID: 19018717.

*(Among 58 Japanese patients with SJS/TEN, none of 7 carbazamepine attributed cases had B*15:02, and only 4 of 10 allopurinol cases had B*58:01, the allele frequency being 20% in cases vs 0.6% in the population).*

Schumacher HR Jr, Becker MA, Wortmann RL, MacDonald PA, Hunt B, Streit J, Lademacher C, Joseph-Ridge N. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008; 59: 1540-8. PubMed PMID: 18975369.

(Among 1072 patients with gout randomized to different treatments for 28 weeks, abnormal liver tests [=1.5 times ULN] occurred in 4-6% on febuxostat, 2% placebo, and 6% allopurinol).

Shalom R, Rimbroth S, Rozenman D, Markel A. Allopurinol-induced recurrent DRESS syndrome: pathophysiology and treatment. Ren Fail 2008; 30: 327-9. PubMed PMID: 18350453.

(65 year old man with mild renal insufficiency developed rash and fever, 1 week after starting allopurinol with eosinophilia [bilirubin 1.0 mg/dL, ALT 76 U/L] and responding to prednisone, but relapsing twice when

prednisone was stopped with fever, rash, eosinophilia and more severe liver abnormalities [bilirubin 1.9 mg/dL, ALT 1784 U/L]).

Khanlari B, Bodmer M, Terracciano L, Heim MH, Fluckiger U, Weisser M. Hepatitis with fibrin-ring granulomas. Infection 2008; 36: 381-3. PubMed PMID: 17926000.

(66 year old woman developed fever and jaundice 4 months after starting allopurinol [bilirubin 1.2 mg/dL, ALT 89 U/L, Alk P 236 U/L] and ring granulomas on liver biopsy; corticosteroids led to worsening and repeat biopsy showed Leishmania: Kala-azar).

Yoon JY, Min SY, Park JY, Hong SG, Park SJ, Paik SY, Park YM. [A case of allopurinol-induced granulomatous hepatitis with ductopenia and cholestasis] Korean J Hepatol 2008; 14: 97-101. PubMed PMID: 18367862.

(69 year old man with renal failure developed rash and fever 2 weeks after starting allopurinol, liver biopsy showing spotty necrosis, cholestasis, ductopenia and granulomas, recovery with corticosteroids: abstract only).

Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, Naldi L, et al; RegiSCAR study group. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics 2008; 18: 99-107. PubMed PMID: 18192896.

*(HLA-B genotyping of a cohort of patients with Stevens Johnson Syndrome [SJS] due to medications found an association of B*58:01 with SJS due to allopurinol in 4 non-Europeans [100%] as well as 27 Europeans [55%] compared to controls [1.5%] and a slight association of B*3801 with SJS due to lamotrigine [24%] and sulfonamides [28%] compared to controls [4.3%]).*

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 between 2004 and 2008, two were attributed to allopurinol).

Tausche AK, Aringer M, Schroeder HE, Bornstein SR, Wunderlich C, Wozel G. The Janus faces of allopurinol-allopurinol hypersensitivity syndrome. Am J Med 2008 ; 121: e3-4. PubMed PMID: 18328291.

(69 year old woman developed rash 3 months after starting allopurinol [bilirubin not given, ALT 10 fold elevated], resolving with corticosteroid therapy)

Eshki M, Allanore L, Musette P, Milpied B, Grange A, Guillaume JC, Chosidow O, et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. Arch Dermatol 2009; 145: 67-72. PubMed PMID: 19153346.

(Retrospective analysis of 15 patients with severe drug rash with eosinophilia and systemic symptoms [DRESS] syndrome from France; 2/3rds women, ages 15-71, onset average of 18 days, 4 due to allopurinol; severe manifestations including hepatitis [n=7], pneumonitis [10], renal failure [5], encephalitis [2], pancytopenia [2], heart failure [1]).

Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, Chucherd P, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics 2009; 19: 704-9. 19696695. PubMed PMID: 19696695.

*(Among 27 Thai patients with SJS/TEN due to allopurinol, all had HLA-B*58:01 compared to 7 of 54 [13%] allopurinol tolerant controls).*

Lindh J. [Hepatic adverse effects of allopurinol]. Lakartidningen 2009; 106: 2374-5. Swedish. PubMed PMID: 19848345.

(Commentary on response to ALT elevations occurring during allopurinol therapy mentions that the acute liver injury occurs in 0.2-0.4% of patients, typically in the first 2 months and with prominent immunoallergic features).

Gyotoku E, Iwamoto T, Ochi M. [A fatal case of drug-induced hypersensitivity syndrome due to allopurinol]. Arerugi 2009; 58: 560-6. Japanese. PubMed PMID: 19487838.

(83 year old woman developed fever and disseminated rash 1 month after starting allopurinol with progressive liver failure and death: abstract only).

Um SJ, Lee SK, Kim YH, Kim KH, Son CH, Roh MS, Lee MK. Clinical features of drug-induced hypersensitivity syndrome in 38 patients. J Investig Allergol Clin Immunol 2010; 20: 556-62. PubMed PMID: 21313995.

(Among 38 patients with DRESS seen at a single referral center in Korea over a 5 year period, 20 were women, ages 24 to 80 years, onset after 3 to 105 days, all had liver involvement; 8 due to carbamazepine, 4 phenytoin, 3 lamotrigine, 2 phenobarbital and 2 allopurinol; 1 death from liver failure).

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, one of which was attributed to allopurinol).

Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol 2010; 146: 1373-9. PubMed PMID: 20713773.

(Among 60 cases of DRESS syndrome seen at a referral center in Taiwan over a 10 year period, the most common causes were allopurinol [31%], phenytoin [18%] and dapsone [17%]; 80% had hepatic manifestations; mean onset of allopurinol cases was 27 days, which was longer than for phenytoin [14 days] and others [19 days]).

Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. BMC Med Genet 2011; 12: 118. PubMed PMID: 21906289.

*(Systematic review of evidence linking HLA-B*58:01 to allopurinol associated Stevens Johnson syndrome [SJS] and toxic epidermal necrosis [TEN], in 4 studies with matched controls, 54 of 55 cases [98%], but only 74 of 678 controls [11%] had the HLA allele whereas in 5 studies using population control, the allele frequency was 50 of 69 cases [72%] vs 171 of 3378 controls [5%]; the analysis combined European and Asian studies).*

Kang HR, Jee YK, Kim YS, Lee CH, Jung JW, Kim SH, Park HW, et al; Adverse Drug Reaction Research Group in Korea. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. Pharmacogenet Genomics 2011; 21: 303-7. PubMed PMID: 21301380.

*(Among 25 Korean patients with severe cutaneous adverse reactions to allopurinol, all except two [92%] had HLA-B*58:01 compared to 10.5% of 57 tolerant Korean patients).*

Génin E, Schumacher M, Roujeau JC, Naldi L, Liss Y, Kazma R, Sekula P, et al. Genome-wide association study of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Europe. Orphanet J Rare Di 2011; 6: 52. PubMed PMID: 21801394.

*(Genome wide association study on 424 cases of SJS/TEN from Europe identified 6 SNPs in the HLA region as being significant; best association being HLA-B*58:01 in 57 patients with allopurinol associated hypersensitivity).*

Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, Roujeau JC. The DRESS syndrome: a literature review. Am J Med 2011; 124: 588-97. PubMed PMID: 21592453.

(Systematic review of literature on DRESS identified 172 cases due to 44 drugs, most frequently carbamazepine [27%] and allopurinol [11%], similar sex distributioon, ages 0.5 to 80 years, onset after 0.5 to 16 weeks [mean=3.9], liver involvement 94%, eosinophilia 64%, mortality 5%).

Natkunarajah J, Goolamali S, Craythorne E, Benton E, Smith C, Morris-Jones R, Wendon J, et al. Ten cases of drug reaction with eosinophilia and systemic symptoms (DRESS) treated with pulsed intravenous methylprednisolone. Eur J Dermatol 2011; 21: 385-91. PubMed PMID: 21527371.

(Prospective study on use of methylprednisolone in 10 patients with DRESS, found rapid improvement in all but one who required a liver transplant).

Jung JW, Song WJ, Kim YS, Joo KW, Lee KW, Kim SH, Park HW, et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. Nephrol Dial Transplant 2011; 26: 3567-72. PubMed PMID: 21393610.

*(Among 448 Korean patients with chronic renal dysfunction treated with allopurinol, 16 [3.6%] had a cutaneous adverse reaction, including 2 with SJS, 7 with allopurinol hypersensitivity syndrome [AHS] and 2 with SJS; HLA-B*58:01 was found in all 9 patients with SJS or AHS but in none with rash only and in only 9.5% who were tolerant to allopurinol).*

Lee MH, Stocker SL, Anderson J, Phillips EJ, Nolan D, Williams KM, Graham GG, et al. Initiating allopurinol therapy: do we need to know the patient's human leucocyte antigen status? Intern Med J 2012; 42: 411-6. PubMed PMID: 21790926.

*(HLA-B*58:01 was present in all 4 Asian patients with SJS due to allopurinol, but in only 2 of 8 Caucasians with SJS/hypersensitivity syndrome and in 0 of 12 with rash alone due to allopurinol).*

Tan SK, Tay YK. Profile and pattern of Stevens-Johnson syndrome and toxic epidermal necrolysis in a general hospital in Singapore: treatment outcomes. Acta Derm Venereol 2012; 92: 62-6. PubMed PMID: 21710108.

(Among 28 cases of SJS/TEN seen at a single referral hospital in Singapore between 2004-2010, 26 were attributed to drugs, but only 2 were due to allopurinol).

Pirmohamed M. Genetics and the potential for predictive tests in adverse drug reactions. Chem Immunol Allergy 2012; 97: 18-31. PubMed PMID: 22613851.

(Brief review of the association of HLA alleles with cutaneous adverse events, focusing upon skin reactions to allopurinol, carbamazepine and abacavir and hepatotoxicity associated with flucloxacillin, lumiracoxib, lapatanib and ximelegatran).

Yun J, Adam J, Yerly D, Pichler WJ. Human leukocyte antigens (HLA) associated drug hypersensitivity: consequences of drug binding to HLA. Allergy 2012; 67: 1338-46. PubMed PMID: 22943588.

(Review of current understanding of the pathogeneis of the assocation of specific HLA alleles with drug induced hypersensitivity reactions, focusing upon abacavir, carbamazepine and allopurinol).

Biagioni E, Busani S, Rinaldi L, Marietta M, Girardis M. Acute renal failure and liver necrosis associated to allopurinol therapy. Anaesth Intensive Care 2012; 40: 190-1. PubMed PMID: 22313089.

Botelho LF, Higashi VS, Padilha MH, Enokihara MM, Porro AM. DRESS: clinicopathological features of 10 cases from an University Hospital in São Paulo. An Bras Dermatol 2012; 87: 703-7. PubMed PMID: 23044561.

(Among 10 patients with DRESS syndrome seen at a referral hospital in Brazil between 2005-2011, ages were 20-66 years, 6 were in men, and onset occurred within 2-6 weeks of starting phenytoin in 4, allopurinol in 2, or carbamazepine, diclofenac, or both in 1 each; 2 died of acute liver failure).

Yaylacı S, Demir MV, Temiz T, Tamer A, Uslan MI. Allopurinol-induced DRESS syndrome. Indian J Pharmacol 2012; 44: 412-4. PubMed PMID: 22701258.

(70 year old Turkish man with hypertension and renal disease developed fever, rash and jaundice 3 months after starting allopurinol [bilirubin 18.9 mg/dL, ALT 429 U/L, Alk P 773 U/L, INR 1.4], with progressive renal and liver failure and death within 24 days of onset).

Cao ZH, Wei ZY, Zhu QY, Zhang JY, Yang L, Qin SY, Shao LY, et al. HLA-B*58:01 allele is associated with augmented risk for both mild and severe cutaneous adverse reactions induced by allopurinol in Han Chinese. Pharmacogenomics 2012; 13: 1193-201. PubMed PMID: 22909208.

*(Among 38 Chinese patients with severe cutaneous reactions from allopurinol, all had HLA-B*58:01 [5 were homozygous] compared to 11% of matched controls [none of whom were homozygous] and 14% of population controls).*

Stamp LK, Taylor WJ, Jones PB, Dockerty JL, Drake J, Frampton C, Dalbeth N. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis Rheum 2012; 64: 2529-36. PubMed PMID: 22488501.

(Among 54 cases of allopurinol hypersensitivity syndrome identified over a 12 year period in New Zealand, 56% were men, ages 24 to 87 years, mean onset in 30 days, 3 were fatal [6%]; compared to controls, cases were more likely to start at a higher dose when corrected for creatinine).

Chiu ML, Hu M, Ng MH, Yeung CK, Chan JC, Chang MM, Cheng SH, Li L, Tomlinson B. Association between HLA-B*58:01 allele and severe cutaneous adverse reactions with allopurinol in Han Chinese in Hong Kong. Br J Dermatol 2012; 167: 44-9. PubMed PMID: 22348415.

*(Among 20 Chinese patients from Hong Kong with severe cutaneous reactions to allopurinol, 19 [95%] had HLA B*58:01 compared to 13% of 30 allopurinol tolerant controls).*

Maekawa K, Nishikawa J, Kaniwa N, Sugiyama E, Koizumi T, Kurose K, Tohkin M, Saito Y. Development of a rapid and inexpensive assay for detecting a surrogate genetic polymorphism of HLA-B*58:01: a partially predictive but useful biomarker for allopurinol-related Stevens-Johnson syndrome/toxic epidermal necrolysis in Japanese. Drug Metab Pharmacokinet 2012; 27: 447-50. PubMed PMID: 22277675.

*(Description of a polymerase chain reaction based assay specifically designed to detect HLA-B*58:01 polymorphisms).*

Profaizer T, Eckels D. HLA alleles and drug hypersensitivity reactions. Int J Immunogenet 2012; 39: 99-105. PubMed PMID: 22136512.

(Review of the HLA associations of drug hypersensitivity reactions to abacavir, allopurinol and carbamazepine).

Bharadwaj M, Illing P, Theodossis A, Purcell AW, Rossjohn J, McCluskey J. Drug hypersensitivity and human leukocyte antigens of the major histocompatibility complex. Annu Rev Pharmacol Toxicol 2012; 52: 401-31. PubMed PMID: 22017685.

*(Review of the molecular pathogenesis of T cell mediated hypersensitivity reactions to small molecule drugs, focusing upon class I HLA B*57:01 associations with abacavir and flucloxacillin], B*58:01 with allopurinol, and B*15:02 with carbamazepine and possibly phenytoin; and type II HLA associations with lapatinib and ximelagantran).*

Wongkitisophon P, Chanprapaph K, Rattanakaemakorn P, Vachiramon V. Six-year retrospective review of drug reaction with eosinophilia and systemic symptoms. Acta Derm Venereol 2012; 92: 200-5. PubMed PMID: 22002792.

(Among 27 patients with DRESS syndrome seen at a single center in Thailand, 14 were men and ages ranged from 23 to 81 years; 96% of cases had hepatic manifestations, 70% eosinophilia, 19% atypical lymphocytosis; common causes were phenytoin [33%] allopurinol [15%], nevirapine [15%]; liver injury resolved in 20-65 days except in 1 patient who died [4%]).

Bollaert M, Jeulin H, Waton J, Gastin I, Tréchot P, Rabaud C, Schmutz JL, Barbaud A. [Six cases of spring DRESS]. Ann Dermatol Venereol 2012; 139: 15-22. PubMed PMID: 22225738.

(Six cases of DRESS syndrome presented at a single hospital during a one month period, suggesting an epidemic, although each case was due to a different drug [allopurinol, carbamazepine, amoxicillin, TMP/SMZ, and others], and all had evidence of reactivation or primary infection with a herpes virus).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, Presentation and Outcomes in Patients with Drug-Induced Liver Injury in the General Population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none were attributed to allopurinol).

Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, Sidoroff A, et al; The RegiSCAR study group. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013; 169: 1071-80. PubMed PMID: 23855313.

(Among 117 cases of DRESS enrolled in a European prospective database over a 6 year period, 18% were due to allopurinol, 75% had liver involvement and only 2 died [2%]).

Paisansinsup T, Breitenstein MK, Schousboe JT. Association between adverse reactions to allopurinol and exposures to high maintenance doses: implications for management of patients using allopurinol. J Clin Rheumatol 2013; 19: 180-6. PubMed PMID: 23669799.

(Analysis of electronic medical records of a multispecialty group practice between 2004-2011 identified 2946 patients who were treated with allopurinol and had a serum creatinine level; 48 [2%] had an adverse drug reaction [mostly rash] and 2 had SJS; no association was found between these reactions and allopurinol dose even after adjustment for renal function).

Kwok J, Kwong KM. Detection of HLA-B*58:01, the susceptible allele for allopurinol-induced hypersensitivity, by loop-mediated isothermal amplification. Br J Dermatol 2013; 168: 526-32. PubMed PMID: 23066948.

*(Description of development of a loop mediated isothermal amplication method for identifying DNA of HLA-B*58:01).*

Ramasamy SN, Korb-Wells CS, Kannangara DR, Smith MW, Wang N, Roberts DM, Graham GG, Williams KM, Day RO. Allopurinol Hypersensitivity: A Systematic Review of All Published Cases, 1950-2012. Drug Saf 2013; 36: 954-80. PubMed PMID: 23873481.

*(Systematic review of literature on allopurinol hypersensitivity syndrome identified 901 patients in 320 publications, including 58% men, 73% Asians, median onset in 3 weeks, mortality rate 14%; among those with liver involvement, mean bilirubin 6.4 mg/dL, ALT 358 U/L, Alk P 518 U/L; 166 of 167 Asian patients tested were HLA-B*58:01 positive).*

Kwok J, Kwong KM. Detection of HLA-B*58:01, the susceptible allele for allopurinol-induced hypersensitivity, by loop-mediated isothermal amplification. Br J Dermatol 2013; 168: 526-32. PubMed PMID: 23066948.

*(Description of a loop mediated isothermal amplication method for identifying DNA of HLA-B*58:01 that can be used clinically and is faster and easier than standard genotyping methods).*

Kim SC, Newcomb C, Margolis D, Roy J, Hennessy S. Severe cutaneous reactions requiring hospitalization in allopurinol initiators: a population-based cohort study. Arthritis Care Res (Hoboken) 2013; 65: 578-84. PubMed PMID: 22899369.

(Using electronic records of 5 large Medicaid programs of appoximately 13 million enrollees, 90,358 patients were started on allopurinol and were followed, among whom 45 were subsequently hospitalized for a severe cutaneous reaction [0.69 per 1000 patient years] and 12 died; rates that were far higher than in non-allopurinol users [0.04 per 1000 patient years).

Ryu HJ, Song R, Kim HW, Kim JH, Lee EY, Lee YJ, Song YW, Lee EB. Clinical risk factors for adverse events in allopurinol users. J Clin Pharmacol 2013; 53: 211-6. PubMed PMID: 23436266.

(Case control study of 94 patients with adverse event [rash, GI upset, hypersensitivity syndrome, severe, neuropathy] due to allopurinol and 378 tolerant controls found risk factors to be renal disease and use of colchicine or statins).

Lee MH, Stocker SL, Williams KM, Day RO. HLA-B*5801 should be used to screen for risk of Stevens-Johnson syndrome in family members of Han Chinese patients commencing allopurinol therapy. J Rheumatol 2013; 40: 96-7. PubMed PMID: 23280169.

*(Letter describing Chinese man who developed SJS after allopurinol exposure and tested positive for HLA-B*58:01 who had a brother who tolerated allopurinol, but was B*58:01 negative).*

Walsh S, Diaz-Cano S, Higgins E, Morris-Jones R, Bashir S, Bernal W, Creamer D. Drug reaction with eosinophilia and systemic symptoms: is cutaneous phenotype a prognostic marker for outcome? A review of clinicopathological features of 27 cases. Br J Dermatol 2013; 168: 391-401. PubMed PMID: 23034060.

(Among 27 patients with DRESS presenting at a single UK referral center over a 6 year period, 2 [7%] were due to allpurinol, 6 phenytoin, 5 carbamazepine; the mortality rate was 11% and severe cases were more likely to have erythema multiforme like lesions by histology).

Choi HG, Byun J, Moon CH, Yoon JH, Yang KY, Park SC, Han CJ. Allopurinol-induced DRESS syndrome mimicking biliary obstruction. Clin Mol Hepatol 2014; 20: 71-5. PubMed PMID: 24757661.

(84 year old man developed fever, rash and jaundice 2 months after starting allopurinol [bilirubin 6.6 rising to 27.1 mg/dL, ALT 343 U/L, Alk P 210 U/L, eosinophils 14%], with progressive worsening and sudden death from a myocardial infarction).

Sultan SJ, Sameem F, Ashraf M. Drug reaction with eosinophilia and systemic symptoms: manifestations, treatment, and outcome in 17 patients. Int J Dermatol 2015; 54 (5): 537-42. PubMed PMID: 24738653.

(Among 17 patients with DRESS syndrome seen at a single medical center in India over a 4 year period, causes were anticonvulsants [65%], dapsone, vancomycin, leflunomide, nitrofurantoin and allopurinol).

Daly AK. Human leukocyte antigen (HLA) pharmacogenomic tests: potential and pitfalls. Curr Drug Metab 2014; 15: 196-201. PubMed PMID: 24694233.

(Discussion of the shortcomings of use of HLA associations in clinical decisions to use drugs associated with severe hypersensitivity reactions including allopurinol).

Karlin E, Phillips E. Genotyping for severe drug hypersensitivity. Curr Allergy Asthma Rep 2014; 14: 418. PubMed PMID: 24429903.

*(Review of the genetic associations and potential clinical applications of genotyping to prevent serious drug adverse reactions, including testing for HLA-B*58:01 to assess the risk of SJS from allopurinol, particularly in Asian populations).*

Thankachen J, Agarwal V. Challenges in diagnosis, management, and treatment of allopurinol-induced DRESS syndrome: case report and literature review. Am J Ther 2015; 22 (3): e77-83. PubMed PMID: 24451301.

(62 year old African American woman developed fever, rash and confusion 3 weeks after a 2 day course of allopurinol [bilirubin not given, ALT 116 U/L, Alk P 198 U/L, eosinophils 16%], rash considered typical of DRESS, responding to corticosteroids, and resolving within 3 months of onset).

Nam YH, Park MR, Nam HJ, Lee SK, Kim KH, Roh MS, Um SJ, Son CH. Drug reaction with eosinophilia and systemic symptoms syndrome is not uncommon and shows better clinical outcome than generally recognised. Allergol Immunopathol (Madr) 2015; 43 (1):19-24. PubMed PMID: 24388810.

(Among 45 patients with DRESS seen over a 2 year period at a single Korean referral center, all had fever, rash and eosinophilia, 87% had liver involvement and 1 died of liver failure and 1 of sepsis; common causes included cephalosporins [29%], penicillins [9%], anticonvulsants [27%], NSAIDs [9%] and allopurinol [7%]).

Yang MS, Kang MG, Jung JW, Song WJ, Kang HR, Cho SH, Min KU. Clinical features and prognostic factors in severe cutaneous drug reactions. Int Arch Allergy Immunol 2013; 162: 346-54. PubMed PMID: 24193402.

(Allopurinol accounted for 17% of 41 cases of SJS/TEN and 31% of cases of DRESS syndrome; ALT elevations occurred in 46% of SJS/TEN and 75% of DRESS cases).

Lee T, Lee YS, Yoon SY, Kim S, Bae YJ, Kwon HS, Cho YS, et al. Characteristics of liver injury in drug-induced systemic hypersensitivity reactions. J Am Acad Dermatol 2013; 69: 407-15. PubMed PMID: 23632341.

(Among 136 Korean patients with drug hypersensitivity reactions, 61 had liver dysfunction, 29 with DRESS and 11 with SJS/TEN, and allopurinol was the most common cause in SJS/TEN cases).

Gonçalo M, Coutinho I, Teixeira V, Gameiro AR, Brites MM, Nunes R, Martinho A. HLA-B*58:01 is a risk factor for allopurinol-induced DRESS and Stevens-Johnson syndrome/toxic epidermal necrolysis in a Portuguese population. Br J Dermatol 2013; 169: 660-5. PubMed PMID: 23600531.

*(Among 6 Portuguese patients with SJS/TEN and 19 with DRESS due to allopurinol, HLA-B*58:01 was present in 16 [64%] compared to 4% of 28 allopurinol tolerant persons and 2% of normal controls; rates similar to those reported in other European populations).*

Fernando SL. Drug-reaction eosinophilia and systemic symptoms and drug-induced hypersensitivity syndrome. Australas J Dermatol 2014; 55: 15-23. PubMed PMID: 23866082.

(Review of the definition, epidemiology, causes, clinical features, pathology, pathogenesis and management of DRESS syndrome; allopurinol being the second most common cause).

Limpawattana P, Choonhakarn C, Kongbunkiat K. Clinical profiles of Stevens-Johnson syndrome among Thai patients. J Dermatol 2014 May 10. [Epub ahead of print] PubMed PMID: 24815085.

(Among 45 patients with SJS seen at a single referral center in Thailand over a 10 year period, liver injury occurred in 67%, but was usually mild and allopurinol accounted for 13% of cases, including 6 of 13 cases in patients over the age of 65).

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 allopurinol).

Miederer SE, Miederer KO. [Allopurinol hypersensitivity syndrome: Liver transplantation after treatment of asymptomatic hyperuricaemia]. Dtsch Med Wochenschr 2014; 139: 2537-40. PubMed PMID: 25423467.

(41 year old man developed fever, rash and liver test abnormalities 1 month after starting allopurinol [bilirubin rising to 54 mg/dL, ALT 548 U/L, Alk P 1268 U/L], and undergoing successful liver transplantation).

Jung JW, Kim DK, Park HW, Oh KH, Joo KW, Kim YS, Ahn C, Leet al. An effective strategy to prevent allopurinol-induced hypersensitivity by HLA typing. Genet Med 2015; 17: 807-14. PubMed PMID: 25634024.

*(Among 401 Korean patients with renal disease planning to start allopurinol, 46 had HLA-B*58:01 and received a tolerance induction protocol [n=30] or another medication [n=16], and none developed serious cutaneous reactions, nor did any of the 355 who tested negative for this HLA allele).*

Ko TM, Tsai CY, Chen SY, Chen KS, Yu KH, Chu CS, Huang CM, et al; Taiwan Allopurinol-SCAR Consortium. Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study. BMJ 2015; 351: h4848. PubMed PMID: 26399967.

*(Among 2926 Taiwanese patients planning to start allopurinol, 571 had HLA-B*58:01 and were advised not to take it, of whom none developed rash; among the 2173 without this HLA allele who took allopurinol, 97 [3%] had mild rash, but none had a severe cutaneous reaction).*

Yip VL, Alfirevic A, Pirmohamed M. Genetics of immune-mediated adverse drug reactions: a comprehensive and clinical review. Clin Rev Allergy Immunol 2015; 48: 165-75. PubMed PMID: 24777842.

*(Review of the genetics of immune mediated drug reactions focusing upon skin injury from abacavir [HLA-B*57:01], carbamazepine [B*15:02, A*31:01], and allopurinol [B*58:01] and hepatotoxicity from amoxicillin/clavulanate [several], flucloxacillin [B*57:01], ximelagatran, lumiracoxib, lapatinib, ticlopidine and nevirapine).*

Imai H, Kamei H, Onishi Y, Yamada K, Ishizu Y, Ishigami M, Goto H, Ogura Y. Successful living-donor lLiver transplantation for cholestatic liver failure induced by allopurinol: case report. Transplant Proc 2015; 47: 2778-81. PubMed PMID: 26680093.

(39 year old man developed severe cholestatic liver injury 2 months after starting allopurinol for hyperuricemia [bilirubin rising to 60.9 mg/dL, INR 3.5], undergoing successful living donor liver transplantation 4 months later).

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, 7 cases [0.9%] were attributed to allopurinol, 3 of which were severe and one fatal).