Role of Allopurinol in Optimizing Thiopurine Therapy in Patients with Autoimmune Hepatitis: A Review

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Autoimmune hepatitis (AIH) is a chronic immune mediated liver disease characterized by elevated transaminases, hyper gammaglobulinemia, presence of autoantibodies and interface hepatitis in the absence of a known etiology of liver disease. Thiopurines (azathioprine [AZA]/6-mercaptopurine [6MP]) and steroids remain the first line of treatment of AIH in both children and adults. However, a small proportion of AIH patients are either non-responders or develop side effects with AZA. The metabolism of AZA is complex and mediated by multiple enzymes. After absorption and getting converted to 6MP, it is converted to 6-thiouric acid, 6-methyl mercaptopurine (6MMP) and 6-thioguanine (6TG) by different enzymes. Elevated 6MMP levels are associated with hepatotoxicity and also poor efficacy due to simultaneous lower levels of 6TG, which is the active drug metabolite related to both efficacy and myelosuppression. Allopurinol, a xanthine oxidase inhibitor shifts the metabolism of AZA away from 6MMP toward 6TG. This combination of allopurinol with reduced dose of AZA is an alternative to more expensive and toxic second line therapy to induce remission in patients with AIH. This article discusses the mechanism of action of allopurinol in inducing response to AZA, reviews the published literature on this combination therapy and gives guidelines on the use of allopurinol in patients with AIH. (J CLIN EXP HEPATOL 2017;7:55–62)

Autoimmune hepatitis (AIH) is a chronic immune mediated liver disease characterized by elevated transaminases, hyper gammaglobulinemia (IgG), presence of autoantibodies and typical liver histology (interface hepatitis, portal lymphoplasmacytic infiltrate, rosette formation and emperipolesis) in the absence of a known etiology of liver disease.¹ The disease affects all age groups with a prevalence of 16–18 per 100,000 persons in adults in Europe to 42.9 per 100,000 persons in Alaskan Natives.¹ There is a marked heterogeneity in presentation from asymptomatic elevation of transaminases to acute liver failure to cirrhosis.^{2–4} AIH is classified into two types,

based on the type of antibodies: Type 1 (antinuclear antibody [ANA] and/or anti-smooth muscle antibody [SMA]) and type 2 (anti-liver kidney microsomal [LKM 1] and/or anti-liver cytosol 1 [anti-LC1] antibody).^{1,4} Type I AIH is more common and seen predominantly in adults while type II AIH is more frequently seen in young children. The diagnosis of AIH is based on the revised or simplified diagnostic criteria, with the revised diagnostic criteria being more suited for patients with atypical features.^{5,6} In adults, nearly 75–80% patients present with chronic liver disease and a third have cirrhosis.⁷ “Overlap syndrome” is used to define AIH patients who have features of both AIH and primary biliary cirrhosis (AIH-PBC) or primary sclerosing cholangitis (AIH-PSC).³

Immunosuppression with prednisone alone [60 mg day] or a lower dose of prednisone [30 mg day] along with azathioprine (AZA, 50 mg/day or 1–2 mg/kg body weight/day), is the first line of therapy in AIH with the aim of inducing remission, i.e. normal levels of transaminases, IgG and gamma globulin and absence of inflammation on liver histology.⁴ In children, prednisone is given at a dose of 1–2 mg/kg/day (max of 60 mg day) and AZA at 1–2 mg/kg/day or 6-mercaptopurine (6MP) at 1.5 mg/kg/day.⁴ Both the induction regimens of prednisone alone vs. prednisone and AZA have been shown to be equally effective in a systematic review of randomized controlled trials.⁸ Recently a combination of budesonide and AZA has been shown to be equally effective in inducing remission with less of steroid side effects in non-cirrhotic adults with

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Abbreviations: ANA: antinuclear antibody; AIH: autoimmune hepatitis; AZA: azathioprine; HGPRT: hypoxanthine guanine phosphoribosyl transferase; IgG: immunoglobulin G; IBD: inflammatory bowel disease; LC: liver cytosol; LKM: liver kidney microsomal; 6MP: 6-mercaptopurine; 6MMP: 6-methyl mercaptopurine; 6-MTIMP: 6-methyl thioinosine monophosphate; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; SMA: smooth muscle antibody; 6TG: 6-thioguanine; TIMP: thioinosine monophosphate; TPMT: thiopurine methyltransferase; XO: xanthine oxidase

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AIH.⁹ For maintenance therapy, both prednisone and AZA and AZA alone are similar and superior to prednisone monotherapy.⁸ In AIH patients presenting as ALF, steroid monotherapy with strict monitoring and early consideration for liver transplantation in non-responders is recommended.¹⁰ For patients with overlap syndrome of AIH-PSC or AIH-PBC a combination therapy of immunosuppression with urso deoxy cholic acid (UDCA) is recommended.^{1,11}

AZA and 6MP are well tolerated in majority, with few adverse effects including nausea, vomiting, rash, arthralgia, fever, pancreatitis, hepatotoxicity and/or cytopenia which require dose modification or discontinuation. There is no established second line therapy for AIH patients who fail, i. e. intolerant or non-responsive to AZA therapy due to lack of randomized controlled trials. The choice of second line therapy is largely empiric and options include mycophenolate mofetil (MMF), calcineurin inhibitors (tacrolimus and cyclosporine), rituximab, infliximab, sirolimus and everolimus.¹ However, the experience is limited and in addition these drugs are costly, have serious side effects and need monitoring of drug levels. Thus, there is a need to use strategies to improve the efficacy of AZA in these cases before proceeding to the second line therapy.

MECHANISM OF ACTION OF THIOPURINES

AZA is a thiopurine analogue prodrug of 6MP and it works by antagonizing endogenous purines and thus interfering with DNA synthesis.¹²⁻¹⁴ It has an anti-proliferative effect on T cells. One of the hypotheses explaining its anti-inflammatory effect is that a metabolite of AZA, 6-thioguanine (6TG) accumulates in lymphocytes and blocks expression of cytokines which mediate inflammation.^{12,15}

The metabolism of AZA is complex and involves many enzymatic pathways¹⁴ (Figure 1a). After getting absorbed from the gastrointestinal tract, ~85-90% of AZA is non-enzymatically converted to 6MP.^{14,15} Thereafter, 6MP is either converted to 6-thiouric acid by xanthine oxidase (XO) or to 6-methyl mercaptopurine (6MMP) after methylation by thiopurine methyltransferase (TPMT) or into thioinosine monophosphate (TIMP) by hypoxanthine guanine phosphoribosyl transferase (HGPRT). TIMP is then converted to 6TG. 6MMP is associated with hepatotoxicity while 6TG is associated with both therapeutic effect as well as the serious side effect of myelosuppression.^{14,15}

TPMT is the rate limiting enzyme in the metabolism of AZA. 6MP is targeted competitively by XO, TPMT and HGPRT enzymes. TPMT also metabolizes TIMP to 6-methyl thioinosine monophosphate (6MTIMP), an inactive metabolite. There is wide variation in the activity of TPMT among individuals due to genetic polymorphism to the tune of 50-fold variation.^{14,15} Low activity of TPMT enzyme results in a greater conversion of 6MP to 6TG via HGPRT pathway which results in greater efficacy as well as

myelotoxicity.¹² In comparison, high TPMT enzyme activity results in increased production of 6MMP and less production of 6TG which results in increased hepatotoxicity with lower efficacy.

Estimation of AZA metabolites (6MMP and 6TG) has been shown to be helpful in management of patients with inflammatory bowel disease (IBD). A 6TG level of >230 pmol/8 × 10⁸ RBC is supposed to be associated with clinical efficacy of AZA.¹⁵ Thus, if there is no response even with a 6TG level of >400 pmol/8 × 10⁸ RBC, the patient is labeled as refractory to AZA and will not respond to further escalation of the dose. The optimal levels of 6TG have not been extensively evaluated in patients with AIH, but a 6TG value of >220 pmol/8 × 10⁸ RBC was associated with clinical response with a sensitivity of 83% and specificity of 62%.¹⁶ If both 6TG and 6MMP are low, it is likely that patient is not ingesting the drug and so compliance needs to be addressed. Higher 6MMP levels (>5700 pmol/8 × 10⁸ RBC) are associated with hepatotoxicity with raised transaminases and also with therapeutic failure largely due to concomitant lower levels of biologically active 6TG.¹⁷ In adult IBD patients, 4.6-10% cases were shown to develop thiopurine related hepatotoxicity.^{18,19} Hepatotoxicity however, is not seen in all patients with high levels of 6MMP. This hepatotoxicity due to high 6MMP is especially problematic in AIH patients as raised transaminases can also be attributed to non-response or relapse of the disease. Similarly, high levels of 6TG are associated with increased myelotoxicity but again it is not seen consistently in all patients. Thus regular monitoring of hemogram and liver function tests is essential in all patients on TP therapy to detect liver and bone marrow toxicity.¹⁵

ROLE OF ALLOPURINOL IN OPTIMIZING THIOPURINE THERAPY IN PATIENTS WITH AUTOIMMUNE HEPATITIS

Some patients with failure to therapy have an increased conversion of AZA to 6MMP rather than 6TG, despite genetically determined normal TPMT activity which can be confirmed only by measurement of metabolites (ratio of 6MMP:6TG ≥ 15).²⁰ In adult and pediatric patients with IBD, use of allopurinol, along with lower dose of thiopurines (AZA or 6MP), has been shown to be of benefit in non-responders and patients with hepatotoxicity by achieving higher 6TG and lower 6MMP levels.²¹⁻²³ The exact mechanism of action of allopurinol is still not clear. Allopurinol blocks XO, acts as a “shunter” which inhibits conversion of 6MP to inactive 6-thiouric acid and most of 6MP is then shunted down the 6TG pathway²² (Figure 1b). Some evidence suggests that allopurinol gets converted to oxypurinol by aldehyde oxidase which then gets converted to oxypurinol riboside monophosphate which is a competitive inhibitor of TPMT.²⁴ Recently Blaker et al. suggested that allopurinol mediated increase in thioxanthine levels

6-MP: 6-Mercaptopurine; 6-MMP: 6-Methyl Mercaptopurine; HGPRT: Hypoxanthine-guanine-phosphoribosyl-transferase; 6-TG: 6-Thioguanine; 6-TIMP: thio inosine mono phosphate; 6-MTIMP: 6-methyl Thioinosine monophosphate; IMPDH: Inosine mono phosphate dehydrogenase; GMPS: guanosine mono-phosphatase synthetase; TPMT: Thiopurine S-methyltransferase; 6-TU: 6- Thiouric acid; XO: Xanthine oxidase

Figure 1 Metabolism of thiopurines (azathioprine/6-mercaptopurine). (A) Normal scenario and (B) after adding allopurinol.

also inhibit the TPMT enzyme activity.²⁵ An unidentified cofactor is also thought to play a role in shunting of thiopurine metabolism from 6MMP pathway to 6TG pathway by allopurinol.²²

ALLOPURINOL COMBINATION THERAPY AND AUTOIMMUNE HEPATITIS: REVIEW OF LITERATURE

There is a growing interest in combination therapy of allopurinol and AZA in patients with AIH.²⁶ A detailed search of Pubmed, COCHRANE, EMBASE, GOOGLE Scholar databases was done by 2 independent reviewers to identify all the published literature on use of

combination therapy of allopurinol and AZA/6MP in adult as well as pediatric patients with AIH and/or overlap syndrome.

Four articles and two letters to editor evaluating allopurinol and thiopurine combination therapy in AIH were identified.²⁶⁻³⁰ A total of 14 patients (13 with AIH and one with autoimmune pancreatitis) on thiopurine/allopurinol treatment were included in the detailed analysis. Thirteen AIH patients were started electively on combination therapy due to refractory disease or toxicity. One patient was a 55 years woman with autoimmune pancreatitis who failed to form active metabolites despite adequate dose of thiopurines (AZA followed by 6MP).²⁸ She responded to addition of allopurinol and went on to form toxic levels of

thiopurine metabolites which resolved on stopping allopurinol.

The age of the AIH patients ranged from 3 to 65 years with 69.2% being females (9/13). Majority were type 1 AIH, however details of type were not available in the largest case series.²⁰ Five (5/13, 38.5%) patients had overlap syndrome (4 with AIH-PSC [3 children, 1 adult] and one adult with AIH-PBC). Patient details including indication for use of combination therapy is shown in Table 1. All received standard steroid dose for induction. Eight patients had received AZA while five were treated with 6MP before allopurinol combination therapy. Major indication for co-prescription was non-response with elevated transaminases in all 3 children and 4/10 adult patients, i.e. 54% (7/13) cases. Three cases had loss of previously attained response on tapering/stoppage of steroids while 3 cases had thiopurine intolerance with nausea, vomiting, arthralgia and headache. Allopurinol was added in a dose of 100 mg/day in all adult cases and 25–50 mg/day in children (age 3–10 years). Concomitantly, the dose of AZA/6MP was reduced to 25–50% of the original dose. All patients went into remission and the side effects while on AZA disappeared on combination therapy. The time taken for normalization of transaminases ranged from 1 to 6 months. In follow-up, 12/13 (92.3%) patients continued to be in remission, with ~50% (6/13) having sustained remission of >1 year. (Table 1) Overall the combination therapy was well tolerated in all but two patients (2/13, 15%). The adverse reaction reported were reversible neuropathy and myelosuppression manifesting as uncomplicated mild pancytopenia in one case each.²⁰ The patient with neuropathy was a known case of multiple sclerosis who presented with myalgia and numbness, after 4 months of combination therapy. She was shifted back to her previous therapy with 6MP and subsequently neuropathy improved. Authors were unsure of the culprit (multiple sclerosis disease activity vs. allopurinol) as neuropathy is a rare side effect of chronic allopurinol use.³¹ The second patient who developed mild pancytopenia (Hb-7.1 mmol/L, TLC $2.9 \times 10^9/L$, platelets $145 \times 10^9/L$) was also on hydroxychloroquine for associated Sjogren's syndrome. The blood counts remained stable, patient was continued on combination therapy and did well over a follow-up of 15 months.

CHANGES IN THIOPURINE METABOLITE LEVELS

All the subjects who were put on combination therapy due to hepatotoxicity had high transaminases and prior documented sub-therapeutic 6TG levels with elevated 6MMP levels indicating preferential shunting of AZA/6MP toward 6MMP pathway. In the series of 8 adult patients on combination therapy, all patients had documented decrease in

6MMP levels (from pretreatment median value of 6090 pmol/ 8×10^8 RBC to 175 pmol/ 8×10^8 RBC at 3 months; $P = 0.01$) and increase in 6TG levels (from pretreatment median value of 100 pmol/ 8×10^8 RBC to 200 pmol/ 8×10^8 RBC at 3 months; $P = 0.04$) after combination therapy in comparison to baseline value.²⁰ The median 6MMP:6TG ratio decreased significantly from a pre-treatment value of 55.7 (18–122) to 1.3 (0–2; $P = 0.01$) after combination therapy in these 8 cases.²⁰ This signifies the importance of monitoring serum metabolite levels in these patients to guide therapy.

DISCUSSION

Combination therapy of thiopurines with allopurinol has proven to be effective in IBD patients.^{21–22} Reviewed literature in patients with autoimmune liver disease also suggests that this approach is beneficial and safe. Although the studies are few with only 13 patients reported so far, they have shown that addition of allopurinol along with reduction in dose of thiopurines in cases with high 6MMP levels, hepatotoxicity and/or inadequate response is beneficial. It has been shown to correct the thiopurine induced hepatotoxicity and lead to normalization of transaminases. The combination therapy was well tolerated in the majority. The utility of this approach is that it allows patients to reduce/discontinue steroids and also avoid the use of second line therapy.

When prescribing the combination therapy, three things should always be kept in mind. First the side effects and drug interaction of allopurinol should be monitored. Second the dose of azathiopurine should be reduced to 25–33% of baseline in order to avoid the serious side effect of pancytopenia secondary to very high level of 6TG. Third, at present the combination therapy should be given only with monitoring of drug metabolites and demonstration of raised 6MMP along with low-normal 6TG levels.

Allopurinol is usually well tolerated, the adverse effects include fever, malaise, myalgia, leukopenia, raised transaminases, neuropathy and dermatologic manifestations ranging from maculopapular rash to drug reaction with eosinophilia and systemic symptoms (DRESS) to allopurinol hypersensitivity syndrome (AHS).^{32,33} The dose of allopurinol needs to be reduced in patients with renal failure which is not uncommon in adults with chronic liver disease.³⁴ Detailed drug history also needs to be noted as interactions with allopurinol are also known (angiotensin converting enzyme inhibitors, amoxicillin, anticoagulants, theophylline, cyclosporine, cyclophosphamide, etc.).³⁵ The metabolite monitoring can also help in guiding therapy by identifying non-compliant patients, i.e. low levels of both 6TG as well as 6MMP. Strict and regular monitoring of hemogram and liver function tests is essential in patients on combination therapy. Figure 2 gives a

Table 1 Patient Characteristics and Outcome of Allopurinol–Thiopurine Combination Therapy.

Author, year, reference	Dunken et al., 2010, 26			Al-Shama et al., 2013, 27	Al-Shama et al., 2013, 29	De Boirs et al., 2013, 20							
Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (years)	8	10	3	62	NA	66	66	60	58	61	53	40	25
Gender	F	M	F	F	NA	F	F	M	M	F	F	F	M
Diagnosis	AIH-1 + PSC	AIH-1 + PSC	AIH-1 + PSC	AIH 1	AIH	AIH + PSC	AIH	AIH	AIH	AIH + PBC	AIH	AIH	AIH
Thiopurine used/daily dose	AZA/ 1.5 mg/kg	6MP/ 2 mg/kg	AZA/ 4 mg/kg	AZA/ 150 mg	AZA/NA	AZA/ 50 mg	6MP/ 50 mg	6MP/ 38 mg	AZA/ 150 mg	6MP/ 50 mg	AZA/ 100 mg	AZA/150 mg	6MP/ 150 mg
Duration of therapy (months)	3	6	2	2	>3	13	3	21	2	18	2	2	21
ALT (U/L)	108	285	173	147	60–90	Median 62 (range 26–111)							
6TG levels (pmol/8 × 10 ⁸ RBC)	121	123	158	100	257	Median 100 (range 50–185) Lower in 3 intolerant patients (median 92) vs. In 5 non/loss to response group (median 139)							
6MMP levels (pmol/8 × 10 ⁸ RBC)	6179	5605	7341	5800	8941	Median 6090 (range 1700–9000) Lower in 3 intolerant patients (median 1860) vs. In 5 non/loss to response group (median 7430)							
Reason for combination therapy*	2	2	2	1	2	3	3	3	2	1	2	2	1
Allopurinol dose (mg/day)	25	50	50	100	NA	100	100	100	100	100	100	100	100
Thiopurine dose reduction (by %)	66	66	75	75	NA	AZA median dose 25 (range 25–50 mg/day); 6MP 25 mg/day in all 4 cases, i.e. a dose reduction of 50–80%, i.e. to 20–50% of the pre combination therapy dose							
Time to remission (months)	3	4	4	1	Rapid	1–3							
ALT after remission (U/L)	55	29–33	42	10–15	NA	Median 35 (range 28–48) at 3 months and 29 (range 19–112) at 6 months							
Follow-up (months)	34	8	8	12	NA	8	16	15	18	16	4	7	11
Response	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Steroid dose reduction	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	-	No	No
WBC (×10 ⁸ /L)	6–5	6.8	6	NA	NA	Median 4.9 (range 4.4–7.6)							

AIH: autoimmune hepatitis; F: female; M: male; PSC: primary sclerosing cholangitis; PBC: primary biliary cirrhosis; AZA: azathioprine; 6MP: 6-mercaptopurine; ALT: alanine aminotransferase; 6TG: 6-thioguanine; 6MMP: 6-methyl mercaptopurine; mo: months; WBC: white blood cell count; reason for combination therapy*—1: loss of response; 2: nonresponse; 3: intolerance to thiopurine; intolerance to thiopurine (nausea, vomiting in 2, arthralgia in 1 and headache in 1), 2 of 3 patients with non-response in series by De Boirs et al. also had side effects in form of myalgia and arthralgia. Side effects disappeared in all of them after combination therapy on follow-up.

AZA: azathioprine, 6MP: 6 mercaptopurine, CBC: complete blood counts, mo: months * adapted from ref 20.

Figure 2 Suggested protocol for azathioprine and allopurinol combination therapy in patients with autoimmune hepatitis/overlap syndrome.

flow diagram of management of AIH/overlap patients with combination therapy in view of current evidence.

Guidelines for combined allopurinol and TP therapy in IBD suggest that CBC should be monitored frequently at least once every 7–14 days for initial few weeks till the medication doses and blood parameters are stable. Thereafter, CBC needs to be done once every 2–3 months till the therapy is continued. Levels of thiopurine metabolites also need to be measured every 1–2 months till the target level of 6TG is achieved, and then every 6 monthly.^{36,37} However as there is no established target therapeutic value of 6TG in the setting of AIH, the utility of repeated drug metabolite monitoring after the patients has achieved normalization of transaminases is not yet clear. The present evidence suggests that combination therapy of allopurinol and thiopurine can be tried as an option in patients with intolerance/non-response to thiopurines before shifting to second line therapy. Thiopurines score over the second

line therapeutic agents like calcineurin inhibitors and biologics in terms of cost, safety, and durability of response.³⁸ Variation in TPMT and XO activity across ethnic groups have been described which may affect the metabolism of thiopurines.^{39,40} However, there is no published information about any difference in the frequency of “selective MMP shunters” or response to the allopurinol-thiopurine combination therapy across populations.

Despite the success of combination therapy, the evidence is still limited and we need more trials with larger number of patients. The cut off values for therapeutic level of 6TG and 6MMP in patients with AIH is still not adequately established. In patients intolerant to allopurinol, the role of combination therapy with the newer XO inhibitor fibuxostat is unknown as there is no available clinical report on its efficacy in AIH patients.⁴¹

Metabolite measurement is expensive and not readily available especially in the developing world. However, the

same patients are most likely to benefit by the judicious use of combination therapy as access to second line therapy (MMF/calculinurine inhibitors) is limited by cost constraints. In the opinion of the authors, despite the need, routine use of combination therapy without doing metabolite measurements, in patients with non response or loss of response in the developing world would not be safe and thus not advisable at this stage.

CONCLUSION

Limited evidence suggests that administration of combination therapy of allopurinol (25–100 mg/day) with a lower dose of thiopurine (25–40% of baseline dose) is a safe and effective way to optimize thiopurine treatment in patients with AIH or overlap syndrome with intolerance and/or non-response due to unfavorable TP metabolism. We suggest that metabolites (6MMP and 6TG) should be measured in these patients with AIH/AIH-PBC/AIH-PSC on TP therapy before shifting to the second line therapy. This will help guide the further course of therapy by identifying both non-compliant patients and those with preferential 6MMP metabolism. These cases can then be continued on TP either by ensuring compliance in non-compliant cases or adding allopurinol with reduced TP dose in patients with abnormal metabolism. Use of combination therapy without measurement of drug metabolites is not advisable as of today.

CONTRIBUTION OF AUTHORS

Both authors have contributed to the review and approve the final submitted version.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

- European Association for Study of Liver. EASL practice guidelines: autoimmune liver disease. *J Hepatol.* 2015;63:971–1004.
- Liberal R, Vergani D, Mieli-Vergani G. Update on autoimmune hepatitis. *J Clin Transl Hepatol.* 2015;3:42–52.
- Vierling JM. Autoimmune hepatitis and overlap syndromes: diagnosis and Management. *Clin Gastroenterol Hepatol.* 2015;13:2088–2108.
- Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology.* 2010;51:2193–2213.
- Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol.* 1999;31:929–938.
- Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology.* 2008;48(1):169–176.
- Czaja AJ, Freese DK. American Association for the Study of Liver Disease. Diagnosis and treatment of autoimmune hepatitis. *Hepatology.* 2002;36(2):479–497.
- Lamers MM, van Oijen MG, Pronk M, Drenth JP. Treatment options for autoimmune hepatitis: a systematic review of randomized controlled trials. *J Hepatol.* 2010;53(1):191–198.
- Manns MP, Woynarowski M, Kreisel W, et al. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology.* 2010;139(4):1198–1206.
- Czaja AJ. Challenges in the diagnosis and management of autoimmune hepatitis. *Can J Gastroenterol.* 2013;27(9):531–539.
- Yokokawa J, Saito H, Kanno Y, et al. Overlap of primary biliary cirrhosis and autoimmune hepatitis: Characteristics, therapy, and long term outcomes. *J Gastroenterol Hepatol.* 2010;25(2):376–382.
- Nguyen TM, Daubard M, Le Gall C, Larger M, Lachaux A, Bouliou R. Monitoring of azathioprine metabolites in pediatric patients with autoimmune liver disease. *Ther Drug Monit.* 2010;32:433–437.
- Rumbo C, Emerick KM, Emre S, Shneider BL. Azathioprine metabolite measurements in the treatment of autoimmune liver disease in pediatric patients: a preliminary report. *J Pediatr Gastroenterol Nutr.* 2002;35:391–398.
- Gearry RB, Barclay RL. Azathioprine and 6-mercaptopurine pharmacogenetics and metabolite monitoring in inflammatory bowel disease. *J Gastroenterol Hepatol.* 2005;20:1140–1157.
- Yarur AJ, Abreu MT, Deshpande AR, Kerman DH, Sussman DA. Therapeutic drug monitoring in patients with inflammatory bowel disease. *World J Gastroenterol.* 2014;20:3475–3484.
- Dhaliwal HK, Anderson R, Thornhill EL, et al. Clinical significance of azathioprine metabolites for the maintenance of remission in autoimmune hepatitis. *Hepatology.* 2012;56(4):1401–1408.
- Dubinsky MC, Lamothe S, Yang HY, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology.* 2000;118(4):705–713.
- Bastida G, Nos P, Aguas M, et al. Incidence, risk factors and clinical course of thiopurine-induced liver injury in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2005;22(9):775–782.
- Shaye OA, Yadegari M, Abreu MT, et al. Hepatotoxicity of 6-mercaptopurine (6-MP) and azathioprine (AZA) in adult IBD patients. *Am J Gastroenterol.* 2007;102:2488–2494.
- de Boer YS, van Gerven NMF, de Boer NKH, Mulder CJJ, Bouma G, van Nieuwkerk CMJ. Allopurinol safely and effectively optimises thiopurine metabolites in patients with autoimmune liver disease. *Aliment Pharmacol Ther.* 2013;37:640–646.
- Amin J, Huang B, Yoon J, Shih DQ. Update 2014: advances to optimize 6-mercaptopurine and azathioprine to reduce toxicity and improve efficacy in the management of IBD. *Inflamm Bowel Dis.* 2015;21:445–452.
- Goel RM, Blaker P, Mentzer A, Fong SC, Marinaki AM, Sanderson JD. Optimizing the use of thiopurines in inflammatory bowel disease. *Ther Adv Chronic Dis.* 2015;6:138–146.
- Kennedy NA, Asser TL, Mountfield RE, Doogue MP, Andrews JM, Bampton PA. Thiopurine metabolite measurement leads to changes in management of inflammatory bowel disease. *Intern Med J.* 2013;43:278–286.
- Duley JA, Chocair PR, Florin THJ. Observation in the use of allopurinol in combination with azathioprine or mercaptopurine (letter). *Aliment Pharmacol Ther.* 2005;22:1161–1162.
- Blaker PA, Arenas-Hernandez M, Smith MA, et al. Mechanism of allopurinol induced TPMT inhibition. *Biochem Pharmacol.* 2013;86(4):539–547.
- Dunkin D, Kerkar N, Arnon R, Suchy F, Miloh T. Allopurinol salvage therapy in pediatric overlap autoimmune hepatitis-primary sclerosing cholangitis with 6-MMP toxicity. *J Pediatr Gastroenterol Nutr.* 2010;51(4):524–526.
- Al-Shamma S, Eross B, McLaughlin S. Use of a xanthine oxidase inhibitor in autoimmune hepatitis. *Hepatology.* 2013;57(3):1281–1282.

28. Wong DR, Derijks LJ, den Dulk MO, Gemmeke EH, Hooymans PM. The role of xanthine oxidase in thiopurine metabolism: a case report. *Ther Drug Monit.* 2007;29(6):845–848.
29. Al-Shamma S, McCrudden R, McLaughlin S. Allopurinol co-therapy is safe and effective in autoimmune hepatitis (Letter). *Aliment Pharmacol Ther.* 2013;37:918–920.
30. de Boer YS, van Gerven NMF, de Boer NKH, Mulder CJJ, Bouma G, van Nieuwkerk CMJ. Allopurinol co-therapy is safe and effective in autoimmune hepatitis (Letter – authors' reply). *Aliment Pharmacol Ther.* 2013;37(920):918–920.
31. Azulay JP, Blin O. Reversible peripheral neuropathy. *Eur Neurol.* 1993;33:193.
32. Grosser T, Smyth E, Fitzgerald GA. Chapter 34. Anti-inflammatory, antipyretic and analgesic agents; pharmacotherapy of gout. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 12th ed. McGraw Hill; 2011.
33. Stamp LK, Day RO, Yun J. Allopurinol hypersensitivity: investigating the cause and minimizing the risk. *Nat Rev Rheumatol.* 2016;12(4):235–242.
34. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken).* 2012;64(10):1431–1446.
35. Rahhal RM, Bishop WP. Initial clinical experience with allopurinol-thiopurine combination therapy in pediatric IBD. *Inflamm Bowel Dis.* 2008;14:1678–1682.
36. Geary RB, Day AS, Barclay ML, Leong RWL, Sparrow MP. Azathioprine and allopurinol: a two-edged interaction. *J Gastroenterol Hepatol.* 2010;25:649–656.
37. Min MX, Weinberg DI, McCabe RP. Allopurinol enhanced thiopurine treatment for inflammatory bowel disease: safety considerations and guidelines for use. *J Clin Pharmacy Ther.* 2014;39:107–111.
38. Heneghan MA, Al-Chalabi T, McFarlane IG. Cost-effectiveness of pharmacotherapy for autoimmune hepatitis. *Expert Opin Pharmacother.* 2006;7(2):145–156.
39. Kudo M, Moteki T, Sasaki T, et al. Functional characterization of human xanthine oxidase allelic variants. *Pharmacogenet Genomics.* 2008;18(3):243–251. <http://dx.doi.org/10.1097/FPC.0b013e3282f55e2e>.
40. Collie-Duguid ES, Pritchard SC, Powrie RH, et al. The frequency and distribution of thiopurine methyltransferase alleles in Caucasian and Asian populations. *Pharmacogenetics.* 1999;9(1):37–42.
41. Stamp Lisa K. Safety profile of anti-gout agents: an update. *Curr Opin Rheumatol.* 2014;26:162–168.