East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Prescribing Clinical Network

Medicine and proposed indication	Azathioprine/ 6MP in combination with allopurinol for Inflammatory Bowel Disease
Requested by	Azhar Ansari/Patrick Kerr (2012) highlighted for review 2016

SUMMARY

Clinical Effectiveness

Ulcerative colitis (UC) and Crohn's disease (CD) are the two major forms of inflammatory bowel disease (IBD) and have a prevalence of approximately 400 patients per 100,000 population.

The immunomodulators azathioprine (AZA) and 6-mercaptopurine (6MP) are established therapies for moderate/ severe IBD. This review is intended to review the evidence on the use of AZA/6MP in combination with allopurinol for the treatment of IBD with the aim to facilitate the development of improved care pathways and outcomes for patients with IBD.

AZA / 6MP are used as steroid sparing agents in both UC and Crohn's disease and the British Society of Gastroenterology guidelines state it should be considered as a treatment option for patients who:

- require two or more courses of corticosteroid treatment within one year
- suffer a disease relapse as the dose of prednisolone is reduced
- suffer a disease relapse within six weeks of stopping prednisolone
- require postoperative prophylaxis of fistulising or extensive Crohn's disease

In patients with moderate to severe IBD in whom immunomodulators are considered to be an appropriate treatment option the initial treatment to induce remission will be recommended, and provided, by the specialist IBD clinician until patient is stabilised and shared care agreed.

Azathioprine / 6MP are effective treatment options for both active disease and maintaining remission in Crohn's disease and Ulcerative Colitis (confirmed by several Cochrane reviews). Although they are used widely to treat IBD they are unlicensed for this indication. As these are generic medicines, it is unlikely that a licence will be sought for this indication.

Azathioprine is metabolised to 6MP and subsequently to numerous 6-thioguanine nucleotides. The exact mode of action of these metabolites is still unknown, although it is thought to be multifactorial, including purine antimetabolite action, inhibition of several pathways in nucleic acid biosynthesis (preventing proliferation of cells involved in the immune response) and damage to DNA through the incorporation of thiopurine analogues.

Thiopurine methyltransferase (TPMT) is an enzyme that deactivates 6-mercaptopurine. The TPMT level is checked by the specialist IBD clinician before starting AZA / 6MP. Patients deficient in TPMT are at an increased risk of bone marrow suppression if treated with AZA / 6MP.

Allopurinol is a xanthine oxidase inhibitor that partially inhibits the breakdown of AZA/ 6MP. The BNF (March 16) recommend a dose reduction to one quarter of the normal AZA/ 6MP dose when allopurinol is used in combination. This review will look at the evidence for the using the combination of allopurinol with AZA/6MP for the treatment of IBD.

Safety

AZA / 6MP are established treatments for IBD however therapeutic failure caused by adverse drug reactions or a lack of response to treatment occur frequently.

A significant number of patients do not tolerate AZA/6MP treatment. Allopurinol partially inhibits the breakdown of AZA/6MP thus requiring a reduction in dose to one quarter of the normal AZA/6MP dose. It has been demonstrated that non-responders to azathioprine or mercaptopurine (6-mercaptopurine) have high normal thiopurine methyltransferase activity and preferentially metabolize mercaptopurine to produce 6-methylmercaptopurine instead of the active 6-tioguanine (6-tioguanine) metabolites

Patient factors

IBD has a peak incidence in the late teens/ early twenties (critical points in development) and a second peak in the mid-fifties. It is uncommon after the age of 65 years (20%). IBD is a lifelong relapsing remitting inflammatory disorder without cure. It frequently presents with abdominal pain, bloody diarrhoea and constitutional symptoms: weight loss, tiredness and pyrexia. Whilst UC affects only the colon, CD can involve any part of the digestive tract including the mouth. For patients with moderate to severe IBD the induction and maintenance of remission results in an improved quality of life. Optimising thiopurine use reduces steroid exposure, major abdominal surgery, hospitalisations, possible risk from colorectal cancer and use of high cost biologic drugs.

Biologic drugs do not have complete efficacy (approximately 75% response to the first Anti-TNF, dropping down to 30% with a second line treatment). In addition, there is still a scarcity of longitudinal studies for long term studies. There is emerging data of development of antibodies to the anti-TNFs and it is possible that other inflammatory processes can also play a role in limiting the duration of efficacy with anti-TNF therapy.

Cost implications

The combination of allopurinol with AZA / 6MP for the treatment of IBD is expected to lead to the following (see supporting evidence below):

- a reduction in the treatment limiting side effects of AZA/ 6MP thus allowing more IBD patients to tolerate immunomodulator therapy
- a higher % of patients with IBD who achieve remission as more patients are able to tolerate / respond to immunomodulator therapy
- a reduction and delay in the number of patients progressing onto biologic therapy (annual cost approx £10,000/pt/annum)

Relevant guidance / reviews

National Guidelines:

Crohn's disease: management. NICE guidelines [CG152] Published date: October 2012

Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if:

there are two or more inflammatory exacerbations in a 12-month period, or the glucocorticosteroid dose cannot be tapered.

Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values).

Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient:

Monitor the effects of azathioprine, mercaptopurine and methotrexate as advised in the current online version of the British national formulary (BNF) or British national formulary for children (BNFC). Monitor for neutropenia in those taking azathioprine or mercaptopurine even if they have normal TPMT activity.

Ensure that there are documented local safety monitoring policies and procedures (including audit) for adults, children and young people receiving treatment that needs monitoring. Nominate a member of staff to act on abnormal results and communicate with GPs and people with Crohn's disease and/or their parents or carers, if appropriate.

Ulcerative colitis: management. NICE guidelines [CG166] Published date: June 2013

Consider oral azathioprine or oral mercaptopurine to maintain remission after two or more inflammatory exacerbations in 12 months that require treatment with systemic corticosteroids or if remission is not maintained by aminosalicylates.

To maintain remission after a single episode of acute severe ulcerative colitis: consider oral azathioprine or oral mercaptopurine. Consider oral aminosalicylates in people who cannot tolerate or who decline azathioprine and/or mercaptopurine, or in whom azathioprine and/or mercaptopurine are contraindicated.

British Society of Gastroenterology Guidelines for the management of inflammatory bowel disease in adults; 2011

Thiopurines Azathioprine (AZA) or mercaptopurine (MP) are widely used in ulcerative colitis and Crohn’s disease as adjunctive therapy and as corticosteroid-sparing therapies although they are unlicensed therapies for IBD. Their slow onset of action precludes usage as sole therapy for active disease. Purine antimetabolites inhibit ribonucleotide synthesis, but the mechanism of immunomodulation is by inducing T cell apoptosis by modulating cell (Rac1) signalling.

AZA is non-enzymatically metabolised to MP, which involves loss of a nitro-imidazole side chain; this is thought to explain some of the side effects seen with AZA and which may be less of a problem

with MP. MP is subsequently metabolised to 6-thioguanine nucleotides (6-TGN). 6-TGN has been used for treatment of IBD, but caution is appropriate because of potential hepatotoxicity.

Review of evidence relating to the combination of allopurinol with AZA/6MP

An evidence review was requested and provided by Guys and St Thomas' MI to include evidence from 2012 (date of previous PCN pater) onward.

Full details are included in the evidence review section below and demonstrate that combination therapy can provide successful treatment for a significant number of patients who would otherwise have been labelled as thiopurine failures. It appears to be more effective, better tolerated and safer (less haematological disturbance) than full dose azathioprine.

This could provide significant annual cost savings through the prevention of escalation to biologics. These cost savings are likely to be even more significant in the long term since a significant proportion of patients treated with biological therapy require dose escalation. We believe adopting this strategy more widely could lead to significant healthcare savings.

Recommendation to PCN

Commissioners are supportive of services which strive to optimise oral maintenance therapy for the treatment of IBD including AZA/6MP in combination with allopurinol with the aim to facilitate the development of improved care pathways and outcomes for patients with IBD.

Benchmarking services to patients with IBD within the PCN boundaries to inform outcome based commissioning decisions

Evidence review

1. **Title: Safety and efficacy of low dose azathioprine and allopurinol co-therapy: A large single centre experience** Citation: Gut, June 2014, vol./is. 63/(A3-A4), 0017-5749 (June 2014) Author(s): Stamoulos P., Stournaras E., Bull C., Cowan M., Mackenzie G., Stenner J., Coulthard S., Ansari A.

Abstract: Introduction The effectiveness of full dose azathioprine (FDA) for inflammatory bowel disease (IBD) has been questioned in recent scientific literature. A popular strategy to improve its outcomes recommends the use of low dose azathioprine with allopurinol co-therapy (LDAA) for patients profiled as "hypermethylators" (30% of non-responders). The aim of this study was to determine the safety and efficacy of LDAA without using thiopurine metabolite (TM) profiling.

Methods Records of IBD patients treated with LDAA were retrospectively analysed. Patients who had poor response and/or side-effects to FDA were offered LDAA by all Consultants whilst a single IBD physician also offered LDAA to thiopurine-naive patients. Azathioprine dose was reduced to 25% of the thiopurine methyl transferase (TPMT) adjusted dose (0.5 mg/kg for wild type and 0.25 mg/kg for heterozygotes) followed by conventional haematological monitoring. Non-adherence was assessed by TM measurements. Full response (FR) was defined as steroid free remission (Harvey Bradshaw index <3, Truelove-Witts normal) for greater than 3 months after a 3 month induction

period for LDAA.

Results Of 300 LDAA patients, adequate data was available for 295 cases. Group 1 (G1) were treated 1st line (n,105) and Group 2 (G2) were switched from FDA to LDAA (n,190). Overall, for both groups, there were 207 (70%) full responders (FR), 20 partial responders (PR) and 68 non-responders (NR). Full response rate was 78% in G1 and 66% in G2. The commonest indication for switching to LDAA was non-response to FDA (n,118). (Table Presented) Analysis of haematological indices revealed significant changes ($p < 0.05$) in erythrocyte sedimentation rate, white cell count and platelet count after therapy induction. Myelotoxicity occurred in 5 patients (all NR, WCC >2 and <3.5) and 12 patients had asymptomatic hepatotoxicity (ALT range: 100-700) which resolved by increasing allopurinol to 200 mg in 9 patients (all FR). Time on treatment: 208 patients took LDAA for more than twelve months with a median length of therapy of 24 months.

Conclusion Appropriately dosed LDAA therapy delivers a therapeutically effective dose of azathioprine without the need for dose escalation. It appears to be more effective, better tolerated and safer (less haematological disturbance) than FDA. These results will serve to allay the fear of toxicity of LDAA and question the need for thiopurine metabolite level profiling prior to using this apparently superior therapeutic approach.

Publication Type: Journal: Conference Abstract Source: EMBASE Full Text: Available from Highwire Press in Gut

2. **Title: Optimising outcome on thiopurines in inflammatory bowel disease by co-prescription of allopurinol** Citation: Journal of Crohn's and Colitis, October 2012, vol./is. 6/9(905-912), 1873-9946;1876-4479 (October 2012) Author(s): Smith M.A., Blaker P., Marinaki A.M., Anderson S.H., Irving P.M., Sanderson J.D.

Abstract: Background and aims: Azathioprine and mercaptopurine remain first line immunomodulatory treatments for inflammatory bowel disease. Toxicity and non-response are significant issues. Co-prescription of allopurinol with reduced-dose (25-33%) azathioprine or mercaptopurine may overcome these problems. We present the outcome of co-prescription in a large single-centre cohort.

Method: Patients on thiopurine/allopurinol co-prescription were identified. Indication for and outcome on combination treatment were established. Blood parameters and metabolite results were compared on single agent and combination treatment. Toxicity associated with combination treatment was sought.

Results: 110 patients on combination treatment were identified. Clinical remission was achieved in 60/79 (76%) of patients in whom the effect of thiopurine could be studied in isolation. 20/25 patients with hepatotoxicity tolerated combination treatment and normalised their liver function tests. 24/28 patients with atypical side effects tolerated co-therapy. 13/20 non-responders responded to combination treatment. In patients started on combination treatment as first line therapy, 15/23 achieved clinical remission. Thioguanine nucleotides were significantly higher and methylated metabolites significantly lower on combination therapy. Mean cell volume was higher and total white cell and neutrophil counts lower on combination treatment. 13 adverse events occurred, including 6 specific to co-therapy (3 rash, 2 abnormal liver function tests, 1 dosing error).

All were minor and self-limiting.

Conclusion: This is the largest published experience of the use of allopurinol to optimise outcomes on thiopurine treatment. Combination therapy permitted successful treatment of a significant number of patients who would otherwise have been labelled as thiopurine failures. A few self-limiting side effects were encountered. © 2012 European Crohn's and Colitis Organisation.

Publication Type: Journal: Article Source: EMBASE Full Text: Available from Elsevier in Journal of Crohn's and Colitis Available from Oxford University Press in Journal of Crohn's and Colitis

3. **Title: Safety and effectiveness of long-term allopurinol-thiopurine maintenance treatment in inflammatory bowel disease.** Citation: Inflammatory bowel diseases, Feb 2013, vol. 19, no. 2, p. 363-369 (February 2013) Author(s): Hoentjen, Frank, Seinen, Margien L, Hanauer, Stephen B, de Boer, Nanne K H, Rubin, David T, Bouma, Gerd, Harrell, Laura E, van Bodegraven, Adriaan A

Abstract: Thiopurines are the mainstay of conventional maintenance therapy in inflammatory bowel disease (IBD). Unfortunately, up to 50% of patients discontinue immunosuppressive therapy within 2 years due to intolerance or lack of efficacy. Allopurinol with low-dose thiopurine can optimize thiopurine metabolism for IBD patients with preferential shunting toward 6-methyl mercaptopurine (6-MMP) formation.

The aim of this study was to assess long-term maintenance effectiveness and tolerability of allopurinol-thiopurine therapy in a larger multicenter cohort of IBD patients. Enrolled patients who failed monotherapy with thiopurines due to a skewed metabolism were subsequently treated with a combination therapy of allopurinol and low-dose thiopurine. Adverse events were monitored and therapeutic adherence was assessed.

Results:Seventy-seven IBD patients were enrolled with a mean follow-up of 19 months. The median 6-thioguanine nucleotide concentration increased from 145 during monotherapy to 271 pmol/8 × 10(8) red blood cell (RBC) after at least 8 weeks of combination therapy while reducing the thiopurine dosage ($P < 0.001$). In contrast, median 6-MMP concentrations decreased from 10,110 to 265 pmol/8 × 10(8) RBC ($P < 0.001$). Leukopenia occurred in 12 patients (16%), requiring dose adaptation. Liver test abnormalities normalized in 81% of patients after the addition of allopurinol. Sixteen (21%) patients had to discontinue combination therapy. The percentage of patients still using combination therapy at 6, 12, 24, and 60 months was 87%, 85%, 76%, and 65%, respectively.

Conclusion:Long-term combination therapy with allopurinol and low-dose thiopurines is an effective and well-tolerated treatment in IBD patients with a skewed thiopurine metabolism.

Source: Medline Full Text: Available from Wiley-Blackwell Free Backfiles NHS in Inflammatory Bowel Diseases Available from Ovid in Inflammatory Bowel Diseases

4. **Title: Low dose AZA and allopurinol co-therapy: Is it safe to use without metabolite monitoring?** Citation: Gastroenterology, May 2014, vol./is. 146/5 SUPPL. 1(S-248), 0016-5085 (May 2014) Author(s): Eross B.M., Johnson H.E., Weaver S., McLaughlin S.D.

Abstract: Background: Low dose azathioprine(AZA)/mercaptopurine (MP) & allopurinol co-therapy

(LDAA) is a proven therapeutic option in inflammatory bowel disease (IBD) patients who develop side effects or hepatotoxicity to standard dose AZA/MP. It has been suggested that this combination is not safe to be used without measurement of thiopurine metabolite levels (TML). This is a significant barrier to implementing LDAA.

Aim: To establish whether LDAA therapy is safe without TML measurement.

Methods: We maintain a prospective IBD database. LDAA therapy was introduced in our unit in 2010. Standard dose AZA is given at a dose of 2mg/kg in TPMT wild-type & 1mg/kg in heterozygotes. MP dosed at 1mg/kg & 0.5mg/ kg respectively. LDAA therapy is given at 25% of the standard AZA/MP dose. After commencing LDAA we monitor full blood count (FBC) & liver function test (LFT) weekly for 8 weeks & 3 monthly thereafter. 6-Thioguanine (TGN) & 6-Methyl-MP nucleotide (MMPN) levels checked at 4-16 weeks. We searched our database for patients who started LDAA. Diagnosis, indications for therapy, FBC, LFT, TML and outcomes were recorded.

Results: 76 patients started LDAA, 31 (40.8%) were male. Median age; 47 years (range: 16-79), disease type was: ulcerative colitis (26), Crohn's disease (44), IBD-U (3), microscopic colitis (3). Indications; drug side effects to standard dose AZA/MP, 42; hepatotoxicity, 19; Hypermethylation (MMPN:TGN ratio >11),9; gout, 4; high TPMT, 2; TML were available in 64 (84%). 11 (14%) stopped LDAA due to: intolerance; 9 (12%), leucopenia; 1(1%), 1(1%) non-compliant. Median TGN was 375.5 pmol/10*8 red blood cells (RBC) (range: 86-1083) with 6TGN (>250) in 50 (78%). 6MMPN <100 in 23 (30%). The remaining 41 (54%) median 6MMPN level was 170 (range 103-1205). Of the 64 (84%) patients remaining on LDAA at 6 weeks total white cell count <3.5 10*9/L in 3 patients. LDAA was stopped in 1, dose reduced in 1 and 1 continued LDAA. TGN levels were 275, 483 & 686 pmol/10*8 RBC. Dose adjustment was made in a further 11 patients following TML; LDAA dose was increased in 9 due to low TGN; median 177 pmol/10*8 RBC (range 97-321) & reduced in 2 due to high TGN (1033 & 790). 2 of 19 patients on LDAA for hepatotoxicity had abnormal LFTs on starting LDAA; 1, autoimmune hepatitis/PSC&1 under investigation. Neither stopped or reduced LDAA.

Conclusion: In this study decisions regarding stopping LDAA were made based on FBC rather than TML monitoring. TML monitoring was used to ensure adequate dosing. These data therefore suggest that LDAA therapy dosed by weight TPMT status with weekly FBC monitoring is safe without TML monitoring.

Publication Type: Journal: Conference Abstract Source: EMBASE

5. **Title: Adjunctive Allopurinol in Azathioprine/ mercaptopurine non-responders optimises 6-thioguanine nucleotide production and improves clinical outcomes in inflammatory bowel disease: The multicentre, prospective, double blind, dose-ranging AAA study** Citation: Journal of Gastroenterology and Hepatology (Australia), September 2015, vol./is. 30/(118-119), 0815-9319 (September 2015) Author(s): Friedman A.B., Brown S.J., Bamptom P., Barclay M., Chung A., Macrae F., Mckenzie J., Reynolds J., Gibson P.R., Hanauer S.B., Sparrow M.P.

Abstract: Objectives: 15% of IBD patients who do not respond to azathioprine (AZA) or mercaptopurine (MP) are "shunters". They preferentially metabolise MP to 6-methylmercaptopurine (6MMP) instead of the efficacious 6-thioguanine nucleotides (6TGN). Allopurinol may reverse this shunting. This multicentre, prospective, double-blind, dose-ranging, randomised trial aimed to determine whether a regimen of low-dose allopurinol with thiopurine achieves steroid-free clinical

remission and minimises toxicity in patients with IBD who are shunters and have active disease; and to compare outcomes of allopurinol 50 vs 100 mg/d.

Methods: Patients with clinically-active or steroid-dependent IBD, thiopurine shunting (6TGN < 260 pmol/8x10⁸ RBCs and 6MMP: 6TGN ratio >20) and total leucocyte count >3.5 x10⁹/L were randomised to a blinded dose of 50 or 100 mg/d allopurinol and 25% of their screening thiopurine dose. Thiopurine doses were then optimised, aiming for 6TGN >260. The primary endpoint was steroid-free clinical remission after 24 weeks (SFR24) using the Harvey Bradshaw Index and the Simple Clinical Colitis Activity Index. An intention-to-treat analysis was performed.

Results: 73 patients were enrolled: 46 had Crohn's disease and 27 ulcerative colitis. Mean daily doses of AZA reduced from 164 mg at screening to 67 mg at week 24 and MP from 88 mg to 45 mg (both $p < 0.001$). Significantly greater thiopurine dose reductions were seen in the 100 mg allopurinol arm than the 50 mg arm (63-65% vs 35-53% reduction, $p = 0.006$ and 0.008). 39 patients [53% (95% CI 42-65)] achieved SFR24 with no difference in rates of SFR24 between 50 and 100 mg arms ($p = 0.913$). Mean 6TGN levels increased from 177 +/- 14 to 402 +/- 16 ($p < 0.001$), 6MMP levels decreased from 9949 +/- 485 to 1235 +/- 547 ($p < 0.001$) and 6MMP:6TGN ratio fell from 64 to 4 ($p < 0.001$). There was no significant difference in 6TGN between allopurinol arms, but mean 6MMP was significantly higher in the 50 mg arm (1987 vs 483, $p = 0.023$). Hepatitis decreased with ALT improving from 52 +/- 6 U/L to 27 +/- 6 U/L ($p < 0.001$) across both arms. 26 of 32 patients (81%) were able to cease steroids ($p = 0.011$). Total leucocyte count decreased from a mean of 7.1 x 10⁹/L to 5.9 x 10⁹/L ($p < 0.001$). Only two transient episodes of mild leucopenia occurred in 1 patient, resolving with a reduced thiopurine dose. Faecal calprotectin reduced in steroid-dependent CD patients from a mean of 864 to 122 mug/g ($p = 0.043$), and CRP reduced in UC patients from a mean of 6.1 to 3.6 mg/L ($p = 0.019$). 15 serious adverse events occurred; however, only two (one dental abscess and one perianal abscess) were possibly related to the drug combination.

Conclusions: This prospective study has validated that low dose allopurinol-thiopurine combination safely and effectively optimises 6TGN and concurrently reduces 6MMP. Optimisation of thiopurine metabolites with allopurinol and dose-reduced thiopurines improves disease outcomes without additional toxicity. No clinically significant differences were seen between allopurinol doses.

Publication Type: Journal: Conference Abstract Source: EMBASE Full Text: Available from Wiley in Journal of Gastroenterology and Hepatology

6. **Title: Low dose azathioprine and allopurinol in azathioprine intolerant patients: Is it tolerated and is it effective in IBD?** Citation: Gut, June 2014, vol./is. 63/(A29), 0017-5749 (June 2014) Author(s): Johnson H.E., Weaver S.A., McLaughlin S.D.

Abstract: Introduction Despite the advancement and introduction of new biological therapies, thiopurines remain effective treatment options for the maintenance of remission for both ulcerative colitis (UC) and Crohn's disease (CD). Once tolerated and therapeutic, thiopurines have many advantages over biologics for long-term maintenance therapy. However, it has been documented that intolerance and adverse events are common. We have previously published our 36 month follow-up data reporting that 56.5% of our patients stop thiopurines due to side effects, abnormal liver function tests (LFTs) or therapeutic failure. Low dose azathioprine and allopurinol (LDAA) co-

therapy is a well proven treatment option for patients who develop side effects or hepatotoxicity with standard dose azathioprine. LDAA has been used at our institution since 2010.

Aim to report the safety, tolerability and therapeutic outcome at 12 months, for LDAA in patients who have failed standard dose azathioprine.

Methods We maintain a prospective IBD data-base. After starting LDAA we monitor full blood count and LFTs weekly for 8 weeks. 6-Thioguanine (6-TGN) and 6-Methyl-mercaptopurine (6 MMPN) nucleotide levels are checked at 4-6 weeks. We searched our database for patients who started LDAA and had a minimum of 12 months follow-up. We recorded the indications for therapy, metabolite levels, and blood monitoring and clinical outcomes.

Results 62 patients were started on LDAA. 25 (40%) were male. Mean age was 47 (range 16 - 77). Disease type was UC, 21; CD, 35; IBD(U), 6. Reasons intolerant to standard dose azathioprine were: drug side effects (nausea and arthralgia) 24; hepatitis (ALT 2x upper limit normal) 20; Hypermethylation (TGN: MMPN ratio >11), 12. Gout 4; High TPMT 2. At 12 months 44 (70%) remained on LDAA and were in clinical remission (HBI <1 for CD), (stool frequency <4 and no bleeding for UC) with therapeutic 6TGN levels on LDAA, of these 7 (11%) required additional treatment with biologic therapy. Of the remaining 18 (29%) patients, 3 (5%) were lost to follow up and 1 (2%) chose to stop LDAA. 1 patient (UC) required a colectomy. 3 (5%) stopped LDAA to conceive. 10/62 (16%) remained intolerant and treatment was stopped. One patient developed myelosuppression WCC <3 and stopped therapy. No patients developed abnormal LFTs on LDAA.

Conclusion LDAA is well tolerated and effective in patients who failed standard dose azathioprine due to drug side effects and hepatotoxicity. This therapy results in resolution of hepatotoxicity and will allow more IBD patients to achieve clinical remission.

Publication Type: Journal: Conference Abstract Source: EMBASE Full Text: Available from Highwire Press in Gut

7. Title: **A combination of low-dose thiopurine and allopurinol (ThioComp) is long-term efficacious and well-tolerated in IBD patients** Citation: Journal of Crohn's and Colitis, February 2014, vol./is. 8/(S307), 1873-9946 (February 2014) Author(s): Almer S., Wagner A., Mahl M., Hindorf U.

Abstract: Background: Up to half of thiopurine (TP)-treated patients with IBD experience adverse events or stop treatment due to lack of effect. An aberrant or 'skewed' metabolism is present in about 15 per cent of patients and is related to lack of response. A combination of low-dose thiopurine and allopurinol (ThioComp) reverses this kind of metabolism and leads to increased tolerance and effect. Methods: Observational long-term follow-up study of patients treated with ThioComp. Results are given as median (range). Statistics used was the Wilcoxon's Signed Rank Test.

Results: 58 patients (33 women; 38 (15-80) years) treated since January 2007 were included. Diagnoses were ulcerative colitis (n = 38), Crohn's disease (18), lymphocytic colitis (1), eosinophilic colitis (1). All patients had been treated with a thiopurine; azathioprine (AZA, n = 57), AZA and mercaptopurine (MP, n = 21), MP (1); 18 had previous or ongoing treatment with anti-TNF-antibodies. Half of the patients (n = 29) had suffered adverse events on previous TP-treatment. All had a normal TPMT genotype (*1/*1) and TPMT activity, 13.5 (10.1-23.7) U/ml pRBC. 52 (90%)

displayed an aberrant metabolism with high meTIMP/TGN-ratios, 61 (22-541). AZA was reduced to 29 (17-57)% and MP to 33 (17-40)% of previous TP-doses and 100 mg allopurinol daily was added two weeks later. TGN-levels increased from 147 (54-452) to 198 (44-512) after 2 weeks of ThioComp-treatment (P < 0.001) and to 255 (101-665) pmol/8x10⁸ pRBC at 6 months (P < 0.001). meTIMP-levels decreased from 8650 (1000-74600) to 100 (0-7200) at 2 weeks (P < 0.001) and remained low, 100 (0-4200) pmol/8x10⁸ pRBC, at 6 months (P < 0.001). At last follow-up, 38 patients had continued treatment for 561 (53-2200) days; 34 (ITT 59%) were in clinical remission. The remaining 20 patients stopped treatment after 315 (14-1785) days due to lack of response (n = 9), wish to conceive (4; all in clinical remission), adverse events (4, of which 2 related to allopurinol), lack of compliance (1), or for unknown reason (2). Six of the 9 patients with lack of response underwent colectomy.

Conclusions: ThioComp treatment is very well tolerated and leads to dramatic changes in thiopurine metabolism resulting in long-standing clinical remission in two thirds of a group of difficult-to-treat IBD patients.

Publication Type: Journal: Conference Abstract Source: EMBASE Full Text: Available from Elsevier in Journal of Crohn's and Colitis Available from Oxford University Press in Journal of Crohn's and Colitis

8. Title: **Co-prescription of allopurinol can overcome adverse events of thiopurine therapy and lead to remission in inflammatory bowel disease patients** Citation: Journal of Crohn's and Colitis, February 2014, vol./is. 8/(S290-S291), 1873-9946 (February 2014) Author(s): Beswick L., Dwyer J.P., Friedman A.B., Jakobovits S.L., Paul E., Headon B., McFarlane A., Gibson P.R., Van Langenberg D.R., Sparrow M.P.

Abstract: Background: Thiopurines are an established therapy in inflammatory bowel disease (IBD). Treatment failure due to intolerance can occur in up to 30% of patients. Allopurinol usage to optimise thiopurine therapy is well documented in non-responders who preferentially metabolise thiopurines to produce 6-methyl-mercaptopurine (6MMP) instead of the active 6-thioguanine nucleotides (6TGN). The aim was to examine the ability of a reduced-dose thiopurine-allopurinol combination therapy to enable avoidance of adverse effects while achieving a clinical response in patients intolerant of monotherapy.

Methods: Patients intolerant to azathioprine (AZA) and/or 6-mercaptopurine (6MP) due to side effects that included nausea, fatigue, arthralgias, hepatotoxicity and headache were treated with 100 mg allopurinol and thiopurine at 25%-33% of intended monotherapy dose. Patient outcomes and adverse effects were recorded. Results: 30 patients were identified from July 2011 to July 2013 at two Australian IBD centres. The mean age of the patients was 40 (range 22-68) years with 14 being male. 25 patients had Crohn's disease, 4 ulcerative colitis and 1 indeterminate colitis. 13 patients trialled AZA then 6MP monotherapy, whilst 17 patients had trialled solely AZA (n = 11) or 6MP (n = 6) prior to combination therapy. 10 patients developed hepatotoxicity, 18 suffered non-hepatotoxic reactions and 2 had a combination of hepatotoxic and non-hepatotoxic reactions on monotherapy. Median AZA dose at the onset of adverse effects was 150 mg (1.97 mg/kg)/day and median 6MP dose was 75 mg (1.06 mg/kg)/day. On monotherapy, 17 patients were documented thiopurine 'shunters', 9 patients had metabolites in the normal/low range and in the remaining 4 patients thiopurine metabolites were not measured prior to starting combination therapy. Twenty-

seven patients (90%) tolerated combination therapy. 63% were in clinical remission on the combination after a median follow-up of 8.4 (0.4-22.8) months. Significant differences were seen in pre and post intervention median 6TGN:6MMP ratio 6TGN & 6MMP levels ($p < 0.001$), alanine aminotransferase levels ($p < 0.005$), white cell ($p < 0.002$) and neutrophil counts ($p < 0.001$). There were no significant differences in lymphocyte count or CRP. 3 patients who did not tolerate combination therapy required cessation of treatment due to development of similar symptoms while on monotherapy. There were no adverse effects due to allopurinol for patients on combination therapy.

Conclusions: Combination therapy with allopurinol and lowdose thiopurine can be used to overcome adverse drug effects in the majority of patients, whether 'shunters' or not. Remission can be achieved in two-thirds. This is an important therapeutic manoeuvre in the limited IBD medication armamentarium.

Publication Type: Journal: Conference Abstract Source: EMBASE Full Text: Available from Elsevier in Journal of Crohn's and Colitis Available from Oxford University Press in Journal of Crohn's and Colitis

9. Title: **Low dose thiopurine and allopurinol co-therapy results in significant cost savings at a district general hospital** Citation: Frontline Gastroenterology, October 2015, vol./is. 6/4(285-289), 2041-4137;2041-4145 (01 Oct 2015) Author(s): Dharmasiri S., Dewhurst H., Johnson H., Weaver S., McLaughlin S.

Abstract: Background Thiopurines are widely used for maintenance of remission in Crohn's disease (CD). Published data report >50% of patients stop thiopurines due to therapeutic failure, hepatitis or side effects. In this situation, many UK clinicians start biologics in CD patients. This has significant cost implications. An alternative strategy is low dose thiopurine and allopurinol (LDTA) co-therapy. We report the annual cost savings from adopting this strategy at our centre.

Methods Patients with CD treated with LDTA in preference to biological therapy were identified using a prospective local inflammatory bowel disease database. The annual drug cost of treatment with LDTA compared with biologic therapy was calculated. Cost of attending the day unit for an infusion was not included.

Results 26 patients with CD who failed standard dose thiopurine and were treated with LDTA were identified over a 12-month period and followed up for 1 year. 12 patients failed LDTA and progressed to biological therapy. The remaining 14 patients entered sustained clinical remission on LDTA. The cost savings achieved using the LDTA strategy in this group of patients was 146 413 per year with an average saving of 10 458 per patient per year.

Conclusions This study has identified a significant annual cost savings with this treatment strategy through the prevention of escalation to biologics. These cost savings are likely to be even more significant in the long term since a significant proportion of patients treated with biological therapy require dose escalation. We believe adopting this strategy more widely could lead to significant healthcare savings.

Publication Type: Journal: Article Source: EMBASE Full Text: Available from Highwire Press in Frontline Gastroenterology

10. Title: **Short term prevalence of nodular regenerative hyperplasia of the liver in IBD patients treated with allopurinol-thiopurine combination therapy** Citation: Journal of Crohn's and Colitis, February 2015, vol./is. 9/(S298), 1873-9946 (February 2015) Author(s): Seinen M., Van Asseldonk D., De Boer N., Bouma G., Mulder C., Bloemena E., Van Bodegraven A.

Abstract: Background: Tioguanine has been associated with nodular regenerative hyperplasia (NRH) of the liver. Combination therapy of allopurinol and adapted dose conventional thiopurine leads to a pharmacokinetic profile partly comparable with that of tioguanine ((high 6-thioguanine nucleotides (6-TGN) and low 6-methylmercap-topurine (6-MMPR) concentrations)). Therefore, combination therapy of allopurinol and conventional thiopurines may induce NRH of the liver in a comparative way. We assessed short term prevalence of NRH in IBD-patients treated with allopurinol-thiopurine combination therapy.

Methods: This was an observational, single-centre cross-sectional study. All adult IBD-patients who were treated at least one year with allopurinol-thiopurine combination therapy were eligible. Subjects were identified at the Outpatients' clinic and they were consecutively invited to participate. All patients underwent a liver biopsy, and venous blood was drawn to measure haematological and hepatic parameters, including thrombocyte count and alkaline phosphatase, but also to determine thiopurine metabolite concentrations. Histopathology was assessed by an experienced hepatopathologist.

Results: Eighteen IBD-patients, of which thirteen were diagnosed with Crohn's disease were included. The median age at inclusion was 36 year (IQR 25-42). Combination therapy was initiated in nine patients as a result of elevated transaminase activities during thio-purine monotherapy. The median duration of combination therapy at inclusion was 24 months (IQR 20-28). The median 6-TGN and 6-MMPR level was 685 pmolx108 RBC (IQR 498-940) and 305 pmolx108 RBC (IQR 198-608). In none of the patients NRH was observed; sinusoidal dilatation was observed in four patients. No trombocytopenia was observed.

Conclusions: Short term prevalence of NRH in IBD-patients who were treated with a combination of allopurinol and low dose conventional thiopurine, was low, as in none of the included eighteen patients NRH was observed.

Publication Type: Journal: Conference Abstract Source: EMBASE Full Text: Available from Elsevier in Journal of Crohn’s and Colitis Available from Oxford University Press in Journal of Crohn's and Colitis

11. Title: **Low-dose thiopurine and allopurinol co-therapy results in significant cost savings at a district general hospital** Citation: Gastroenterology, May 2013, vol./is. 144/5 SUPPL. 1(S777), 0016-5085 (May 2013) Author(s): Johnson H.E., Dewhurst H.M., Weaver S., McLaughlin S.D.

Abstract: Background Thiopurines are used for maintenance of remission in IBD. In England and Wales biologics are approved by NICE (National institute for health and clinical excellence) for Crohn's disease (CD) but not ulcerative colitis. Adalimumab is recommended in preference to infliximab in patients over 65kg due to cost. Published data report .50% of patients stop thiopurines due to therapeutic failure, hepatitis or side effects. In this situation most UK clinicians start biologics

in CD patients. This has significant cost implications. An alternative treatment strategy is low dose thiopurine and allopurinol (LDTA) co-therapy which is effective in most patients who fail standard dose thiopurines. Some patients require liquid thiopurine to achieve the correct (low) dose -this formulation is significantly more costly than tablets. We report the annual cost savings from adopting this strategy at our centre.

Methods We maintain a prospective IBD database. Patients with CD treated with LDTA in preference to biologic therapy were identified. The annual drug costs of their treatment with LDTA compared with biologic therapy (adalimumab for patients over 65kg, Infliximab for patients ,65kg) were calculated including the cost for the formulation of thiopurine used (liquid/capsules/tablets) and the dose prescribed. Costs of attending the day unit for an infusion were not included.

Results 17 CD patients who failed standard thiopurine and were eligible for biologics were identified over a 1 year period (Sept 2011-Sept 2012). Of these 4 (24%) failed LDTA and progressed to biologics, 13 (76%) entered a sustained clinical remission. Mean weight of patients= 77.3kg (range: 53.5-105), 6 (46%) patients required liquid thiopurine, Mean calculated costs were: thiopurine $727.427 (range: $78.022 - 2,165.549), biologics: $18,237.877 (range: $16,996.914 - 25,883.281). Mean cost saving per patient: $17,510.359 (range: $ 14,832.053 - 24,378.334). Total cost saving: $227,634.

Conclusion We have previously reported that low dose thiopurine and allopurinol co-therapy is safe and effective. In the present study we have identified significant annual cost savings can be made when this treatment strategy is used to prevent escalation to biologics. These cost savings are likely to be even more significant in the long term since a significant proportion of patients treated with biologic therapy require dose escalation. We believe adopting this strategy more widely could lead to significant health-care savings. (Table Presented).

Publication Type: Journal: Conference Abstract Source: EMBASE

12. Title: **District general hospital experience of optimising treatment outcome on thiopurines by co-prescription of allopurinol in patients with inflammatory bowel disease** Citation: Gut, July 2012, vol./is. 61/(A400), 0017-5749 (July 2012) Author(s): Cherian S., Gera A., Saxena V., Loganayagam A.

Abstract: Introduction: Numerous patients, especially those with elevated thiopurine methyltransferase (TPMT) activity, selectively methylate thiopurine drugs, generating high levels of methylated metabolites and low thioguanine nucleotides. This pattern of metabolism is related to hepatotoxicity and non-response to therapy. Co-prescription of thiopurines (TP) (at 25% of standard dose) with allopurinol (xanthine oxidase inhibitor) seems to avoid this problem, optimising both metabolite profile and clinical response. British experience on the use of this combination therapy (CT) remains limited. In this study we report a district general hospital (DGH) experience for the indications of toxicity (mainly hepatic) and very high TPMT activity in patients with inflammatory bowel disease (IBD).

Methods: Retrospective notes review of patients at a district general hospital treated with CT using 25% dose of TP and 100 mg allopurinol was undertaken. Particular attention was paid to whether CT overcame the specific problem that prevented thiopurine monotherapy

Results 15 patients (age 24-77 yrs, male=6, Crohn's=6, ulcerative colitis=9) were identified. All 15 patients were on an oral five amino salicylic acid preparation and 12 patients had previously been on a TP. Two patients with fibrotic stricture and one patient with hepatic steatosis were excluded from the analysis. Of those patients receiving co-prescription for side effects (four hepatoxicity and five others: rash, nausea, headache, fatigue), 78% were able to tolerate CT with complete resolution of liver function abnormality where relevant. Clinical remission was achieved in 100% of the patients who tolerated CT. In the three patients where CT was commenced for very high TPMT activity, 1 (33%) developed non-specific side effects (headache, nausea) leading to discontinuation of therapy and 2 (67%) achieved clinical remission.

Conclusion: CT with low-dose TP and allopurinol avoids hepatotoxicity and improves chances for clinical remission. CT may also prevent other side effects. CT should be fully utilised in a DGH for hepatoxicity and other side effects. Using CT as first line in those with high TPMT activity remains questionable and requires further scrutiny in a prospective study.

Publication Type: Journal: Conference Abstract Source: EMBASE Full Text: Available from Highwire Press in Gut

13. Title: **Outcomes of increased dose of allopurinol in IBD patients who developed hepatotoxicity on low azathioprine and allopurinol co-therapy treatment** Citation: Gut, June 2014, vol./is. 63/(A84-A85), 0017-5749 (June 2014) Author(s): Pericleous M., Abdulrehman A., Bull C., Mackenzie G., Stenner J., Cowan M., Hillman G., Ansari A.

Abstract: Introduction The thiopurines (azathioprine (AZA) and metcaptopurine (6MP)) are established first line therapies for inflammatory bowel disease (IBD). However, when these agents are used at their target dose side effects are common, gastrointestinal intolerance (10-20%) and hepatotoxicity (>10%).1 These side effects can often be bypassed by using low dose AZA and allopurinol (ALLO) co-therapy (LDAA). The current opinion is that hepatotoxicity is secondary to high red cell methylated metabolites (MMPR/MMP). However, many patients develop hepatotoxicity without high MMP levels.2 We report a series of patients who regardless of low MMP developed hepatotoxicity whilst on allopurinol co-therapy, 3 of which were TPMT heterozygotes.

Aim to determine outcomes of increasing the dose of Allopurinol from 100 to 200 mg in patients with hepatotoxicity to LDAA.

Methods Patient records and our IBD database were searched for patients on LDAA who developed hepatotoxicity whilst on LDAA (100 mg of ALLO). Liver function tests (LFTs), liver screen, ultrasound results and clinical outcomes were determined.

Results From the 2500 patients with IBD locally, 600 were exposed to thiopurines and 300 were on LDAA. Nine patients had sustained hepatotoxicity, 3 were TPMT heterozygotes. Seven of these patients responded fully to increased dose of ALLO to 200mg. Two had a suboptimal response (1 had PSC as a potential cause). All patients had asymptomatic abnormalities of LFTS, negative chronic liver screen apart from 2 who had ultrasound proven fatty liver disease without abnormal LFTs prior to LDAA. We observed that all patients had improvements in their LFTs, whilst 7 had complete correction of abnormal AST, ALP and bilirubin. Median time for treatment was 24 months (range 12-48 months), with full response to therapy in all 7 patients.

Conclusion This is the first series which reports improvement of LFTs by increasing ALLO dose for patients on LDAA. This subgroup of patients were unlikely to have high MMPR as 3 of them were TPMT heterozygotes and all were on LDAA therapy, therefore a different mechanism, of hepatotoxicity is proposed (Figure 1). It is possible that reactive oxygen species generated from the oxidation of metcaptopurine are responsible, and this can be further improved by adjusting the dose of ALLO. Further studies are required.

Publication Type: Journal: Conference Abstract Source: EMBASE Full Text: Available from Highwire Press in Gut

14. Title: **Low allopurinol doses are sufficient to optimize azathioprine therapy in inflammatory bowel disease patients with inadequate thiopurine metabolite concentrations**. Citation: European journal of clinical pharmacology, Aug 2013, vol. 69, no. 8, p. 1521-1531 (August 2013) Author(s): Curkovic, Ivanka, Rentsch, Katharina M, Frei, Pascal, Fried, Michael, Rogler, Gerhard, Kullak-Ublick, Gerd A, Jetter, Alexander

Abstract: Recent studies in patients with inflammatory bowel diseases (IBD) on thiopurine therapy suggest that too low 6-thioguanine nucleotide concentrations (6-TGN) and too high methylmercaptopurine nucleotide concentrations (MMPN) can be reversed by a combination therapy of allopurinol and low-dose thiopurines. To date, however, optimal dosing has not been established.

The aim of this study was to evaluate the minimal allopurinol doses necessary to achieve adequate 6-TGN concentrations in combination with low-dose azathioprine.

Methods A stepwise dose-escalation of allopurinol was performed in 11 azathioprine-pretreated IBD patients with inadequately low 6-TGN concentrations (<235 pmol/8 × 10(8) erythrocytes) and/or elevated MMPN concentrations (>5,000 pmol/8 × 10(8) erythrocytes) and/or elevated liver enzymes (alanine aminotransferase and/or aspartate aminotransferase levels one- to threefold the upper limit of normal). Six patients were recruited into an open study, and five were treated in the context of an individualized therapeutic approach. Adverse effects, azathioprine metabolites, liver enzymes and whole blood counts were monitored two to three times per month.

Results Adequate 6-TGN concentrations were achieved with a combination of 25 mg allopurinol and 50 mg azathioprine in one patient and with 50 mg allopurinol and 50 mg azathioprine in nine patients. Median 6-TGN concentrations (range) were 336 (290-488) pmol/8 × 10(8) erythrocytes after an 8-week-long intake of the final dose combination. One patient dropped out due to nausea after the first intake. MMPN concentrations and liver enzymes normalized immediately in all affected patients. All patients finishing the dose-escalation regimen tolerated the treatment without toxicity.

Conclusion Combination therapy with only 50 mg allopurinol and 50 mg azathioprine daily is sufficient, efficacious and safe in most IBD patients with inadequate thiopurine metabolite concentrations to optimize azathioprine-based IBD therapy.

Source: Medline Full Text: Available from ProQuest in European Journal of Clinical Pharmacology Available from SpringerLink in European Journal of Clinical Pharmacology

CASE REPORTS

(1) Title: **Allopurinol: A useful adjunct to thiopurine therapy for pediatric ulcerative colitis in the biologic era** Journal of Pediatric Gastroenterology and Nutrition, July 2014, vol./is. 59/1(22-24), 0277-2116;1536-4801 (01 Jul 2014) Ihekweazu F.D., Kellermayer R.

Abstract: Thiopurines are used as a maintenance therapy in patients with ulcerative colitis (UC). For some patients the metabolismof thiopurines is unfavorable, leading to increased adverse effects, including hepatotoxicity. There are many reports in the adult literature concerning the manipulation of thiopurine metabolism with allopurinol; however, there is only 1 publication in this respect for pediatric UC.

We present 3 pediatric cases of UC wherein the combination of allopurinol and low-dose 6-mercaptopurine allowed for shunting of thiopurine metabolites to a more favorable pattern.

This intervention supported clinical remission in all, including one case poorly responsive to infliximab.

Publication Type: Journal: Article Source: EMBASE Full Text: Available from Ovid in Journal of Pediatric Gastroenterology and Nutrition

(2) Title: **Successful pregnancies with thiopurine-allopurinol co-therapy for inflammatory bowel disease** Gut, June 2014, vol./is. 63/(A85-A86), 0017-5749 (June 2014) Sheikh M., Nelson-Piercy C., Stenner J., Mackenzie G., Duley J., Florin T., Ansari A.

Abstract: Introduction Combination of low dose thiopurine with allopurinol can improve the clinical efficacy and bypass some of the adverse reactions of thiopurine monotherapy. Thiopurines can be used safely during pregnancy but there is scarce data regarding allopurinol. We report twelve cases of safe use of thiopurine and allopurinol co-therapy to manage IBD during pregnancy.

Methods Patients were retrospectively identified at two hospitals in the UK and in Australia, using our local IBD databases. All pregnancies of co-therapy patients were included. TPMT activity and pre-pregnancy weight were used to calculate thiopurine dosing. Data regarding pregnancy and fetal outcomes were collected from patient notes.

Results Eleven females on co-therapy became pregnant, totalling twelve pregnancies with eight live births (Table 1) and four ongoing pregnancies. There were no reported terminations, miscarriages or spontaneous pre-term deliveries (<37 weeks). Four patients gave birth by spontaneous vaginal delivery (SVD); four by Caesarean section (C-section). There were no low birth weight (<2.5kg) babies. The APGAR scores of all babies were normal and no congenital malformations were identified either on fetal ultrasound scans or on neonate checks. The median duration of follow-up of babies was 6.5 months with no indication of morbidity. (Table Presented)

Conclusion All twelve cases were treated successfully with co-therapy without any adverse pregnancy related events or adverse fetal outcomes. Intrauterine exposure of the fetus to thiopurine metabolites is not greater with combination therapy compared with thiopurine monotherapy. There are only two reports of congenital malformations with maternal allopurinol use. The case for an

association based on two cases is weak, moreover a negative publication bias with respects to successful maternal allopurinal use is suspected. Our study provides support for clinicians and patients wishing to continue thiopurine-allopurinol co-therapy during pregnancy.

Publication Type: Journal: Conference Abstract Source: EMBASE Full Text: Available from Highwire Press in Gut

(3) Title: **Allopurinol use in pregnancy in three women with inflammatory bowel disease: Safety and outcomes: A case series** BMC Gastroenterology, December 2013, vol./is. 13/1(no pagination), 1471-230X (17 Dec 2013) Fazal M.W., Doogue M.P., Leong R.W., Bampton P.A., Andrews J.M.

Abstract: Background: Allopurinol is a frequently prescribed drug. In inflammatory bowel disease patients who shunt thiopurine metabolism towards more toxic and less desirable pathways, allopurinol is proving to be an effective add on therapy with good resultant disease control and less treatment side effects. As many such patients are young, the potential for pregnant women to be exposed to allopurinol is increasing. The safety of allopurinol in pregnancy is not known however.

Case presentation: We report three cases of safe use of allopurinol in pregnancy for women with inflammatory bowel disease. This included 2 patients with ulcerative colitis and 1 patient with fistulising Crohn's disease. Allopurinol was used throughout pregnancy in all patients. All 3 pregnancies resulted in normal healthy babies born at term by Caesarean section.

Conclusion: It is important to evaluate and document the safety of allopurinol during pregnancy, as it is finding new roles in young patients. These three cases add significantly to the very limited data on allopurinol use in pregnancy. We encourage reporting of all cases of allopurinol use in pregnant patients and suggest an allopurinol pregnancy registry to document drug exposures and outcomes. © 2013 Fazal et al.; licensee BioMed Central Ltd.

Publication Type: Journal: Article Source: EMBASE Full Text: Available from BioMed Central in BMC Gastroenterology Available from National Library of Medicine in BMC Gastroenterology

(4) Title: **A skewed thiopurine metabolism is a common clinical phenomenon that can be successfully managed with a combination of low-dose azathioprine and allopurinol**. Journal of Crohn's & colitis, Jul 2013, vol. 7, no. 6, p. 510-513 (July 2013) Appell, Malin Lindqvist, Wagner, Agnieszka, Hindorf, Ulf

Abstract: A skewed thiopurine metabolism is a phenomenon associated with both poor treatment response and toxicity. Our aim was to evaluate the frequency of this phenomenon and the relationship to thiopurine methyltransferase (TPMT) function. All thiopurine metabolite measurements in adult patients (n=4033) between January 2006 and April 2012 were assessed to evaluate the occurrence of a skewed metabolism and the relationship to TPMT genotype and activity. A skewed metabolism was observed in 14% of all patients. It only developed in patients with a normal TPMT genotype, but was observed at all TPMT activity levels within the normal range (9.1-24.2 U/ml RBC). Two cases that illustrate typical clinical scenarios of a skewed metabolism and the effect of combination treatment with low-dose azathioprine and allopurinol are presented. A skewed metabolism is a common clinical phenomenon in patients with a normal TPMT function, which can develop at all TPMT activity levels within the normal range. We suggest that metabolite

measurements should be considered in patients not responding to treatment and in those with hepatotoxicity or myelotoxicity in order to detect a skewed metabolism, since this phenomenon can be successfully managed by a combination of low-dose azathioprine and allopurinol.

Source: MedlineFull Text: Available from Oxford University Press in Journal of Crohn's and Colitis

REVIEW ARTICLES

(1) Title: **Update 2014: Advances to optimize 6-mercaptopurine and azathioprine to reduce toxicity and improve efficacy in the management of IBD** Citation: Inflammatory Bowel Diseases, 2015, vol./is. 21/2(445-452), 1078-0998;1536-4844 (2015) Author(s): Amin J., Huang B., Yoon J., Shih D.Q.

Abstract:

Background: The thiopurine drugs, 6-mercaptopurine (6-MP) and azathioprine (AZA), remain as a mainstay therapy in inflammatory bowel disease (IBD). Differences in metabolism of these drugs lead to individual variation in thiopurine metabolite levels that can determine its therapeutic efficacy and development of adverse reactions. In this update, we will review thiopurine metabolic pathway along with the up-to-date approaches in administering thiopurine medications based on the current literature.

Methods: A search of the PubMed database by 2 independent reviewers identifying 98 articles evaluating thiopurine metabolism and IBD management.

Results: Monitoring thiopurine metabolites can assist physicians in optimizing 6-MP and AZA therapy in treating patients with IBD. Of the dosing strategies reviewed, we found evidence for monitoring thiopurine metabolite level, use of allopurinol with thiopurine, use of mesalamine with thiopurine, combination therapy with thiopurine and anti-tumor necrosis factor agents, and split dosing of AZA or 6-MP to optimize thiopurine therapy and minimize adverse effects in IBD.

Conclusions: Based on the currently available literature, various dosing strategies to improve therapeutic response and reduce adverse reactions can be considered, including use of allopurinol with thiopurine, use of mesalamine with thiopurine, combination therapy with thiopurine and anti-tumor necrosis factor agents, and split dosing of thiopurine.

Publication Type: Journal: Review Source: EMBASE Full Text: Available from Wiley-Blackwell Free Backfiles NHS in Inflammatory Bowel Diseases

(2) Title: **Thiopurine prescribing and monitoring behaviour, including metabolites testing and allopurinol co-therapy: An Australian perspective from 2008 to 2013** Citation: Journal of Gastroenterology and Hepatology (Australia), October 2014, vol./is. 29/(114), 0815-9319 (October 2014) Author(s): Sze K.C.P., Siriwardana A., Sechi A., Ng W.S.W., Connor S.J.

Abstract:

Background: Thiopurines (TP) are a mainstay of inflammatory bowel disease (IBD) therapy. Thiopurine methyltransferase (TPMT) and TP metabolites testing have been suggested to predict variation in metabolism and response to therapy. However, prospective data to confirm clinical benefits of metabolites guided dosing is still limited, as are guidelines for TP monitoring. Aim: To evaluate Australian gastroenterologists' practice in TP use for IBD, including TPMT and metabolites testing, full blood count (FBC) monitoring, allopurinol co-therapy, effects on clinical outcomes, and how practices changed over time.

Methods: An anonymous survey was distributed to gastroenterologists by email and at meetings across Australia over 6 months in 2013, and results were compared with a similar survey conducted in 20081. The Chi-squared and Fisher exact tests were used to calculate statistical significance.

Results: 168 responses were received (135 online; 33 paper), of which 137 (81.5%) were complete, while the remainder 31 (18.5%) were partially complete. The results found a statistically significant increase in 2013 from 2008 with respect to the proportion of respondents who utilized TPMT testing (79.1% vs 44.5%, $p < 0.0001$), and TP metabolites testing (87.7% vs 29.1%, $p < 0.0001$). A large proportion of those who utilized TP metabolite testing used it not just for non-response (84.8%), but also for dose adjustment to optimize response (80.4%). With respect to allopurinol co-therapy, this was utilized by the majority of respondents (71%) amongst whom a significant proportion used it for shunters irrespective of LFTs (24.7%) or for side effects irrespective of LFTs (36.6%). Overall the majority of respondents believed the availability of metabolites testing had improved clinical outcomes by improved response rates, reduced complication rates, and changed clinical practice (80.6%, 60.4% and 79.2% of respondents, respectively). Additionally, variability was found in full blood count monitoring intervals during the first three months of commencing TP therapy, reflecting a lack of consensus on myelotoxicity monitoring.

Publication Type: Journal: Conference Abstract Source: EMBASE Full Text: Available from Wiley in Journal of Gastroenterology and Hepatology

(3) Title: **Allopurinol-thiopurine combination therapy in inflammatory bowel disease**

Citation: Clinical Investigation, October 2014, vol./is. 4/10(873-879), 2041-6792;2041-6806 (01 Oct 2014) Author(s): Seinen M.L., De Boer N.K.H., Van Bodegraven A.A., Hanauer S.B., Hoentjen F.

Abstract: Combination therapy with allopurinol and low-dose thiopurine (azathioprine and mercaptopurine) has been described as an alternative immunosuppressive strategy in adult inflammatory bowel disease patients. Currently, this combination treatment is used in clinical practice to optimize ineffective or non-tolerated weight-based thiopurine monotherapy. In the setting of persistent disease or thiopurine intolerances in combination with an aberrant ('skewed') thiopurine metabolism (6-MMP/6-TGN > 20) allopurinol-thiopurine combination therapy can be a safe and effective approach. Here we will discuss the efficacy and safety of allopurinol-thiopurine combination therapy in inflammatory bowel disease patients. Furthermore, we will review the mechanism of action, recommendations for the use of combination therapy in daily clinical practice and points of interest for future research.

Publication Type: Journal: Article Source: EMBASE

Date:

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Lead Commissioning Pharmacist, Supporting Guildford and Waverley CCG, and Surrey Heath CCG

VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
LC	08/03/16	Liz Clark	draft	
LCcj	14/03/16	Carina Joanes	Draft	Reviewed and minor additions