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INVITED REVIEW

Low-Dose Azathioprine in Combination with Allopurinol: The Past, Present and Future of This Useful Duo

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Abstract

The inflammatory bowel diseases (IBD) are complex immune-mediated inflammatory diseases that are associated with significant morbidity around the world. As our understanding of IBD, and other immune-mediated inflammatory diseases, advances the number of therapeutic targets has increased which has rapidly driven the development and introduction of new therapies. While these new therapies have shown promise they come with the significant drawback of high costs. For many IBD patients around the world the cost of newer therapies is prohibitive which means treating clinicians often need to turn to optimising simpler, older, and inexpensive medications. The concept of optimising well established cheaper medications is not unique to the management of IBD as health systems all over the world look to reduce costs while simultaneously improving patient outcomes. Despite thiopurines being used in the management IBD for over 60 years, many clinicians are still hesitant to use them due to perceptions around limited efficacy and poor tolerance. One method identified to potentially increase utilisation of thiopurines involves the coadministration of allopurinol. In this review we will explore the history, pharmacology, recent studies and give recommendations for the utilisation of the usual duo of azathioprine combined with allopurinol.

Keywords Inflammatory bowel disease · Azathioprine · Thiopurine · Allopurinol · Metabolite monitoring

Why It's Important to Review This Topic

The inflammatory bowel diseases (IBD) continue to represent complex diseases with significant morbidity and quality of life impairment. These immune-mediated inflammatory diseases require the use of immunomodulators and/or biologic agents in a significant proportion of patients. Many treatments for IBD are shared across numerous indications from autoimmune diseases through to organ transplantation. Over the last 50 years there has been an increase in the medications that have become available for the treatment of IBD. However, as the understanding of IBD increases and new treatment targets are identified, the medications being developed are expensive due to high production costs [1–4]. With health care costs rising globally, many health systems may benefit from optimising older, simpler and cheaper therapies [5–7]. Thiopurines, including azathioprine, mercaptopurine and thioguanine, particularly when optimised using therapeutic drug monitoring and/or concomitant allopurinol, are one such class of medications.

While thiopurines have not been able to demonstrate equivalent effectiveness when compared to biologics, such as anti- tumour necrosis factor (anti-TNF) agents, used alone or in combination with immunomodulators, they do have several advantages [7–11]. The most obvious benefits of thiopurines are reduced cost, ease of administration and simpler storage. As a result, thiopurines still have an important role in IBD management globally. The optimisation of thiopurines is associated with increased rates of clinical and endoscopic remission [12, 13]. Intuitively this should translate to reduced rates of escalation of therapy to other classes, including biologics, with resulting cost-savings, although we acknowledge that this perception is not supported by results from well-designed prospective studies.

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While in many countries the combination of azathioprine and allopurinol costs patients approximately 1% of their countries GDP/Capita, biologic therapy can cost patients in wealthy countries more than 100% of their countries GDP/Capita with the relative price being even higher in developing countries [1, 3, 6, 14, 15]. Fortunately, the cost of biologics is falling, in some cases by 90%, with the utilisation of biosimilars [16, 17]. However, despite this reduction in costs biologic therapies remain expensive compared to other therapies which may limit their availability, especially in developing countries [10, 11, 18, 19].

In recent years the tolerability and safety of thiopurines has been questioned, which has limited their use in some jurisdictions, and North America in particular [1]. Fortunately, as is the focus of this review, the combination of allopurinol with azathioprine presents a therapeutic option for some patients who experience intolerance or side effects of azathioprine monotherapy. This includes patients who require thiopurines in combination therapy with biologics, in particular with anti-TNF agents.

History of Azathioprine and Allopurinol

The purine analogues 'thiopurines' were first created by future Nobel laureates George Hitchings and Gertrude Elion in the 1940s as scientists strived to discover new antibiotic medications around the time of World War Two [20]. In their laboratory they revealed that the thiopurines were not useful antibiotics but were noted to be effective against leukemia cells in mice, however toxicity limited their use. By 1951, further refining of thiopurines led to the creation of 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG) which were subsequently used to treat children with acute leukemias who up until that point only had corticosteroids and methotrexate available as treatments. The Food and Drug Administration of the United States of America approved thiopurine medications for use in 1953 [21].

6-TG, which had been synthesised before 6-MP, was more difficult to manufacture and more toxic, leading to 6-MP being favoured. Numerous attempts were made to modify 6-MP to make it more target-specific and better tolerated. The most successful compound, that was created in 1957, was 6-(3-methyl-5-nitroimidazol-4-yl) sulfanyl-7H-purine which would later be named azathioprine. Azathioprine and 6-MP went on to be used extensively in transplantation and leukaemia before first being used in IBD in 1962 where they were used to maintain remission in patients with ulcerative colitis [22]. Since the 1960s thiopurines have continued to be used in the management of IBD and numerous other medical conditions [23, 24].

In parallel to the work on thiopurines, numerous xanthine oxidase inhibitors were being used in laboratory work to modify concentrations of naturally occurring purines. Eventually the desire to use a xanthine oxidase inhibitor for in vivo human experiments led to the development of a minimally toxic medication, 4-hydroxypyrazolo (3,4-d) pyrimidine, which would subsequently be named allopurinol. Allopurinol was trialled to improve the efficacy and reduce the toxicity of thiopurines used to treat leukemias. The initial studies didn't demonstrate significant benefits and the use of the allopurinol for this purpose was discontinued [25]. Interest in allopurinol re-emerged in 1965 when it was recognised that it could be used to reduce uric acid levels in patients with gout and tumour related hyperuricemia [20, 26].

It wasn't until 1993 that the azathioprine-allopurinol combination was utilised again when it was shown to improve graft survival for patients who had undergone renal transplantation [27]. While thiopurines have been used in IBD since 1962, interest in the combination of azathioprine and allopurinol re-emerged in 2005 when the beneficial effects of this combination on thiopurine metabolism and tolerance was demonstrated in patients experiencing inefficacy or adverse effects to thiopurines [28]. This work was replicated by numerous groups, leading to azathioprine and allopurinol currently being routinely used in IBD management globally. More recently its use has expanded to other gastrointestinal indications, including autoimmune hepatitis [29, 30].

Azathioprine: Indications in IBD

In 2022, azathioprine remains a commonly used treatment in IBD. Thiopurines are indicated as steroid-sparing maintenance agents in both Crohn's disease and ulcerative colitis, but not as induction agents due to their slow onset of action [26]. They are efficacious in the prevention of Crohn's disease post-operatively, although probably less so than anti-TNF agents [31–34]. In fistulising Crohn's disease thiopurines are only recommended for use in combination with an anti-TNF as they are ineffective when used as monotherapy in this setting [31–34].

Azathioprine: Mechanism of Action in IBD

The mechanism of action of azathioprine is still incompletely understood and is likely multifactorial (see Fig. 1). The intracellular metabolites of azathioprine, in particular 6-thioguanine nucleotides (6-TGN), are the most active moieties. Due to their similarity to DNA guanines, 6-TGN are incorporated into cellular DNA particularly in the target cell lines of myeloid lineage. This incorporation into DNA at appropriate frequency can lead to a decreased stability of DNA which is amplified during rapid replication which in turn results in cell death [35, 36]. Another mechanism labelled purine starvation involves alkylating of thiol groups

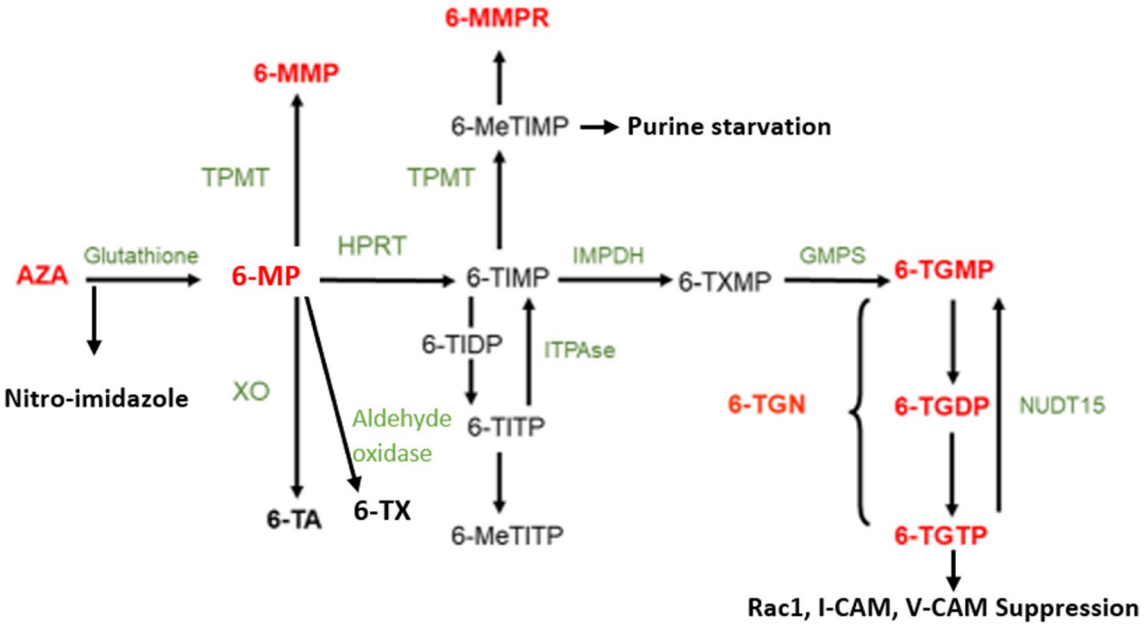

Fig. 1 Thiopurine metabolism. *AZA* azathioprine, *6-MP* 6-mercaptopurine, *TPMT* thiopurine S-methyltransferase, *XO* xanthine oxidase, *6-TA* 6-thiouric acid, *6-TX* 6-thioxanthine, *HPRT* hypoxanthine guanine phosphoribosyltransferase, *6-TIMP* 6-thioinosine monophosphate, *6-MeTIMP* 6-methylthioinosine monophosphate, *IMPDH* inosine-5-monophosphate dehydrogenase, *6-MMPR* 6-methylmercaptopurine ribonucleotides, *6-TIDP* thioinosine diphosphate, *6-TITP* thioinosine triphosphate, *6-meTITP* methylthioinosine triphosphate, *ITPAse* inosine triphosphate pyrophosphohydrolase, *6-TXMP* thioxanthine monophosphate, *GMPS* guanidine-5-monophosphate synthetase, *6-TGMP* thioguanine monophosphate, *6-TGDP* thioguanine diphosphate, *6-TGTP* thioguanine triphosphate, *6-TGN* thioguanine nucleotides, *NUDT15* Nudix hydrolase 15, *Rac1* Rac Family Small GTPase 1, *I-CAM* intercellular adhesion molecule 1, *V-CAM* vascular cell adhesion protein 1. Modified with permission from Nguyen et al. [4]

leading to impaired nucleic acid biosynthesis which leads to interferences with DNA replication. Additionally, 6-methylmercaptopurine ribonucleotides (6- MMPR), formed by the action of thiopurine methyltransferase (TPMT) on the thiopurine metabolite 6-thio inosine monophosphate (6-TIMP), may inhibit de novo purine synthesis by blocking phosphoribosylpyrophosphate amido-transferase which would also result in impaired DNA replication [37].

A further important mechanism of action involves 6-TGN inhibiting the Rac1 pathway leading to downregulation of CD28, ICAM-1 and VCAM-1. Downregulation of CD28 results in reduced T-cell activation via the T-cell receptor (CD3) costimulatory ligand pathway while reduction in the ICAM-1 and VCAM-1 reduce leukocyte migration into inflammatory sites [38–40]. These changes favour immune regulation/tolerance rather than autoimmunity against self-antigens.

Azathioprine: Metabolism, Dosing and Monitoring

Azathioprine has a complex metabolism, leading to variable response and metabolite profiles in individual patients and the need to personalise dosage. Azathioprine is most often prescribed at a dose of 2–2.5 mg/kg orally once daily. Oral azathioprine has a bioavailability of approximately 60% [41] with its absorbance reduced when consumed with food. Azathioprine is excreted as its various metabolites primarily by the kidneys. Once absorbed azathioprine is metabolised in the liver by glutathione-S-transferase into 6-MP and methyl-nitrothioimidazole. Methyl-nitrothioimidazole has minor immunosuppressive effects but causes intolerance in a considerable number of patients who are able to be switched to 6MP successfully [42–44].

6-MP is taken up by the target white blood cell progenitors, particularly the myeloid lineage, in the bone marrow. Once inside leukocytes 6-MP is subject to four competing pathways of metabolism (see Fig. 1) [45, 46]. Xanthine oxidase (XO) oxidizes 6-MP to produce the inactive metabolite 6-thiouric acid. Aldehyde oxidase oxidises 6-MP to 6-thioxanthine (6-TX) which may inhibit TPMT. Hypoxanthine guanine phosphoribosyltransferase followed by inosine-5-monophosphate dehydrogenase and finally guanidine-5-monophosphate synthetase coverts 6-MP to the 6-TGN. The 6-TGN, 6-thioguanine monophosphate, 6-thioguanine diphosphate and 6-thioguanine triphosphate, are the primary metabolites that exerts the immunosuppressive action of azathioprine, of which 6-thioguanine triphosphate is known to be the most active particularly in the inhibition of Rac1 [38]. The final competitive pathway for 6-MP involves the action of TPMT which leads to the creation of hepatotoxic

6-MMPR. The variable activity of these enzymes in an individual leads to the specific profile of metabolites produced.

Of the numerous enzymes involved in the metabolism of azathioprine it is the action of three that are considered most important; TPMT, Nudix Hydrolyase 15 (NUDT15) and XO which is inhibited by allopurinol. Functional activity of TPMT is genetically determined with population studies showing its activity has a trimodal distribution [47]. 89% of the population possesses normal or high activity (homozygous), 11% have intermediate activity (heterozygotes) and 0.3% have low or absent enzyme activity [48]. Up to 20% of the population preferentially create 6-MMPR through overactivity of the TPMT pathway and they are known as hypermethylators or 'shunters' [49]. Patients with low or absent TPMT activity are at risk of bone marrow suppression from the high levels of 6-TGN relative to the dose received [46, 47]. TPMT testing, by phenotype or genotype, is now recommended in all patients prior to commencing a thiopurine [8, 47]. More recently, polymorphisms of Nudix NUDT15 have also been associated with myelotoxicity, especially in Asian ethnicities. Accumulation of 6- thioguanosine triphosphate, which is normally inactivated by wildtype NUDT15, is believed to be the cause of this toxicity [50–52].

Due to the complex and highly variable metabolism of thiopurines it was identified that the use of therapeutic monitoring could be employed to optimise both safety and efficacy [53, 54]. Initially monitoring was limited to plasma 6-MP and urinary excretion of 6-thiouracic acid [20]. Measuring thiopurine metabolites in myeloid cells proved to be challenging however it was discovered that thiopurines metabolites are absorbed into red blood cells (RBC) and therefore metabolite measurement using RBC levels provided a practical surrogate for myeloid metabolite levels [55]. Numerous studies have shown that a red blood cell 6-TGN levels of greater than 235 pmol/8×10^8 RBC are associated with significantly higher pooled odds ratio [OR] (OR 3.15 95% CI 2.41–4.11 p value ≤ 0.0001) of clinical response to thiopurine therapy [12, 56, 57]. Higher 6-TGN levels of around 400 pmol/8×10^8 RBC have been associated with the harder endpoint of endoscopic healing [13, 58], while levels greater than 450 pmol/8×10^8 RBC have correlated with increased toxicity and minimal further therapeutic gain [12, 57]. Studies have also indicated that red blood cell 6-MMPR levels of greater than 5,700 pmol/8×10^8 RBC are associated with an increased risk of dose limiting hepatotoxicity [57]. It must be acknowledged that most data supporting measurement of thiopurine metabolites comes from retrospective studies. There have been two prospective randomized controlled trials comparing weight-based versus metabolite-based thiopurine dosing. The first study in 2007 concluded that metabolite monitoring did not offer benefit, however it was a small trial and the average 6-TGN levels were below 300 pmol/8×10^8 RBC in both groups [59]. The second trial in 2013 was terminated early due to slow recruitment, however, analyses of the incomplete data suggested trends to improvement in patients with a therapeutic 6-TGN level (> 250 pmol/8×10^8 RBC) [60]. A guide to the interpretation of thiopurine metabolites is provided in Table 1.

Azathioprine: Adverse Effects

Azathioprine is discontinued in patients due to side effects in up to 20–40% of patients with most occurring in the first three months [61–63]. Adverse events can be divided into idiosyncratic/allergic reactions, dose (metabolite) dependent reactions and malignancies. Idiosyncratic/allergic reactions include gastrointestinal toxicity, skin toxicity, pancreatitis, constitutional symptoms, and drug induced hypersensitivity reactions. Changing a patient from azathioprine to 6-MP can overcome intolerances in up 50% of cases, consistent with methyl-nitrothioimidazole being the cause of intolerance in these patients [64]. Rat models have suggested that the generation of reactive oxygen species could be another reason for azathioprine toxicity that might not be explained by measurements of metabolites [65].

Table 1 Guide to interpretation of azathioprine metabolites

6-TGN	6-MMPR	Meaning	Action
Nil/negligible	Nil/negligible	Poor adherence	Patient education and pharmacist engagement
Low (< 235)	Low	Under-dosing	Increase dose and recheck bloods and levels in 4 weeks
Low (< 235)	High (6-MMPR:6-TGN ratio > 11)	Thiopurine hypermethylator (Shunter)	Switch to low dose AZA or 6-MP (25–33% weight-based dose) and introduce allopurinol 100 mg. Ongoing monitoring
Therapeutic (235–450)	Normal (< 5700)	Therapeutic range	Maintain if clinical indication, response and tolerated. Consider targeting a 6-TGN of 400 for endoscopic healing. Consider change of class if no response
High (> 450)	Elevated (> 5700)	Over-dosing	Consider reducing dose and recheck metabolites in 4 weeks

All 6-TGN and 6-MMPR values are in pmol/8×10^8 red blood cells

6-TGN thioguanine nucleotides, *6-MMPR* 6-methylmercaptopurine ribonucleotides, *AZA* azathioprine, *6-MP* 6-mercaptopuine

Dose (and metabolite)-dependent adverse events include myelosuppression, hepatotoxicity, and infections [63, 66, 67]. It is suspected that approximately 20% of patients commenced on azathioprine will experience adverse effects due to toxic levels of the metabolites 6-MMPR (> 5,700 pmol/8 × 10^8 RBC) and/or 6-TGN (> 450 pmol/8 × 10^8 RBC) [49]. The increased risk of malignancies in patients with IBD treated with thiopurines may include leukaemia, lymphoma, non-melanoma skin cancer, urothelial and cervical cancer [68–71]. While the association with non-melanoma skin cancer (hazard ratio 1.4–4.3) and lymphoma (hazard ratio 2.2–5.3) is consistent across numerous studies, the risks of other malignancies, particularly compared to patients treated with biologics, remains less definite [72–75].

Trials Examining the Use of Azathioprine and Allopurinol in IBD

With respect to retrospective studies, there are numerous groups that have published about the efficacy and safety of combination azathioprine and allopurinol use. All these groups demonstrated that combination azathioprine and allopurinol was useful, safe and effective in the management of IBD [76–81]. These studies reported a lower level of cessation for the combination therapy groups when compared to the azathioprine monotherapy groups as well as improved efficacy over monotherapy alone. The dosage of allopurinol used in these studies varied between 100 and 300 mg with 100 mg being the most common dose used. Some groups demonstrated that patients who experienced LFT derangement even after the switch from azathioprine monotherapy to combination azathioprine and allopurinol could have their LFT derangement normalised with an increased dose of allopurinol, from 100 mg to 200–300 mg daily, in almost all cases [76, 79, 81].

There have been four prospective trials that have looked at azathioprine used in combination with allopurinol for the treatment of IBD. The first study, reported in 2013, was a small 11-patient prospective non-randomised study from Switzerland that reported sufficient safety and efficacy despite its small numbers [82]. The second and fourth studies, reported by a Danish group in 2016 and 2022 [58, 83], randomised patients to receive azathioprine monotherapy or combination low-dose azathioprine and allopurinol therapy. The third study, published in 2018 by an Australian group, [84] randomised patients by the dose of allopurinol that was used in combination with an adjusted dose of azathioprine.

In a 2016 pilot study, Kiszka-Kanowitz et al. [83] randomised 46 thiopurine naïve patients with IBD to either azathioprine monotherapy or a combination of low dose azathioprine and allopurinol. After 24 weeks a significant proportion, 69.6%, of the patients treated with combination azathioprine and allopurinol were in clinical steroid free remission compared to 34.7% of the patients treated with azathioprine monotherapy (Relative Risk [RR], 2.10 [95% CI 1.07–4.11]). The study also reported that in the azathioprine group, 47.8% of the patients had to cease the medication due to adverse events compared to 30.4% of the patients in the combination azathioprine and allopurinol group (RR, 1.47 [95% CI 0.76–2.85]).

In 2022 Kiszka-Kanowitz et al. [58] published the findings of their follow up study in 89 patients with ulcerative colitis who were thiopurine naïve and had achieved remission with either steroids or infliximab, and were randomised to receive first-line azathioprine monotherapy or a combination of low dose azathioprine and allopurinol. After 52 weeks, 43% of patients treated with low dose azathioprine and allopurinol achieved remission in comparison with 21% of the patients who had received azathioprine monotherapy (OR 2.54 95% CI 1.00 to 6.78, p value ≤ 0.048). Of note, the week 52 6-TGN levels of the low dose azathioprine and allopurinol group were significantly higher, at a mean of 475 pmol/8 × 10^8RBC, compared to the azathioprine monotherapy group, with a mean of 303 pmol/8 × 10^8RBC (p value ≤ 0.001). Further trials including the ongoing DECIDER Study should help clarify the potential role of first line thiopurine-allopurinol combination therapy [76, 79, 85].

In 2018 Friedman et al. [84] reported on 73 patient identified as thiopurine shunters with- ongoing active IBD or steroid-dependence who were randomised to either 50 or 100 mg of allopurinol in combination with low dose azathioprine which was adjusted based on 6-TGN monitoring. 53% (95% CI 42–65) of patients achieved the primary endpoint of steroid-free remission and 81% of patients were able to discontinue steroids. Allopurinol 100 mg was more effective than 50 mg at reducing 6-MMPR levels. The trial also noted that patients who achieved therapeutic 6-TGN had lower average calprotectin levels, reflecting better disease control.

Allopurinol: Mechanism of Action and Safety

Allopurinol has an oral bioavailability of approximately 80% [86]. It has a half-life of one hour, however, the half-life of the active metabolite oxypurinol is much longer at 23 h. Allopurinol is predominately excreted by the kidneys as its active metabolite oxypurinol [86]. Xanthine oxidoreductase, commonly named xanthine oxidase (XO), is the enzyme that is inhibited by allopurinol therapy. XO oxidises xanthines while also directly reducing oxygen to superoxide. However, the mechanism by which allopurinol alters the mechanism of azathioprine is not fully understood. The best explanation to date comes from Blaker et al., published in 2011 [45]. They suggested that when 6-MP enters cells it undergoes four competitive pathways as outlined above. Because allopurinol

inhibits the creation of 6-TA (6-thiouric acid) there is greater conversion of 6-MP to 6-TX via aldehyde oxidase. 6-TX then results in direct inhibition of TPMT. This mechanism would explain why patients treated with a combination of thiopurine and allopurinol have significantly decreased 6-MMPR levels. Another possibility is that allopurinol could be inhibiting an enzymic co-factor involved in thiopurine metabolism. Phosphoribosylpyrophosphate (PRPP) is a necessary substrate for several enzymes involved in the synthesis of purine-based ribonucleotides including 6-MMPR. Studies predating metabolite measurements showed that allopurinol causes rapid depletion of erythrocyte PRPP which would therefore inhibits 6-MMPR production [87]. There are also data suggesting that allopurinol itself has anti-inflammatory actions in the treatment of inflammatory bowel disease by the scavenging of intestinal reactive oxygen species [88, 89].

Allopurinol is generally well tolerated with rare but well described side effects that range from mild to potentially life threatening. The most common side effects of allopurinol, occurring in between 1 and 10% of patients treated, are rash, flare of gout, nausea, vomiting and a rise in creatinine [90]. The other rarer reactions that need to be monitored for are drug reaction with eosinophilia and systemic symptoms (DRESS), Steven Johnson's syndrome, hepatoxicity, cardiac toxicity, bone marrow toxicity and neurotoxicity [90]. Fortunately, DRESS and Stevens-Johnson syndrome from allopurinol are very rare and occur in < 100 per 1,000,000 patient years and < 2 per 1,000,000 person years respectively [91–93]. Of note, patients of Asian descent and in particular Han Chinese, associated with their higher incidence of the HLA-B5801 allele, have higher rates of Stevens-Johnson syndrome from allopurinol [92, 94].

Recommendations: How and Where Does This Combination Belong in the Treatment Algorithm

Combination azathioprine and allopurinol occupies an important place in the treatment of IBD. Not only does the combination allow physicians to salvage azathioprine in patients who are shunters or are intolerant, but it also increases the number of clinical scenarios where azathioprine can be used safety.

We suggest the following situations are when combination azathioprine and allopurinol should be used:

- Patients who demonstrate significant shunting/hypermethylation (6-MMPR:6-TGN ratio > 11)
- Patients who achieve a target 6-TGN level but develop hepatotoxicity. A trial of switching from azathioprine to mercaptopurine should be tried first if azathioprine was used, but if hepatotoxicity persists allopurinol and reduced dose thiopurine should be commenced
- Patients who are receiving allopurinol for another indication (most commonly gout), in whom lower thiopurine doses will be required
- Patients with dose-dependent thiopurine intolerance, independent of metabolite levels, and when metabolite measurements are not available

Once the decision is made to transition a patient to combination azathioprine and allopurinol we suggest the following recommendations:

- Reduce the dose of azathioprine (same relative reduction for 6-MP) to 25–33% of weight-based target dose (i.e. 0.5–0.7 mg/kg for azathioprine)
- C–ommence allopurinol at 100 mg daily
- Monitor FBC, LFT and symptoms every two weeks for the first eight weeks
- Recheck metabolites (6-MMPR/6-TGN) after four weeks of therapy
- Continue to monitor bloods every 3 months for the first 12 months
- If low 6-TGN levels are found on metabolite monitoring first ensure adherence is adequate before proceeding with small (e.g. 25 mg) incremental increases in azathioprine dose
- If LFT derangement is persistent despite allopurinol cotherapy then consider increasing the allopurinol dose (to 200 or 300 mg) with close monitoring for improvement, or worsening, of LFTs

Conclusions

Combination low dose thiopurine-allopurinol therapy is a practical, safe and effective therapeutic strategy that may allow 15–20% more patients with IBD to tolerate and benefit from thiopurine therapy. Further data from ongoing prospective studies are awaited to confirm whether first line allopurinol-reduced dose thiopurine therapy can be used in all thiopurine-naïve patients. Despite an increasing number of therapies available in the IBD clinic, optimisation of each therapy before switching within or out of class remains good medicine. Although the role of thiopurines in IBD management is likely to reduce with time due to the availability of newer biologics and small molecules, many global jurisdictions will still rely on thiopurines for the foreseeable future. Optimising thiopurines, including with the use of concomitant allopurinol, therefore remains an important option for IBD clinicians, and potentially those managing other immune-mediated inflammatory diseases.

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