BRIEF COMMUNICATION

Use of allopurinol with low-dose 6-mercaptopurine in inflammatory bowel disease to achieve optimal active metabolite levels: A review of four cases and the literature

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BACKGROUND: At least one-third of patients with inflammatory bowel disease do not respond or are intolerant to therapy with 6-mercaptopurine (6-MP). A subgroup fails to attain optimal levels of 6-thioguanine nucleotide (6-TGN) and instead shunts to 6-methylmercaptopurine nucleotide (6-MMPN).

PATIENTS AND METHODS: A retrospective chart review was conducted, and four patients are described who had been previously unable to achieve optimal 6-TGN metabolite levels until allopurinol was added to their treatment.

RESULTS: All four patients achieved optimal 6-TGN levels and undetectable 6-MMPN with a mean 6-MP dose of 0.49 mg/kg. Three achieved steroid-free clinical remission. Two of those three patients had normalization of liver enzymes; one patient had baseline normal liver enzymes despite an initial 6-MMPN level of 27,369 pmol/8 x 10^8 red blood cells. Two patients experienced reversible leukopenia.

CONCLUSIONS: Combination allopurinol and low-dose 6-MP is an effective means to achieve optimal metabolite levels and steroid-free clinical remission in previously refractory patients. Caution is advised.

Key Words: 6-Mercaptopurine; 6-Thioguanine; Allopurinol; Inflammatory bowel disease; Metabolites

The successful use of 6-mercaptopurine (6-MP) was first reported by Present et al (1) more than two decades ago. Approximately two-thirds of patients respond to appropriate dosing; however, one-third of patients fail to respond or are intolerant of therapy.

Azathioprine (AZA) and 6-MP are inactive prodrugs that are metabolized by three principal pathways (Figure 1). 6-MP can undergo catabolism intracellularly to the inactive metabolite 6-thioguanine (6-TGN) and 6-methylmercaptopurine nucleotide (6-MMPN). 6-Methylmercaptopurine and 6-MMPN are formed via the enzyme thio purine methyltransferase (TPMT). There is interpatient variability in the degree of TPMT enzyme activity, with the majority of patients having 'normal' (high) activity (2). 6-TGN is formed via the enzymes hypoxanthine phosphoribosyltransferase and inosine monophosphate dehydrogenase. Xanthine oxidase (XO) is responsible for the oxidation of 6-MP to the inactive 6-thiouric acid.

Levels of the two active metabolites 6-TGN and 6-MMPN are more significant than medication dosage in determining a patient's likelihood of therapeutic response or intolerance. While approximately one-third of patients achieve clinical remission with a lower 6-TGN level, an improved therapeutic response rate has been shown with 6-TGN levels higher than 230 pmol/8 x 10^8 erythrocytes (red blood cells [RBCs]), and

Utilisation de l'allopurinol avec la 6-mercaptopurine à faible dose dans la maladie inflammatoire de l'intestin pour l'obtention de taux optimum de métabolites actifs : Revue de quatre cas et survol de la littérature

HISTORIQUE : Au moins le tiers des patients atteints de maladie inflammatoire de l'intestin ne répondent pas au traitement par 6-mercaptopurine (6-MP) et un sous-groupe n'atteint pas de taux optimum de nucléotides de la 6-thioguanine (6-TGN) et présente plutôt des nucléotides de la 6-méthyl-mercaptopurine (6-MMPN).

PATIENTS ET MÉTHODES : Les auteurs ont procédé à une revue rétrospective des dossiers et décrivent quatre cas où il était impossible d'obtenir des taux optimum du métabolite 6-TGN jusqu'à ce que de l'allopurinol soit administré en traitement d'appoint.

RÉSULTATS : Avec une dose moyenne de 6-MP de 0,49 mg/kg, les quatre patients ont obtenu des taux optimum de 6-TGN et des taux indécélables de 6-MMPN. Trois d'entre eux ont obtenu une rémission clinique sans corticothérapie. Deux de ces trois patients ont vu leurs enzymes hépatiques se normaliser. Un patient présentait des enzymes hépatiques normales au départ, malgré un taux initial de 6-MMPN de 27 369 pmol/8 x 10^8 globules rouges. Deux patients ont présenté une leukopénie réversible.

CONCLUSION : Ensemble, l'allopurinol et la 6-MP à faible dose constituent un moyen efficace d'obtenir des taux optimum de métabolites et une rémission clinique sans corticothérapie chez des patients auparavant réfractaires. La prudence est de mise.
increased hepatotoxicity is seen with 6-MMPN levels higher than 5700 pmol/8×10⁸ RBCs (3,4). A subgroup of patients fails to attain optimal 6-TGN levels despite medication dosage escalation and instead, preferentially shunts to the potentially hepatotoxic metabolite 6-MMPN (5,6).

A retrospective chart review was conducted of inflammatory bowel disease (IBD) patients at our institution who were treated with combined allopurinol and 6-MP. Clinical remission was defined by disease activity scores obtained from detailed outpatient records. The Crohn's Disease Activity Index (CDAI) (7) was used to assess patients with Crohn's disease, and the Simple Clinical Colitis Activity Index (SCCAI) (8,9) was used to assess patients with ulcerative colitis. The institutional review board at our medical centre approved the study, and informed consent was obtained from subjects.

We present the cases of four patients who were unable to achieve clinical remission off of corticosteroids or therapeutic levels of the metabolite 6-TGN despite 6-MP dose escalation (Table 1). Whereas all four patients had demonstrated shunting from 6-TGN to 6-MMPN on high doses of 6-MP, low doses of 6-MP in combination with allopurinol 100 mg daily resulted in optimal metabolite levels in all four patients, with three out of the four patients achieving sustained, steroid-free clinical remission.

CASE PRESENTATIONS

Case 1
A 36-year-old, 120 kg man with Crohn’s colitis that had been diagnosed three years previously was referred for management. The patient complained of eight to 10 semi-formed, non-bloody bowel movements per day. He had been treated in the past with various regimens, including infliximab and a clinical trial of adalimumab, without symptomatic improvement.

The patient was taking 6-MP 100 mg (0.83 mg/kg) daily but no corticosteroids, and had normal liver enzyme levels. 6-MP was increased to 150 mg (1.25 mg/kg). Four weeks later, bloodwork revealed the following levels: 6-TGN, 144 pmol/8×10⁸ RBCs; 6-MMPN, 5612 pmol/8×10⁸ RBCs; and alanine aminotransferase (ALT), 99 U/L.

6-MP was then reduced to 50 mg (0.42 mg/kg) daily. One week later, allopurinol 100 mg daily was started. After two weeks of unchanged symptoms, 6-MP was increased to 75 mg (0.63 mg/kg). One week later, the 6-TGN level was 275 pmol/8×10⁸ RBCs and 6-MMPN was undetectable. Continued symptoms six weeks later despite optimal 6-TGN levels prompted an ileocolonoscopy, which revealed colonic pseudopolyps throughout the colon, histologically quiescent colitis and a normal terminal ileum. A small bowel capsule endoscopy was normal. Simultaneous to these findings, the white blood cell (WBC) count decreased to 2.5×10⁹/L, with an absolute neutrophil count (ANC) of 1.4×10⁹/L.

6-MP and allopurinol were discontinued. Nine days later, the patient developed facial herpes zoster with a WBC count of 3.1×10⁹/L (ANC 1.3×10⁹/L). Antiviral therapy with oral famciclovir was started, and the leukopenia and shingles resolved within one week.

Although the patient did not benefit from combined allopurinol and 6-MP therapy (CDAI score 157), it was believed that the patient’s continued loose stools were due not to active inflammation but rather to burnt-out disease. This assessment was based on colonoscopic and histological findings; persistent C-reactive protein measurement of less than 1 mg/L; lack of response to various therapies, including anti-tumour necrosis factor therapy; and symptoms that improved (CDAI score 134) with antidiarrheal medications.

Case 2
A 30-year-old, 82 kg man with a six-year history of ulcerative colitis had been only partially controlled on mesalamine and 6-MP 100 mg (1.22 mg/kg) daily, and had required intermittent use of corticosteroids. In an effort to control symptoms of increased stool frequency, urgency and hematochezia, 6-MP was increased to 125 mg (1.52 mg/kg); however, this caused an abnormal ALT level of 128 U/L, with a 6-TGN level of 10⁹ pmol/8×10⁸ RBCs and a 6-MMPN level of 9432 pmol/8×10⁸ RBCs.

6-MP was reduced to 50 mg (0.61 mg/kg) daily. The addition of allopurinol 100 mg daily was delayed until eight weeks later because of the patient’s travel. After tolerating combination therapy for two weeks, 6-MP was increased to 75 mg (0.91 mg/kg) daily. Thirty days later, bloodwork revealed a 6-TGN level of 294 pmol/8×10⁸ RBCs despite 6-MP dose escalation and instead, preferentially shunts to the potentially hepatotoxic metabolite 6-MMPN (5,6).

Although the patient did not benefit from combined allopurinol and 6-MP therapy (CDAI score 157), it was believed that the patient’s continued loose stools were due not to active inflammation but rather to burnt-out disease. This assessment was based on colonoscopic and histological findings; persistent C-reactive protein measurement of less than 1 mg/L; lack of response to various therapies, including anti-tumour necrosis factor therapy; and symptoms that improved (CDAI score 134) with antidiarrheal medications.

Case 3
A 48-year-old 90 kg man with ulcerative colitis that had been diagnosed more than 10 years previously had been only partially controlled on oral and rectal mesalamine, 6-MP 150 mg (1.67 mg/kg) daily and prednisone 10 mg every other day. Over the years, the patient’s disease had flared repeatedly when corticosteroids were discontinued. 6-MP metabolite analysis revealed a 6-TGN level of 82 pmol/8×10⁸ RBCs and a...
6-MMPN level of 27,369 pmol/8 × 10^8 RBCs. Despite this markedly elevated 6-MMPN level, the patient always had normal liver enzyme concentrations.

In an effort to discontinue prednisone and obtain better disease control, 6-MP was reduced to 25 mg (0.28 mg/kg) for one month, during which time a flare was experienced that was quickly controlled with increased prednisone. Allopurinol 100 mg daily was then added. Four weeks later, allopurinol 100 mg daily was added. After four weeks of combination therapy with allopurinol and 6-MP, the 6-TGN level was 319 pmol/8 × 10^8 RBCs and 6-MMPN remained undetectable. The patient was successfully tapered off of prednisone for the first time in many years, and he has maintained steroid-free clinical remission (SCCAI score 1) for 12 months as of the present chart review.

Case 4
A 21-year-old, 71 kg man with ulcerative colitis that had been diagnosed 14 months previously was referred for management. The patient had required mesalamine and high-dose steroids to achieve clinical remission. Repeated flares on tapering doses of corticosteroids prompted 6-MP therapy. Escalating doses of 6-MP had been used ineffectively in an effort to taper corticosteroids. 6-MP 100 mg (1.41 mg/kg) resulted in an abnormal ALT concentration of 208 U/L, with a 6-TGN level of 181 pmol/8 × 10^8 RBCs and a 6-MMPN level of 13,757 pmol/8 × 10^8 RBCs.

6-MP was then reduced to 25 mg (0.35 mg/kg) daily while the patient was continued on prednisone 40 mg daily. Four weeks later, allopurinol 100 mg daily was added. After four weeks of combination therapy with allopurinol and 6-MP, the 6-TGN level was 357 pmol/8 × 10^8 RBCs, 6-MMPN was undetectable and liver enzymes were normal. The patient was then successfully tapered off of prednisone for the first time since diagnosis, and he has remained in steroid-free clinical remission (SCCAI score 0) for nine months as of the present chart review.

**DISCUSSION**

The interaction between allopurinol and 6-MP/AZA has been recognized since the 1960s. Combined therapy is well reported in the oncology literature to enhance the therapeutic efficacy of 6-MP while avoiding the potentially nephrotoxic

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**TABLE 1**

Described cases involving combined therapy with 6-mercaptopurine (6-MP) and allopurinol

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36 years</td>
<td>30 years</td>
<td>48 years</td>
<td>21 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Weight</td>
<td>120 kg</td>
<td>82 kg</td>
<td>90 kg</td>
<td>71 kg</td>
</tr>
<tr>
<td>Ethnic background</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Caucasian</td>
<td>Indian</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Crohn's colitis</td>
<td>Ulcerative colitis</td>
<td>Ulcerative colitis</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Duration of disease before initiation of allopurinol</td>
<td>Three years</td>
<td>Six years</td>
<td>&gt;10 years</td>
<td>14 months</td>
</tr>
<tr>
<td>Thiopurine methyltransferase</td>
<td>Not tested (assumed normal clinically)</td>
<td>Normal alleles</td>
<td>Not tested (assumed normal clinically)</td>
<td>Not tested (assumed normal clinically)</td>
</tr>
<tr>
<td>Shunting demonstrated by 6-TGN/6-MMPN levels (pmol/8 × 10^8 RBCs)</td>
<td>134/9558</td>
<td>109/9432</td>
<td>82/27,369</td>
<td>181/13,757</td>
</tr>
<tr>
<td>Justification for allopurinol combination therapy</td>
<td>Shunting; abnormal ALT levels; steroid dependent</td>
<td>Shunting; abnormal ALT levels; steroid dependent</td>
<td>Shunting; steroid dependent</td>
<td>Shunting, abnormal ALT levels; steroid dependent</td>
</tr>
<tr>
<td>Concomitant IBD therapy</td>
<td>–</td>
<td>Mesalamine</td>
<td>Mesalamine</td>
<td>Mesalamine</td>
</tr>
<tr>
<td>6-MP dose prior to initiating allopurinol</td>
<td>150 mg (1.25 mg/kg)</td>
<td>125 mg (1.52 mg/kg)</td>
<td>150 mg (1.67 mg/kg)</td>
<td>100 mg (1.41 mg/kg)</td>
</tr>
<tr>
<td>6-MP dose in combination with allopurinol to achieve optimal metabolites</td>
<td>50 mg* (0.42 mg/kg)</td>
<td>50 mg† (0.61 mg/kg)</td>
<td>50 mg (0.56 mg/kg)</td>
<td>25 mg (0.35 mg/kg)</td>
</tr>
<tr>
<td>Optimal 6-TGN/6-MMPN levels achieved with combination therapy (pmol/8 × 10^8 RBCs)</td>
<td>275/undetectable</td>
<td>294/undetectable</td>
<td>319/undetectable</td>
<td>357/undetectable</td>
</tr>
<tr>
<td>Time from initiation of allopurinol to optimal metabolites</td>
<td>25 days</td>
<td>28 days</td>
<td>69 days</td>
<td>28 days</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Zoster rash associated with transient leukopenia</td>
<td>Transient leukopenia</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>6-MP plus allopurinol ceased because of lack of benefit to patient; patient later diagnosed with nonalcoholic steatohepatitis</td>
<td>Continued 6-MP plus allopurinol in steroid-free clinical remission at least eight months</td>
<td>Continued 6-MP plus allopurinol in steroid-free clinical remission for 12 months as of chart review</td>
<td>Continued 6-MP plus allopurinol in steroid-free clinical remission for nine months as of chart review</td>
</tr>
</tbody>
</table>

*Although the patient was taking 75 mg at the time of the blood draw, the timing, shortly after increasing 6-MP from 50 mg to 75 mg, suggests that the lower dose of 6-MP was reflected in the metabolite levels; †The patient was ultimately maintained on alternating doses of 25 mg and 50 mg (0.46 mg/kg) with a 6-thioguanine nucleotide (6-TGN) level of 222 pmol/8 × 10^8 red blood cells (RBCs) and undetectable 6-methylmercaptopurine nucleotide (6-MMPN). ALT Alanine aminotransferase; Anti-TNF Anti-tumour necrosis factor; IBD Inflammatory bowel disease.
effects of purine overload caused by rapid destruction of neoplastic tissue by chemotherapy (10-12). Combined allopurinol and 6-MP/AZA has also been reported to provide benefit in renal transplantation (13). Recently, Sparrow et al (14,15) reported success with allopurinol in increasing 6-TGN levels to the therapeutic range while decreasing 6-MMPN in IBD patients previously refractory to 6-MP/AZA because of shunt- ing to 6-MMPN. A short-term (three-month) clinical improvement, as well as normalization of liver enzymes, was also noted (14,15).

Allopurinol is an inhibitor of XO, which is located in the liver and intestinal mucosa. Allopurinol decreases the yield of the pathway of 6-MP to inactive 6-thiouric acid and inhibits first-pass metabolism. This thereby increases the fraction of the drug available for anabolism to the active nucleotide forms 6-TGN and 6-MMPN (16,17).

In a study of allopurinol and oral 6-MP, there was no effect of adding allopurinol on time to peak plasma concentration or elimination half-life of 6-MP. However, it was shown that the mean peak plasma concentration and area under the curve of 6-MP increased nearly fivefold (10). The improved bioavailability of 6-MP results in higher 6-TGN levels. This explains the well-known adverse event of bone marrow suppression (18-20). For this reason, the literature has historically urged that when combined with allopurinol, the dose of 6-MP should be significantly reduced (10-12,20,21).

It has recently been suggested that the principal metabolites within 6-TGN are the active 6-thioguanosine triphosphate (6-TGTP), which results in T-cell apoptosis, and the inactive 6-thioguanosine diphosphate (6-TGDP) (22,23). Patients with high 6-TGN levels made up predominantly of 6-TGTP have been shown to have improved outcomes compared with those with high 6-TGN made up predominantly of 6-TGDP (23). The effect that allopurinol or the lower dose of 6-MP used in combination therapy has on the newly described 6-TGTP and 6-TGDP metabolites is unclear. Our clinical experience suggests that perhaps 6-TGTP production is augmented.

In patients with established preferential shunting toward 6-MMPN, the use of allopurinol should theoretically lead to a further increase in 6-MMPN. Our findings confirm those of Sparrow et al (14,15) indicating that this is not so. In fact, levels of 6-MMPN in our patients declined from potentially toxic to undetectable levels. The effect of allopurinol on 6-MMPN may logically be explained by the inhibition of TPMT. Unpublished data, however, have demonstrated no effect of allopurinol on TPMT in vitro or in vivo (15,24). Duley et al (21) propose that perhaps the addition of allopurinol provides oxypurinol metabolites, which antagonize TPMT, although unpublished experiments have not found this to be the case (15). Another possibility is that a usually omnipresent co-enzyme (perhaps XO) is necessary for TPMT to metabolize 6-MP to 6-MMPN.

Whatever the mechanism, the addition of allopurinol to a low dose of 6-MP appears to be an effective means of shifting the metabolism away from 6-MMPN toward 6-TGN. This should increase the likelihood of clinical response and eliminate hepatotoxicity associated with increased levels of 6-MMPN.

6-MMPN levels higher than 5700 pmol/8x10^10 RBCs are associated with an increased risk of abnormal liver enzymes; however, the mechanism responsible for this is unknown. 6-MMPN is not itself hepatotoxic, as shown by the third patient in the present report, who had a markedly elevated 6-MMPN level (27,369 pmol/8x10^10 RBCs) without serological evidence of hepatocellular injury.

Regarding the use of 6-MP with allopurinol, a word of caution is appropriate. The risk of leukopenia and its complications with this combination is of a different order of magnitude than when 6-MP is used alone. Our first two patients developed symptomatic leukopenia despite careful monitoring. In hindsight, both patients likely achieved optimal thioguanine metabolite levels at a dose of 50 mg 6-MP, and the increase of 6-MP to 75 mg was probably responsible for the leukopenia.

In their initial publication, Sparrow et al (14) expressed a theoretical concern about nodular regenerative hyperplasia (NRH), though this concern was not shared by Duley et al (21). Although there have been case reports of AZA associated with NRH (25), this concern likely derives from studies in which the medication 6-thioguanine (6-TG) was associated with NRH (26-29). While vascular compromise is hypothesized to be involved in NRH, the etiology of the association between 6-TG and NRH remains unclear. NRH does not appear to be a significant concern with the use of conventional 6-MP/AZA therapy. Moreover, we cannot presume that the 6-TGN derived from the metabolism of 6-MP and the 6-TGN produced by 6-TG are biochemically the same (27). Perhaps NRH is associated with the very high levels of 6-TGN seen with the direct use of 6-TG.

Our experience, combined with the literature on AZA/6-MP plus allopurinol therapy, leads us to make several recommendations. This combination therapy is intended only for patients with low, subtherapeutic levels of 6-TGN associated with high levels of 6-MMPN despite AZA/6-MP dose escalation. Such patients would be expected to have normal or high levels of the enzyme TPMT. Patient selection, with an emphasis on compliance, is also critical to ensure safety and success. We suggest a reduction in the patient’s 6-MP to a low dose such as 25 mg for two to four weeks. Despite suboptimal levels of 6-TGN, the patient may have derived some benefit from the 6-MP, and it may be necessary to control disease activity with corticosteroids during this ‘washout’ period. Allopurinol 100 mg daily can then be added, and we recommend weekly analysis of the complete blood count and liver enzymes. While balancing a clinical need for monitoring with the reality that the patient’s insurance carrier may not cover these sophisticated tests, it is reasonable to assess 6-MP metabolites after four weeks of combination therapy, as in our third and fourth cases. Checking metabolites earlier than three weeks (30-32).

If the level of 6-TGN remains suboptimal, the dosage of 6-MP can be increased, again monitoring bloodwork weekly, until the metabolites are rechecked in another four weeks. Because corticosteroids can be responsible for an elevated WBC count, careful monitoring for leukopenia is also required when corticosteroids are tapered. Our cases suggest that optimal metabolite levels are achievable within approximately one to two months (mean 38 days), with 6-MP doses in the approximate range of 0.35 to 0.61 mg/kg (mean 0.49 mg/kg).
CONCLUSIONS
The combination of allopurinol 100 mg daily with low-dose 6-MP provides a therapeutic option not previously available to the subset of IBD patients unable to benefit from traditional 6-MP dosing because of preferential shunting to 6-MMPN. This approach requires a high degree of caution using a low dose of 6-MP/AZA, with frequent monitoring and careful patient selection. Additional research is necessary to establish the long-term safety of this approach.

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REFERENCES
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