Combination of thiopurines and allopurinol: Adverse events and clinical benefit in IBD

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KEYWORDS
Azathioprine; 6-Mercaptopurine; Allopurinol; Inflammatory bowel disease; Shunting

Abstract

Background and aims: Allopurinol has been presented as a safe and effective adjunct to thiopurine therapy in inflammatory bowel disease (IBD). We aimed to determine the rate of infectious complications and clinical successes with a combination of thiopurine/allopurinol in IBD, and to identify which variables predict 6-thioguanine, 6-methylmercaptopurine, and white blood cell levels. Additionally we aimed to identify which variables predict complications.

Methods: A retrospective database search identified patients with inflammatory bowel disease on both thiopurines and allopurinol. Regression modeling was used to identify which variables predicted metabolite levels, white blood cell levels, and complications.

Results: Twenty-seven subjects were found, with 20 treated intentionally and 7 inadvertently after a concurrent gout diagnosis. Thirteen of 20 patients had a major clinical improvement and 7 of 16 stopped steroids. Five infectious complications occurred. These included 2 cases of shingles, and one each of PCP, EBV, and viral meningitis. Significant predictors of metabolite levels included the dose of thiopurine and allopurinol, age, and BMI. Low white blood cell count levels were associated with increased doses, high BMI, and older age. Despite having only 5 events, there was a difference in absolute lymphocyte count between patients with and without infection (median 200 per mm$^3$ vs 850 per mm$^3$ respectively, $p=0.0503$).

Conclusions: Adjunctive allopurinol therapy in shunting patients produced major clinical improvement in 48% of patients. However, a surprising number of opportunistic infections have occurred. Low absolute lymphocyte count may be a previously unrecognized indicator of risk of opportunistic infections.

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Abbreviations AZA, azathioprine; 6-MP, 6-mercaptopurine; 6-TGN, 6-thioguanine; 6-MMP, 6-methylmercaptopurine; TPMT, thiopurine methyltransferase; ALC, absolute lymphocyte count.

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1. Introduction

The thiopurines, 6-mercaptopurine (6-MP) and azathioprine (AZA), are considered first line immunosuppressive agents in the treatment of inflammatory bowel disease (IBD). They have been shown to be effective in inducing remission and in reducing steroid dependence in patients with active IBD.1–7 They have also been shown to maintain remission in patients with quiescent IBD.2,4,5,8 Despite their proven efficacy, up to 55% of the patients do not have a clinical response or are intolerant of these medications. Some portion of the nonresponse to this class of drugs has been attributed to genetic variations in drug metabolism.9

The thiopurines are inactive prodrugs; through a series of reactions, they are metabolized to 6-thioguanine nucleotides (6-TGN), 6-methylmercaptopurine (6-MMP) and 6-thiouric acid (Fig. 1).10 Levels of 6-TGN have been shown to correlate with clinical activity and myelotoxicity while levels of 6-MMP have been shown to correlate with hepatotoxicity.9 Dubinsky et al. demonstrated that levels of 6-TGN above 235 pmol/8×108 erythrocytes correlated with clinical improvement and levels of 6-MMP above 5700 pmol/8×108 erythrocytes correlated with hepatotoxicity.

Activity of thiopurine methyltransferase (TPMT) has been shown to be an important determinant of the levels of both 6-TGN and 6-MMP in patients on thiopurines. Patients with very low levels of TPMT (approximately 0.3% of the population) generate large amounts of 6-TGN, resulting in myelosuppression.11 Patients with normal or high levels of the enzyme make up approximately 89% of the population, and very high levels of this enzyme have been shown to correlate with low 6-TGN level and shunting of the metabolites to 6-MMP.12,13

The combination of allopurinol and thiopurines is historically considered to be dangerous without significant dose reductions.14,15 The combination was first demonstrated to be effective for reducing rejection rates in renal transplantation patients.16 The use of allopurinol as an adjunctive agent in IBD has now been described by several groups.17–20 Sparrow et al. have published their experience with 35 patients using the combination.17,18 They have shown that the addition of allopurinol at 100 mg daily along with a concurrent reduction in thiopurine dosage (25–50% of the original dose) led to a reduction in steroid usage and improvement in disease activity scores. The improvement in disease activity scores was statistically significant in the Crohn’s population (p=0.001). Biochemically the combination led to a significant rise in 6-TGN and significant decrease in 6-MMP, thereby reversing the shunting mechanism present due to high TPMT activity. There was a demonstrated reduction in white blood cell count (WBC) and 10/35 patients developed leukopenia (defined by a WBC of ≤3.5×10⁹/L). With further dose reduction, the leukopenia resolved and no infectious complications were noted.

A second group has published similar findings.19 They reduced the thiopurine dose to 0.5 mg/kg/day for AZA, or 0.25 mg/kg/day for 6-MP and added 200 mg of allopurinol in 11 patients who previously developed hepatotoxicity on thiopurines alone. Eight patients were found to be in remission on the combination without further use of steroids or biologics. Of the 11, 3 patients had leukopenia without infectious complications that resolved with further dose reduction.

Given the rate of leukopenia in the previous studies, we hypothesized that the combination of thiopurine and allopurinol would lead to an increased rate of infectious complications. We aimed to describe the University of Michigan experience with allopurinol in combination with thiopurine therapy for IBD. Herein, we describe the complications and rates of clinical success using the combination of thiopurine and allopurinol therapy in IBD patients with thiopurine shunting. In addition, we aimed to determine which variables predict complications of therapy.

2. Materials and methods

An electronic query of the medical records at the University of Michigan Hospitals, a large tertiary care center, was...
performed looking for adults with a diagnosis of Crohn’s disease (CD) or ulcerative colitis (UC) and mention of allopurinol and a thiopurine in the chart dating back to 2000. These records were then reviewed using the University of Michigan electronic medical records search engine (EMERSE) to ensure that the diagnosis and medication information were accurate. The charts which confirmed concurrent use of a thiopurine and allopurinol were then searched for metabolite values, demographic data, drug dosages and other pertinent labs.

2.1. Statistical analysis

Descriptive analyses were calculated; metabolite changes within individuals were analyzed with paired t-tests. Modeling of the 6-MMP and 6-TGN levels was performed using tobit regression, as these levels were not normally distributed, while modeling the WBC outcome was done with standard multivariate regression. For infectious complications, as these are dichotomous outcomes with less power, we minimized the risk of overfitting by using only single variables (ALC and age) in t-tests.

2.2. Ethical considerations

The institutional review board at the University of Michigan approved this study prior to initiation. Neither author has any disclosures regarding conflicts of interest.

3. Results

Twenty-seven patients were found to have a diagnosis of IBD with a history of concurrent thiopurine and allopurinol use. Their demographic and disease characteristics are presented in Table 1.

In 20 of the cases, the use of allopurinol and thiopurine was deliberate, in IBD patients with thiopurine shunting to 6-MMP. Seven cases occurred in patients who suffered therapeutic misadventures, in which they were on thiopurines for IBD, developed gout, and were prescribed allopurinol without thiopurine dose reduction by a physician who was not their thiopurine prescriber. Five of the 20 patients on the combination for the synergistic effects were started on the combination simultaneously.

3.1. Medication dosages

The median dose prior to initiation of allopurinol was 150 mg for AZA and 125 mg for 6-MP in the intentionally treated group. In this group, the median dose after initiation of allopurinol decreased to 100 mg for AZA and to 50 mg for 6-MP. The median allopurinol dose in those intentionally treated was 100 mg (range 50–100 mg).

Among those in the group on the combination unintentionally, the median AZA dose was 62.5 mg and the median 6-MP dose was 25 mg. Among the unintentional group the median allopurinol dose was 300 mg. There was not a statistically significant difference in dose per BMI between the intentionally and unintentionally treated groups (p = 0.07).

3.2. TPMT and metabolite measurements

The average changes in 6-TGN and 6-MMP levels after initiation of the combination were +222 pmol/8×10^8 RBCs (p < 0.001) and −8095 pmol/8×10^8 RBCs (p = 0.001), respectively (Figs. 2 and 3). Twelve of the 27 patients had complete metabolite data available (both pre-allopurinol and post-allopurinol data). Fourteen of 19 patients had 6-TGN levels that were above 235 pmol/8×10^8 RBCs after the initiation of the combination (8 did not have a 6-TGN measurement after initiation of the combination).

Of the 27 patients, 9 did not have a recorded TPMT in our record system. Review of our records indicated that 3 different assays of the TPMT enzyme had been ordered. One assay type was qualitative only. The other 2 assays had different reference ranges. The average TPMT level was 30.95 EU (>23.6 EU is considered normal) among the patients who were tested with the most frequently used assay (12 patients). All of the patients had levels that were considered normal.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Population characteristics.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>52%</td>
</tr>
<tr>
<td>Average age</td>
<td>45.1</td>
</tr>
<tr>
<td>Average BMI</td>
<td>26.9</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>513 days (25th–75th percentile 230–813)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>16</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>11</td>
</tr>
<tr>
<td>Intentional use</td>
<td>20</td>
</tr>
<tr>
<td>Patients on AZA (6-MP)</td>
<td>21 (6)</td>
</tr>
<tr>
<td>Median AZA (6-MP) dose prior to allopurinol (intentional only)</td>
<td>150 mg (125 mg)</td>
</tr>
<tr>
<td>Median AZA (6-MP) dose after allopurinol (intentional only)</td>
<td>100 mg (50 mg)</td>
</tr>
<tr>
<td>Median allopurinol dose (intentional only)</td>
<td>100 mg</td>
</tr>
<tr>
<td>Average TPMT level</td>
<td>30.95 EU</td>
</tr>
<tr>
<td>Initially on steroids</td>
<td>16</td>
</tr>
</tbody>
</table>

![Figure 2](https://academic.oup.com/ecco-jcc/article-abstract/4/4/444/490404/444) 6-TGN (pmol/8×10^8 RBCs) change with addition of allopurinol. Gray lines represent individual patients. The black line represents the mean. The dotted line represents 235 pmol/8×10^8 RBCs.
3.3. Clinical improvement and steroid cessation

Of the 16 patients that were on corticosteroids at the time of initiation of the combination therapy, 7 were no longer on steroids as of the most recent follow-up (2 of the 5 patients with CD and 5 of the 11 patients with UC). Thirteen of the patients were described by their gastroenterologist as improved on the combination (4 of 11 CD patients and 9 of 15 UC patients). Nineteen of the patients remained on a thiopurine throughout follow-up. Of all the patients reviewed, 15 remained on the combination treatment while 10 of those intentionally treated remained on the combination.

3.4. Complications of combination therapy

Fourteen patients had complications related to the use of combination of allopurinol and thiopurine therapy requiring either a dose reduction or cessation. Of these, 5 were infectious complications. These included 2 cases of shingles and 1 of each of the following: EBV viremia, PCP pneumonia, and viral meningitis (Table 2). Eight of 20 intentionally treated patients had a WBC nadir below 3.5 × 10⁸/L. Two patients had absolute neutrophil count nadir that was below 0.5 × 10⁸/L (both were on the combination inadvertently). Neither of these patients had infectious complications. All of the patients that had complications were on the drug combination specifically for the synergistic effects of the combination. Four of the 5 patients with infectious complications had dose reductions of the thiopurine prior to initiation (the exception being the patient with viral meningitis). All 5 of these patients were started on 100 mg daily or less of allopurinol. Three of the 5 patients with complications were also on concomitant corticosteroids; all 3 were on 20 mg at the time of documented infection. The range of days till infection was 45 to 475 days. Other intolerances reported by patients included pancytopenia, oral sores and dysguesia, anemia requiring transfusions, and fatigue.

3.5. Modeling predictors of metabolite levels, WBC, and complications

We used the WBC and metabolite data from the 12 patients with complete records to determine predictors. While this is likely to lead to some overfitting of the model, we think it is valuable to present this information in its entirety to the reader. We used likely predictors in a multivariate model to predict 6-TGN values, and found that increased age was associated with increased 6-TGN levels while increased weight was associated with decreased 6-TGN (Table 3). When we modeled 6-MMP values, both increased thiopurine dose and age were associated with increased 6-MMP levels. Our multivariate model of WBC count found decreases in WBC were associated with increases in age, weight, AZA dose and allopurinol dose. When we modeled complications, the small number (5) of infectious complications would not allow us to evaluate multiple variables without overfitting. In our univariate analysis, the median absolute lymphocyte count (ALC) in patients with infection was noted to be 0.2 × 10⁸/L, lower (p = 0.05) than those without infectious complications (0.85 × 10⁸/L) (Fig. 4). In addition, patients with infectious complications had a median age (24 years) that was significantly lower (p = 0.03) than patients without opportunistic infections (47.5 years).

Table 2  Characteristics of 5 patients who suffered infectious complications.

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21</td>
<td>24</td>
<td>32</td>
<td>19</td>
</tr>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>IBD type</td>
<td>UC</td>
<td>UC</td>
<td>CD</td>
<td>UC</td>
</tr>
<tr>
<td>Infection</td>
<td>Shingles</td>
<td>PCP pneumonia</td>
<td>Viral meningitis</td>
<td>EBV viremia</td>
</tr>
<tr>
<td>Thiopurine dose prior</td>
<td>125 mg (6-MP)</td>
<td>100 mg (6-MP)</td>
<td>200 mg (AZA)</td>
<td>150 mg (AZA)</td>
</tr>
<tr>
<td>Allopurinol dose</td>
<td>100 mg</td>
<td>50 mg</td>
<td>100 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Concurrent Prednisone Dose</td>
<td>20 mg</td>
<td>20 mg</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thiopurine dose after</td>
<td>50 mg</td>
<td>50 mg</td>
<td>200 mg</td>
<td>75 mg</td>
</tr>
<tr>
<td>WBC nadir</td>
<td>3.0</td>
<td>2.5</td>
<td>0.9</td>
<td>2.8</td>
</tr>
<tr>
<td>ANC nadir</td>
<td>2.3</td>
<td>1.2</td>
<td>0.6</td>
<td>1.8</td>
</tr>
<tr>
<td>ALC nadir</td>
<td>0.2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Days until infection</td>
<td>55</td>
<td>83</td>
<td>45</td>
<td>318</td>
</tr>
</tbody>
</table>
4. Discussion

In this study of 27 patients, we were able to confirm that the use of allopurinol and thiopurines together in patients with IBD was beneficial in those treated deliberately for shunting metabolism of thiopurines. We documented consistent clinical improvement with a reduction in the need for steroid use. This correlated well with a rise in the known beneficial metabolite, 6-TGN. This elevation is similar to those described in the previous studies on the combination.17,19 Our population had a high average TPMT level which corroborates Cuffari et al.’s findings that high TPMT levels are associated with thiopurine resistance.13

While the previous studies did demonstrate a substantial increase in 6-TGN, there was only one report of an infectious complication: shingles.20 With a rise in 6-TGN, the metabolite that leads to myelosuppression, episodes of leukopenia would be expected. Of the 35 patients previously studied, 10 developed leukopenia which resolved without further complications with a dose reduction in thiopurines.17,18 Our experience with the combination found 13 of 27 patients with leukopenia (<3.5×10^8). One reason for the higher incidence is the inclusion in our data of patients in which patients were placed on the combination by 2 separate providers (i.e. a gastroenterologist was managing the thiopurine usage while another provider started allopurinol for gout). The median dose of allopurinol was 300 mg in this group, and five of these seven patients had leukopenia. Despite exclusion of these patients, the incidence of leukopenia remains elevated (8 of 20) even with thiopurine dose reductions of 50% or more in 9 of 15 of the patients intentionally treated with combination therapy.

In our retrospective study we noted 5 significant infections in patients treated deliberately with combination therapy: 2 cases of shingles, 1 case of PCP pneumonia, 1 case of EBV viremia, and 1 case of viral meningitis. All of the patients initiated at this center were on weekly lab monitoring after initiation of combination thiopurine and allopurinol therapy. Despite this, 4 of the 5 patients developed leukopenia and rapidly developed a subsequent infection. One of the patients developed a case of shingles despite a WBC nadir of 5.2. In this small series of infections we noted that ALC was often low. The 24 year old woman who developed PCP pneumonia in our series had a WBC of 3.1 with an ANC of 2.5 and ALC of 0.1 at the time of presentation of her symptoms. Among this small group of patients with infectious complications, we noted a trend towards lower ALC and youth. In the future, a low ALC may prove to be a marker predictive of infectious complications.

We were able to model predictors of WBC and the metabolite levels. Not surprisingly, WBC decreased with

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Per Unit</th>
<th>WBC</th>
<th>6-TGN</th>
<th>6-MMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopurine dose</td>
<td>1 mg/kg</td>
<td>−1.62</td>
<td>+47.3</td>
<td>+4146</td>
</tr>
<tr>
<td>BMI</td>
<td>1 kg/m^2</td>
<td>−0.11</td>
<td>−15.2</td>
<td>+274</td>
</tr>
<tr>
<td>Allopurinol dose</td>
<td>50 mg</td>
<td>−0.55</td>
<td>+18.4</td>
<td>−644</td>
</tr>
<tr>
<td>Decade of age</td>
<td>10 years</td>
<td>−0.39</td>
<td>+30.9</td>
<td>+416</td>
</tr>
</tbody>
</table>

Figure 4 Predictors of infection. The plot on the left depicts absolute lymphocyte count (ALC) among those with and without infection. The solid line indicates the median value for the 2 groups. The plot on the right shows the patient age in those with and without infection.
increasing doses of AZA and allopurinol. We also found that increasing age and weight led to decreased WBC. This association between age and lowered WBC is surprising given our finding that more patients with infectious complications were young. Perhaps the ALC is more important than total WBC in these opportunistic infections. Older patients tended to have higher levels of both metabolites (the association with 6-MMP was not statistically significant but rather a trend). Increasing doses of allopurinol led to increased 6-TGN and decreased 6-MMP (again both of these were trends). Thiopurine dose was associated with increasing levels of both metabolites. Heavier patients tended to have lower levels of 6-TGN and higher levels of 6-MMP. As other studies have noted, thiopurine dosage remains a poor predictor of 6-TGN levels likely due to large variation in the metabolism of thiopurines between patients. Additionally, our sample was underpowered to detect a statistically significant relationship between doses and 6-TGN levels.

Like the other studies on this combination, the population studied was small. However, the distinguishing feature of this paper is the report of several infectious complications, including the report of potentially life-threatening infections. We recognize that the sample size and the number of infections on which we base our conclusions are small; however, we believe that due to the nature of these infections and the danger posed by the use of this combination that these initial findings would be useful to the gastroenterology community. While we conclude that the combination of allopurinol and thiopurines is an effective option in patients with TPMT levels greater than 30, we recommend the following for optimal safety: (1) the combination dose of the thiopurine should be 0.5 mg/kg for AZA and 0.25 mg/kg of 6-MP, and the initial allopurinol dose should be 50 mg; (2) all patients on thiopurines should be advised that if they are diagnosed with gout, they must consult with their gastroenterologist before starting any medications for gout; (3) the absolute lymphocyte count should be monitored, and doses adjusted for ALC < 1 x 10^9/L; (4) PCP prophylaxis should be used with concomitant steroids of ≥ 20 mg daily. More data need to be collected and continued close lab monitoring needs to be performed on patients on this regimen.

Acknowledgements

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References