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Alimentary Tract

Low-dose thiopurine with allopurinol co-therapy overcomes thiopurine intolerance and allows thiopurine continuation in inflammatory bowel disease

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ABSTRACT

Aims: To assess the utility and tolerability of thiopurine-allopurinol co-therapy in inflammatory bowel disease (IBD) patients with intolerance to thiopurine monotherapy.
Methods: A retrospective observational study assessed cases of thiopurine intolerance then switched to thiopurine allopurinol co-therapy between 2011 and 2015 at two centres. Indications for switch, dosing and subsequent clinical outcomes (including thiopurine persistence) were recorded.
Results: Of 767 patients on thiopurines for IBD, 89 (12%) were switched to co-therapy for intolerance. 64/89 (72%) had Crohn's disease, 38 (43%) were males, median age at switch was 40y (range 17–78), median IBD duration 6y (0–29). Median follow-up was 1.9y (0–5). Reasons for switching to co-therapy included fatigue (37%), hepatotoxicity (23%), nausea (23%), arthralgia (10%), headache (12%) and hypersensitivity reaction (4%). Overall, 66 (74%) patients remained on co-therapy until most recent review and achieved a clinical response. High rates of overcoming intolerance (62–100%) occurred with co-therapy for all reasons above, although fatigue was less amenable to switching than non-fatigue indications (62% vs 91%, $p = <0.001$). Of 34 patients not escalated to biologics with endoscopic data, 15 were in remission (44%) at most recent review.
Conclusion: Low-dose thiopurine combined with allopurinol appears safe and effective in overcoming intolerances to thiopurine monotherapy in many cases.

1. Introduction

The thiopurines, azathioprine (AZA) and mercaptopurine (MP) are established therapies in the management of patients with inflammatory bowel disease (IBD) with demonstrated efficacy and safety [1–3]. Thiopurines are typically utilized as steroid sparing agents and have been shown to enhance efficacy when used in combination with anti-tumour necrosis factor therapy above monotherapy with either agent alone [4]. Despite the advent of biologics, optimizing thiopurines remains clinically important given the limited armamentarium in IBD. They have been shown to minimize steroid dependence, achieve mucosal healing and prevent post-operative recurrence in Crohn's disease [1,3,5,6]. They are effective in achieving clinical and endoscopic remission, reducing corticosteroid requirements and reducing relapse rate in steroid dependent ulcerative colitis [7,8]. Thiopurines also decrease rates of surgery and need for more costly, inconvenient, parenteral agents [1,6]. Nevertheless, up to 60% of patients do not respond to conventional thiopurine dosing and approximately 40% of patients who experience intolerance to AZA are subsequently also unable to tolerate 6-MP [9]. Hence overall, thiopurine failure due to intolerance purportedly occurs in up to 30% of recipients [10].

The use of allopurinol, a xanthine oxidase inhibitor, concurrently with thiopurines in IBD is well documented in non-responders to thiopurine monotherapy. This combination was first described in the renal transplantation setting, and subsequently adopted in patients with IBD where it is now used

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for thiopurine hypermethylators (or 'shunters') who preferentially metabolize thiopurines towards 6-methylmercaptopurine (6-MMP) over 6-thioguanine production (6-TGN) [11,12]. Co-therapy leads to a consistent reduction in the 6-MMP levels and hence 6-MMP:6-TGN ratios with subsequent improvements in clinical outcomes in patients with IBD [13]. While the exact mechanism of action of allopurinol co-therapy with thiopurines remains uncertain, several theories have been proposed, including co-therapy's production of the intermediate metabolite thioxanthine, in turn inhibiting TPMT activity and reducing 6-MMP production [14], or by allopurinol leading to a reduction in the thiopurine dose to a dose that is suboptimal for TPMT function, thus reducing thiopurine methylation [15]. Allopurinol co-therapy leads to a consistent reduction in the 6-MMP level and hence 6-MMP:6-TGN ratio with subsequent improvements in clinical outcomes in patients with IBD [13].

With greater experience of the utility of thiopurine allopurinol co-therapy and thus a broadening of its application, recent studies have suggested a clinical benefit of switching to thiopurine allopurinol co-therapy to overcome thiopurine intolerances irrespective of thiopurine 'shunting' (i.e. high 6-MMP or high 6-MMP:TGN ratio) status. The rate of clinical remission, with resolution of the adverse effect in question, has been observed in 50–78% of patients from one centre [16,17]. Hence in this study, we aimed to further evaluate the effectiveness and utility of thiopurine allopurinol co-therapy to overcome intolerances in the largest IBD patient cohort to date.

2. Materials and methods

A retrospective chart review was performed on all adult IBD patients who were switched to thiopurine allopurinol co-therapy *specifically* due to a documented intolerance to thiopurine monotherapy over four years, between 1st October 2011 and 31st October 2015, across two IBD tertiary referral centres in Melbourne, Australia. Cases were ascertained independently of thiopurine metabolite measurements. Documented adverse drug reactions included nausea, vomiting, fatigue, arthralgias, headaches, fevers, rash and/or hypersensitivity reaction. The occurrence of reactions was counted only when an antecedent cause for the respective symptom/finding was not evident. For instance, patients were only attributed to have developed acute hepatotoxicity in association with thiopurine monotherapy where this resolved upon cessation of the thiopurine and where no other likely cause for hepatic dysfunction was noted either at the time or in retrospect. All patients were on the same thiopurine as the one they developed the original intolerance when switched to allopurinol co-therapy. In addition, baseline patient demographics, indication for co-therapy, clinical outcomes and adverse effects were recorded. Also, all laboratory results performed before and after intervention, including thiopurine metabolites (6-MMP and 6-TGN), liver function tests, C-reactive protein and full blood counts were recorded if available. Hepatotoxicity was considered if the alanine aminotransferase (ALT) was greater than two times the upper limit of normal. The duration of follow-up and time on co-therapy were not used to exclude cases, given that persistence on therapy for all cases was valuable in addressing the study's aims.

Clinical remission was calculated retrospectively based on either a Harvey-Bradshaw Index (for Crohn's disease) less than 5 or Partial Mayo score (UC and IBD-U) less than 2 at last clinic review or time of ceasing co-therapy, whichever occurred first. Endoscopic data was reviewed if it occurred within 12 months of the last review. Endoscopic remission was defined as a Mayo score of 0 to 1 for ulcerative colitis, while Crohn's disease had a simple endoscopy score for Crohn's disease calculated retrospectively, with a score of 0 to 2 being considered to indicate remission.

A 6-MMP to 6-TGN ratio of greater than 20 was considered to indicate thiopurine shunting [18].

All patients received the combination of allopurinol 100 mg daily and 25–33% of the intended target thiopurine monotherapy dose [19].

2.1. Statistical analysis

Statistics were performed using SPSS version 21. Non-parametric statistics were utilized throughout the study analyses according to Shapiro–Wilk test showing a p value < 0.05 for most variables. Medians (ranges) are thus presented for continuous variables and were compared either with Mann–Whitney or Wilcoxon matched pairs signed rank tests (the latter for paired comparisons). Proportions are shown with percentages and were compared with Fisher's exact test. For paired dichotomous variables, McNemar's test was performed.

To assess for factors associated with longer thiopurine persistence (as a continuous variable), initially non-parametric Spearman's correlations were applied with scatter plots and lines of best fit derived. Given the large effect size of two variables (disease duration and duration of thiopurine allopurinol co-therapy use) potentially confounding further analyses, partial correlations were then used, accounting for these two variables, to elucidate other factors associated with thiopurine persistence. Finally, statistically significant associations derived from these correlation analyses were then incorporated in a multiple linear regression model (albeit strictly a parametric tool, this provided the best fit for the data with thiopurine persistence as the dependent variable). Multiple exploratory models were then employed prior to the final model selected according to goodness of fit. Variables of putative clinical importance (continuous or categorical) were included in this multivariate analysis. A p-value of <0.05 was deemed to be significant for all analyses throughout the study.

2.2. Ethical statement

This study was approved by Human Research Ethics Committees at both Alfred Health and Eastern Health. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

3. Results

3.1. Characteristics of patient cohort

In this cohort of 767 patients on thiopurine therapy for IBD, 89 patients were noted to have (1) exhibited one or more intolerances to thiopurine monotherapy, *and* (2) this was documented as the primary reason for switching to thiopurine allopurinol co-therapy. Relevant characteristics of the patient cohort are shown in Table 1. Prior to switching to co-therapy, azathioprine and mercaptopurine were equally represented, with a median azathioprine and mercaptopurine dose of 150 mg and 75 mg daily, respectively (median 2.1 mg/kg/day and 1.1 mg/kg, respectively). After switch to co-therapy, the overall median dosage was 25% of the original thiopurine dose for both mercaptopurine and azathioprine.

3.2. Overall duration of co-therapy and efficacy

Overall, 66 (74%) patients were maintained on co-therapy until most recent review (median follow-up 1.9 years after switch to co-therapy). Most patients were in clinical remission at the time of commencing allopurinol co-therapy with Crohn's disease (42/63, 67%) while 9/25 (36%) with UC were in clinical remission (Table 2).

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