

Allopurinol Co-prescription Improves the Outcome of Azathioprine Treatment in Chronic Eczema

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The efficacy of azathioprine (AZA) treatment for atopic dermatitis (AD) has been demonstrated in a number of randomized controlled trials and open-label studies (1), but recent studies in daily clinical practice have shown less favourable results (2, 3). AZA is a thiopurine prodrug that does not itself have immunosuppressive activity. After conversion in the liver, the most important metabolites are 6-thioguanine nucleotide (6-TGN) and methylated 6-methylmercaptopurine (6-MMP). The immunosuppressive effect of AZA is caused by the 6-TGN metabolites. Highly elevated 6-TGN concentrations are associated with the development of myelotoxicity; highly elevated 6-MMP concentrations are associated with the development of hepatotoxicity.

New insights from assessment of patients with inflammatory bowel disease (IBD) who were on AZA treatment led to strategies to reduce the risk of toxicity and optimize effectiveness and safety. Increased 6-MMP/6-TGN ratios indicate that the patients preferentially metabolize thiopurine to 6-MMP at the expense of the therapeutically active 6-TGN. This phenomenon of skewed drug metabolism, also known as "thiopurine hypermethylation", occurs in up to 20% of the population (4). Treatment with a combination of AZA and allopurinol can bypass thiopurine-related side-effects (5, 6) because allopurinol can shift AZA metabolism towards 6-TGN production (Fig. S1¹).

The aim of this study is to investigate the effects of allopurinol co-prescription in patients with AD and chronic hand/foot eczema who are being treated with AZA, with regard to metabolite levels (6-TGN, 6-MMP), side-effects and clinical effectiveness.

METHODS

This prospective observational study, performed between 1 January 2015 and 1 October 2016, included adult patients with AD and/or chronic hand/foot eczema, which failed to respond to AZA monotherapy, who were starting combination therapy of AZA and allopurinol. Reasons for AZA failure were lack of clinical effectiveness of therapeutic doses of AZA, side-effects, and/or a skewed metabolism. A fixed dose of allopurinol, 100 mg/day, was used. In order to prevent myelotoxic levels of 6-TGN after allopurinol co-prescription, the AZA dose was decreased by at least 50% in all patients.

6-TGN and 6-MMP metabolites were analysed in whole blood by the Clinical Pharmaceutical and Toxicological Laboratory of the Department of Pharmacy, University Medical Center Utrecht, the

Netherlands, using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The Dervieux-method was used (7). Values were expressed in picomoles/ 8×10^8 (red blood cells).

6-TGN and 6-MMP levels were measured before and at least 3 weeks after addition of allopurinol, assuming steady-state levels. 6-MMP/6-TGN ratios were calculated.

Clinical responsiveness before and after allopurinol co-prescription was determined, using the Investigator Global Assessment (IGA, 6-point scale) (8). A responder was defined as an IGA score of 0–2 or a decrease of 2 points in IGA. Non-responders were patients with an IGA score of 3–5 (except those patients with a decrease of 2 points in IGA score, those were responders) or with concomitant oral corticosteroids treatment. Clinical responsiveness and therapeutic drug monitoring were assessed at the same visit.

Hepatotoxicity was defined as an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) twice the upper limit of normal (ALT: >45 U/l in men and >35 U/l in women; AST: >35 U/l in men, >30 U/l in women). Bone marrow suppression was defined as white blood cell count $<4 \times 10^9/l$ and/or thrombocytopenia (platelet count $<150 \times 10^9/l$). Subjective side-effects were evaluated before and after allopurinol co-prescription.

All statistical analyses were performed using SPSS statistics 21. Frequencies, percentages and medians with interquartile ranges (IQR) were calculated. The Mann-Whitney *U* test was used to test whether differences in 6-TGN level, 6-MMP level or 6-MMP/6-TGN ratio before and after the addition of allopurinol were significantly different.

RESULTS

Fifteen patients were enrolled, including 9 patients with AD (60.0%) and 6 patients (40%) with isolated hand- and/or foot-eczema (Table S1¹). Median age at the start of the allopurinol was 45.7 years (IQR 38.3–53.0 years). Patients used combination treatment with allopurinol due to the ineffectiveness of AZA monotherapy ($n=10$), side-effects ($n=4$) or a skewed metabolism ($n=12$). In 10 patients, there was a combination of reasons.

AZA dose varied between 100–200 mg/day before and between 25–100 mg/day after the addition of allopurinol. Median time between start of AZA and the introduction of allopurinol was 0.5 years (IQR 0.3–1.7 years).

The median time between the addition of allopurinol and the measurement of the metabolite levels was 36.0 days (IQR 27.0–56.0 days). There was a large variation in AZA metabolite levels before and after starting allopurinol (Table S1¹; Fig. S2¹). 6-TGN levels increased after the addition of allopurinol in all patients. 6-MMP levels and 6-MMP/6-TGN ratios decreased in all patients after the addition of allopurinol. Median 6-MMP/6-TGN ratio was 247 (IQR 77–341) before and 10.0 (IQR 4–10) after addition of allopurinol ($p < 0.001$).

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Before the addition of allopurinol, 4 patients (patients 1–4; 26.7%) were classified as responders, and this increased to 7 patients (patients 1–7; 46.7%) after the addition of allopurinol ($p=0.013$) (see Table S1¹). Prednisone was tapered successfully in 3 patients. It is noteworthy that, in patient 12, a high dose of prednisone was added without our knowledge by the patient's general practitioner after the addition of allopurinol, due to ineffectiveness of treatment.

One patient (patient 3) met the criteria of hepatotoxicity before the addition of allopurinol. Liver values nearly normalized after reduction of AZA dose and addition of allopurinol. Patients 6 and 11 met the criteria of myelotoxicity after the addition of allopurinol due to extremely high 6-TGN levels. These abnormalities normalized after temporary discontinuation of AZA and allopurinol treatment and remained within safety limits after a resumed treatment with lower AZA dose in combination with allopurinol.

No side-effects of allopurinol were seen. Four patients started co-prescription of allopurinol because of gastrointestinal side-effects on AZA monotherapy. In 2 patients, these side-effects resolved after the addition of allopurinol and dose reduction of AZA.

DISCUSSION

In this study of 15 patients with chronic eczema, the addition of allopurinol resulted in an improvement in hepatotoxicity and subjective side-effects. The number of responders increased and prednisone dose was tapered successfully in some patients. This is all in agreement with earlier findings in studies in patients with IBD (4–6, 9–11).

The addition of allopurinol enables a better balance between 6-TGN and 6-MMP. Although the exact mechanism of action of allopurinol co-prescription remains unclear, there are a few proposed mechanisms (see Fig. S1¹) (4, 12, 13). Competitive inhibition of xanthine oxidase with allopurinol results in an increase in the bioavailability of the active metabolites (12). It has also been suggested that allopurinol may inhibit thiopurine methyltransferase through the production of metabolite 6-thioxanthine (12, 14, 15). The last mechanism involves increased activity of hypoxanthine-guanine phosphoribosyl transferase towards the active pathway (12, 14, 16).

The patients included in our study represent a relative negative selection of patients: patients who were successfully treated with AZA monotherapy were not included. This explains why clinical efficacy in our group before starting allopurinol is very low; only 4/15 patients were classified as responders. In these responders, allopurinol co-prescription was started because of skewed metabolism. In this study, no side effects of allopurinol have been observed. However, allopurinol is known for a variety of side effects, including serious cutaneous reactions.

Limitations of this study include the small size and the use of the IGA score instead of other clinical (such as

Eczema Area and Severity Index) and patient-oriented scores. Finally, because dose reduction and the addition of allopurinol have been performed simultaneously, it is not clear which of those improved the liver function test.

In this study, allopurinol co-prescription resulted in an improvement in treatment outcome, an increase in 6-TGN levels and a decrease in 6-MMP levels. Allopurinol co-prescription should be considered in patients with a skewed metabolism or in patients with subjective side-effects. The dose of AZA should be reduced by at least 50% before the start of allopurinol (100 mg/day for adults), and regular laboratory monitoring for myelotoxicity and hepatotoxicity is needed.

The authors have no conflicts of interest to declare.

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