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Report

Drug-Drug Interaction between Azathioprine and Allopurinol in Patients with Chronic Kidney Disease: A Case Series Study

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The impact of renal impairment on the drug-drug interaction between azathioprine and allopurinol that causes myelosuppression and hepatotoxicity remains unclear. This case series study investigated adverse effects caused by azathioprine owing to drug-drug interaction considering renal impairment. Patients who started the combination therapy of azathioprine and allopurinol at Mie University Hospital between January 2013 and February 2021 were enrolled. The outcome of adverse events associated with azathioprine was assessed according to Common Terminology Criteria for Adverse Events version 5.0. The Drug Interaction Probability Scale was used to determine the probability of drug-drug interaction. Of the three patients, two were identified as exhibiting drug-drug interaction with the Drug Interaction Probability Scale > 5 points. They experienced grade 3 myelosuppression or hepatotoxicity with fatigue, after initiation of azathioprine (1.28 and 0.44 mg/kg once daily) and allopurinol (50 mg once daily). They received appropriate dose-adjusted allopurinol according to renal function. Additionally, both patients had the estimated glomerular filtration rate < 60 mL/min/1.73 m^2. Thus, renal impairment might reduce the excretion of oxypurinol, an active metabolite of allopurinol, which certainly enhances the side effects of azathioprine.

Key words azathioprine, allopurinol, drug-drug interaction, renal function

INTRODUCTION

Azathioprine is metabolized to 6-mercaptopurine, which is further transformed into pharmacologically active metabolites, such as 6-thioguanine nucleotides (one of the end metabolites).[1] Clinically, azathioprine exhibits an immunomodulatory effect against autoimmune diseases, at a daily dose of 2.0 to 2.5 mg/kg.[2–4] A high intracellular concentration of 6-thioguanine nucleotides is responsible for the development of myelosuppression.[5,6] Additionally, 6-methylmercaptopurine ribonucleotide (another end metabolite of azathioprine), which blocks de novo purine synthesis, can cause hepatotoxicity.[6]

Detoxification of 6-mercaptopurine involves via xanthine oxidase (XO).[1] Thus, XO inhibitors, allopurinol and oxypurinol (an active metabolite of allopurinol), potentially inhibit the inactivation of 6-mercaptopurine, thereby increasing 6-thioguanine nucleotides concentrations and the risk of myelosuppression or hepatotoxicity. When azathioprine is co-administered with allopurinol, a 25% to 33% dose reduction of azathioprine is recommended to reduce the risk of toxicity.[7] Oxypurinol is mainly eliminated via the kidney, and allopurinol is recommended to reduce the dose according to the nomogram based on renal function.[8] Additionally, pharmacokinetic simulation demonstrated that the oxypurinol concentration at steady-state surpassed the concentrations to produce a 50% hypouricemic effect in patients with allopurinol 100 mg once daily and creatinine clearance of 20 mL/min.[9,10] Thus, even low-dose allopurinol can sufficiently block XO activity in patients with reduced renal function.

In this study, we evaluated the clinical impact of renal function on drug-drug interaction between azathioprine and allopurinol.

MATERIALS AND METHODS

Study Patients This case series study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Mie University Hospital (approval number: H2021-099). The eligibility criteria included inpatients or outpatients who had initiated combination therapy of azathioprine and allopurinol at Mie University Hospital between January 2013 and February 2021. The exclusion criteria were as follows: (1) age < 15 years, (2) initiation of combination therapy with azathioprine and allopurinol at other hospitals, or (3) lack of data regarding clinical laboratory data or azathioprine dose.

Data Collection We collected the clinical data (e.g., age, body weight, and medications) from electrical medical records. We checked concurrent medications known to affect oxypurinol concentration such as uricosuric agent and furosemide.[8] Renal function was calculated using the prediction formula of estimated glomerular filtration rate (eGFR) as follows: eGFR = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female).[11] eGFR < 60 mL/min/ 1.73 m^2 for at least three

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months was diagnosed as chronic kidney disease.[12]

Outcome The occurrence of adverse events associated with azathioprine (e.g., myelosuppression) was considered the outcome according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[13] We determined the probability of drug-drug interaction between azathioprine and allopurinol using the Drug Interaction Probability Scale (DIPS).[14] A DIPS of > 5 points indicates that a causal drug-drug interaction is probable or highly probable. The follow-up duration was defined as the period from the initiation of combination therapy to the day of improvement in adverse events. If there were no adverse events, the follow-up duration was defined as the period from the initiation of combination therapy to the day of treatment discontinuation or February 2021.

RESULTS

Patient Characteristics We identified five patients who received the combination therapy of azathioprine and allopurinol during the study. Two patients were excluded because they started the combination therapy at another hospital. Finally, we analyzed three outpatients in this study (Table 1). Two patients (patients 1 and 2) received a combination therapy of azathioprine (1.28 and 0.44 mg/kg once daily, respectively) and low-dose allopurinol (50 mg once daily). In contrast, the third patient (patient 3) received azathioprine (0.88 mg/kg once daily) in combination with high-dose allopurinol (100 mg twice daily). All patients fulfilled the diagnostic criteria for chronic kidney disease and received dose-adjusted allopurinol based on renal function as the nomogram recommended.[8] There were no concurrent medications influencing blood oxypurinol concentration. Two out of the three patients developed adverse events associated with azathioprine, and both patients had a DIPS score of > 5 points (Table 2).

Patient 1 received prednisolone therapy to control the further deterioration of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, which the patient was diagnosed 252 days before the start of combination therapy. Patient 1 started azathioprine and allopurinol on day 0 because patient 1 had uncontrolled ANCA-associated vasculitis and high serum uric acid level (7.4 mg/dL). Patient 1 continued taking prednisolone 5 mg once daily during the follow-up period. Patient 2 started azathioprine to control the exacerbation of ulcerative colitis from day 0. Simultaneously, patient 2 continued the treatment of prednisolone (27.5 mg once daily) and 5-aminosalicylic acid (1,200 mg thrice daily). After patient 2 started on combination therapy of azathioprine and allopurinol, prednisolone was tapered by reducing the dose by 2.5 mg daily per week, followed by being discontinued.

Adverse Events The detail of adverse events was summarized in Table 3. Patient 1 developed grade 3 leucopenia, grade 3 neutropenia, and grade 3 anemia at the nadir, whereas patient 2 developed grade 3 elevation of γ-glutamyl transpeptidase and grade 2 elevation of alkaline phosphatase with fatigue at the nadir. Both patients experienced nadir adverse events associated with azathioprine after more than one month. The time to recovery from the development of adverse events at the nadir varied by the type of adverse event (leucopenia, 14 days; neutropenia, 7 days; anemia, 40 days; γ-glutamyl transpeptidase and alkaline phosphatase elevation; 63 days).

Clinical Courses Associated with Adverse Events Clinical courses of adverse events associated with azathioprine are shown in Fig. 1. When adverse events occurred, patient 1 discontinued the combination therapy on day 28, whereas patient 2 discontinued only azathioprine on day 42. Currently, eGFR was comparable with baseline values in the two patients

Table 1. Clinical Features of Patients Treated with Azathioprine and Allopurinol

Patient	Sex	Age, years	BW, kg	BMI, kg/m^2	Diagnosis	AZA, mg/d (mg/kg/d)	ALL, mg/d	sCr, mg/dL	eGFR, mL/min/1.73m^2	Outcome
1	F	79	39.2	16.1	AAV	50 (1.28)	50	1.82	21.2	Yes
2	M	58	57.0	18.6	UC	25 (0.44)	50	1.58	36.7	Yes
3	M	42	56.7	21.1	CD	50 (0.88)	200[a]	1.15	57.0	No

Abbreviations: BW, body weight; BMI, body mass index; AZA, azathioprine; ALL, allopurinol; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; F, female; M, male; AAV, antineutrophil cytoplasmic antibody-associated vasculitis; UC, ulcerative colitis; CD, Crohn's disease.
We calculated the eGFR as follows: eGFR = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female).[11]
a: 100 mg twice daily

Table 2. Drug Interaction Probability Scale Scores of Patients that Suffered from Azathioprine Toxicity

Question		Patient 1	Patient 2
1	Are there previous credible reports of this interaction in humans?	Y (+1)	Y (+1)
2	Is the observed interaction consistent with the known interactive properties of precipitant drug?	Y (+1)	Y (+1)
3	Is the observed interaction consistent with the known interactive properties of object drug?	Y (+1)	Y (+1)
4	Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	Y (+1)	Y (+1)
5	Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug?	NA (0)	NA (0)
6	Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	NA (0)	NA (0)
7	Are there reasonable alternative causes for the event?	N (+1)	N (+1)
8	Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	NA (0)	NA (0)
9	Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug?	Y (+1)	Y (+1)
10	Was the Interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	NA (0)	NA (0)
Total scores (Causality of drug-drug interaction)		6 (Probable)	6 (Probable)

Abbreviations: Y: Yes, N: No, NA: not applicable.
The aforementioned scoring procedure was proposed by Horn *et al*.[14] The object drug is azathioprine, and the precipitant drug is allopurinol. The answers and scores for each question were described. Drug interaction probability score categories are classified into four groups: doubtful (0–1), possible (2–4), probable (5–8), and highly probable (9–11).

Table 3. Occurrence of Adverse Events in Patients Treated with Azathioprine and Allopurinol

Patient	Clinical outcome at the nadir	Time to outcome[a], d	AZA	ALL	Recovery	Time to recovery[b], d
1	Grade 3 leucopenia	37	Discontinued[c]	Discontinued[c]	Yes	14
1	Grade 3 neutropenia	44	Discontinued[c]	Discontinued[c]	Yes	7
1	Grade 3 anemia	44	Discontinued[c]	Discontinued[c]	Yes	40
2	Grade 3 γ-GT elevation	42	Discontinued[d]	Continued	Yes	63
2	Grade 2 ALP elevation	42	Discontinued[d]	Continued	Yes	63

Abbreviations: AZA, azathioprine; ALL, allopurinol; γ-GT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase
Clinical outcomes are evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[13] The reference value of γ-GT was 13 to 64 IU/L in males and 9 to 32 IU/L in females. The reference value of ALP is 38 to 113 IU/L.
a: Time to outcome was defined as the period from the initiation of combination therapy to the occurrence of outcome at the nadir.
b: Time to recovery was defined as the period from outcome at the nadir to the recovery.
c: Patient 1 discontinued azathioprine and allopurinol on day 28.
d: Patient 2 discontinued azathioprine on day 42.

(patient 1; 23.8 mL/min/1.73 m^2 on day 28 and patient 2: 41.2 mL/min/1.73 m^2 on day 42). Notably, the clinical course of anemia was relatively long irrespective of epoetin beta pegol across shortened intervals or with escalated doses (50 μg to 100 μg). An increase in γ-glutamyl transpeptidase and alkaline phosphatase without total bilirubin elevation was observed in patient 2 (Fig. 1B). Additionally, patient 2 had no instances of alcohol intake. We came across the following clinically negative findings at the beginning of the combination therapy: hepatitis B surface antigen, 0.00 IU/mL; hepatitis B surface antibody, > 1000.0 mIU/mL; hepatitis B core antibody, 8.39 COI; hepatitis C antibody, 0.04 COI. HBV-DNA load in the blood was < 2.1 $\log_{10}$ copies/mL during the study period. Furthermore, patient 2 did not have gastrointestinal symptoms and drug rash due to the other medications such as allopurinol. Thus, patient 2 exhibited a cholestatic pattern of hepatotoxicity associated with azathioprine.

DISCUSSION

This study suggests that the drug-drug interaction between azathioprine and allopurinol is clinically relevant, even at low-dose settings in patients with renal impairment. This drug-drug interaction should be taken into consideration to avoid adverse consequences, such as myelosuppression.

Several reports have raised concerns regarding the drug-drug interaction between azathioprine and allopurinol, which are supported by the evidence from most patients that have received a combination of azathioprine (100 to 200 mg daily) and allopurinol (> 100 mg daily).[15–17] Our finding demonstrated that low-dose combination therapy of azathioprine and allopurinol increased the risk of adverse events associated with azathioprine (e.g., myelosuppression). However, there was the minimal impact of allopurinol dose reduction on the development of adverse events such as leucopenia, irrespective of a decrease in 6-tioguanine concentration.[18] Combination therapy with azathioprine and allopurinol has the potential to develop drug-drug interactions despite a low-dose setting.

Renal function contributes considerably to determining drug-drug interaction between azathioprine and allopurinol. Chronic kidney disease prolongs the half-life of oxypurinol because of the decline of clearance, increasing its blood concentration in late phase.[8] Therefore, the increase in oxypurinol concentration in the late phase amplifies the inhibition of XO activity. Additionally, patient 1 was elderly and had sarcopenia (body mass index: 16.1 kg/m^2). Due to a decrease in the serum creatinine level, renal function calculated using the eGFR might be overestimated, implying that the serum oxypurinol concentration is elevated beyond expectation. Although myelosuppression might have been induced by azathioprine alone, the inhibition of XO by oxypurinol may have occurred intensively in patient 1 and increased the severity of adverse events

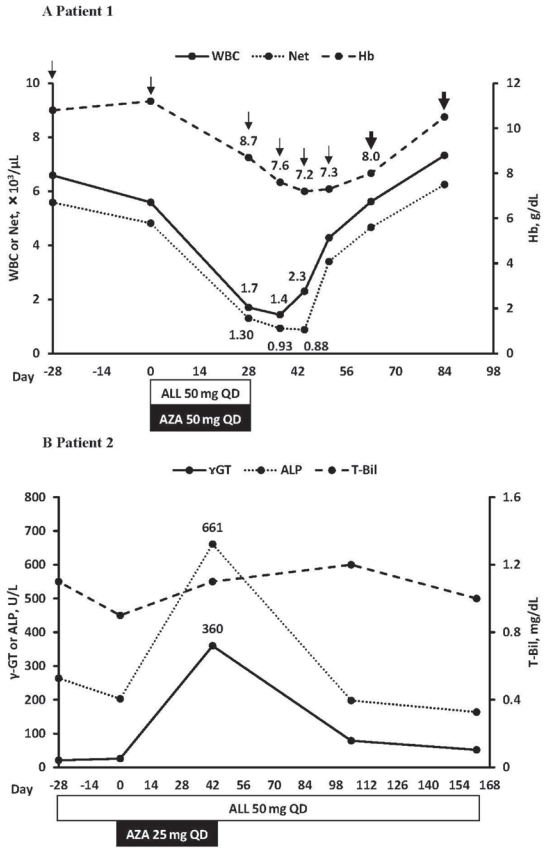

Fig. 1. Changes in Clinical Parameters of Patients that Experienced Adverse Events with Azathioprine Use

The X-axis represents days, and day 0 indicates the day patients initiated the combination therapy of azathioprine and allopurinol. Each closed circle represents a data point, and the notable values are written near the corresponding data point. Black and white bars below the x-axis represent the administration of azathioprine and allopurinol. (Fig. 1A) The left Y-axis represents WBC and Net counts, while the right Y-axis represents Hb level. Thin downward arrows indicate a subcutaneous administration of epoetin beta pegol (50 μg). Bold arrows indicate a subcutaneous injection of 100 μg epoetin beta pegol. Patient 1 discontinued the combination of azathioprine and allopurinol on day 28. (Fig. 1B). The left Y-axis represents γ-GT and ALP levels, while the right Y-axis represents the T-Bil level. Patient 2 discontinued azathioprine on day 42. Abbreviations: AZA, azathioprine; ALL, allopurinol; QD, once daily; WBC, white blood cell; Net, neutrophil; Hb, hemoglobin; γ-GT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; T-Bil, total bilirubin.

associated with azathioprine. Moreover, patient 1 was considered to receive azathioprine with an insufficient dose reduction (1.28 mg/kg) because the prescribing information recommends a 25% to 33% dose reduction during the co-administration of allopurinol (e.g., 0.5 to 0.83 mg/kg).[7] As patients with *nudix hydrolase 15* (*NUDT15*) *R139C* homozygous variant *T/T* or heterozygous variant *C/T* often suffered from leukopenia within 8 weeks,[19] patient 1 experienced myelosuppression at an early stage. However, we could not conclude that patient 1 carries the *T/T* or *C/T* genotype because the allele frequency of *NUDT15 R139C* is about 20% in Japanese patients.[19]

Patient 2 with modest renal impairment developed drug-drug interaction between azathioprine and allopurinol, despite a very low dose of azathioprine (0.44 mg/kg once daily). In fact, allopurinol decreased serum uric acid level from 8.4 mg/dL to 7.1 mg/dL during the study period, indicating that allopurinol certainly blocked XO activity. In a previous study, the frequency of *NUDT15 R139C* variant *C/T* accounted for 17% of Japanese patients.[19] In the *NUDT15 R139C* variant *C/T* group, patients received azathioprine dose with large variability (the maintenance daily dose of 0.57 ± 0.32 mg/kg),[19] suggesting that this finding cannot be applied to the drug response in patient 2. Additionally, *NUDT15 R139C* variant *T/T* accounted for only 3.7%.[19] Thus, since *NUDT15 R139C* variant *T/T* is very rare, it is unlikely that patient 2 carried it. In contrast, patient 3, who received azathioprine 0.88 mg/kg once daily and exhibited mild renal impairment, did not experience adverse events by the drug-drug interaction. The fact is that the accumulation of oxypurinol in renal impairment indicated that the drug-drug interaction between azathioprine and allopurinol is likely to occur.[20] Notably, patient 3 was younger age. A previous study identified older age as a risk factor for infection during azathioprine treatment.[21] Age should be considered in the drug-drug interaction between azathioprine and allopurinol in addition to renal function.

Moreover, adverse events associated with azathioprine persisted for long period. Steady-state of 6-thioguanine nucleotides concentrations were attained after four weeks because the half-life of 6-thioguanine nucleotides was approximately 5 days.[22] This knowledge helped to understand the clinical course of the drug-drug interaction. Many randomized controlled trials exclude patients with renal impairment or intolerance to allopurinol, and a combination of azathioprine and allopurinol might be effective and well-tolerated in patients without characteristics such as renal impairment.[23,24] We recommend the careful selection of patients who are suitable for combination therapy with azathioprine and allopurinol.

There were many limitations in our study. First, this study is a case-series design, and thus, it was difficult to avoid the impact of unknown confounding factors. Second, we could not analyze genetic polymorphisms of thiopurine methyltransferase and *NUDT15*, which affect sensitivity to azathioprine. Third, there were no data on the concentration of oxypurinol and 6-thioguanine nucleotides. Fourth, we could not confirm adherence to pharmacotherapy. Finally, we could not obtain periodic clinical laboratory data, therefore, the time courses may be distorted.

In conclusion, adverse events caused by the interaction between azathioprine and allopurinol were characterized by chronic kidney disease in the two patients who received low-dose azathioprine and allopurinol. Renal function may be an important factor for this drug-drug interaction.

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Conflict of interest The authors declare no conflict of interest.

REFERENCES

1) Gearry RB, Day AS, Barclay ML, Leong RW, Sparrow MP. Azathioprine and allopurinol: A two-edged interaction. *J. Gastroenterol. Hepatol.*, **25**, 653–655 (2010).
2) Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, Hauser T, Neumann I, Tesar V, Wissing KM, Pagnoux C, Schmitt W, Jayne DR. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA*, **304**, 2381–2388 (2010).
3) Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut*, **55**, 47–53 (2006).
4) Cosnes J, Bourrier A, Laharie D, Nahon S, Bouhnik Y, Carbonnel F, Allez M, Dupas JL, Reimund JM, Savoye G, Jouet P, Moreau J, Mary JY, Colombel JF. Early administration of azathioprine vs conventional management of Crohn's Disease: a randomized controlled trial. *Gastroenterology*, **145**, 758–765.e752, quiz, e714–e755 (2013).
5) Andoh A, Tsujikawa T, Ban H, Hashimoto T, Bamba S, Ogawa A, Sasaki M, Saito Y, Fujiyama Y. Monitoring 6-thioguanine nucleotide concentrations in Japanese patients with inflammatory bowel disease. *J. Gastroenterol. Hepatol.*, **23**, 1373–1377 (2008).
6) Dubinsky MC, Lamothe S, Yang HY, Targan SR, Sinnett D, Théorêt Y, Seidman EG. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology*, **118**, 705–713 (2000).
7) Azasan (azathioprine) [prescribing information]. *Bridgewater, NJ: Salix Pharmaceuticals*, (May 2019).
8) Day RO, Graham GG, Hicks M, McLachlan AJ, Stocker SL, Williams KM. Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. *Clin. Pharmacokinet.*, **46**, 623–644 (2007).
9) Stocker SL, McLachlan AJ, Savic RM, Kirkpatrick CM, Graham GG, Williams KM, Day RO. The pharmacokinetics of oxypurinol in people with gout. *Br. J. Clin. Pharmacol.*, **74**, 477–489 (2012).
10) Graham S, Day RO, Wong H, McLachlan AJ, Bergendal L, Miners JO, Birkett DJ. Pharmacodynamics of oxypurinol after administration of allopurinol to healthy subjects. *Br. J. Clin. Pharmacol.*, **41**, 299–304 (1996).
11) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. *Am. J. Kidney Dis.*, **53**, 982–992 (2009).
12) Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.*, **67**, 2089–2100 (2005).
13) Common Terminology Criteria for Adverse Events (CTCAE) Version5.0. (2017).
14) Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. *Ann. Pharmacother.*, **41**, 674–680 (2007).
15) Feinman J, Rollins B, Contreras J, Parikh A. Pancytopenia caused by allopurinol and azathioprine interaction in a heart transplant patient: a case report. *Eur. Heart J. Case Rep.*, **4**, 1–4 (2020).
16) Kennedy DT, Hayney MS, Lake KD. Azathioprine and allopurinol: the price of an avoidable drug interaction. *Ann. Pharmacother.*, **30**, 951–954 (1996).
17) Bacon BR, Treuhaft WH, Goodman AM. Azathioprine-induced pancytopenia. Occurrence in two patients with connective-tissue diseases. *Arch. Intern. Med.*, **141**, 223–226 (1981).
18) Chavoushi SF, Jharap B, Friedrich P, Smid K, Peters GJ, Malingré M. Thiopurines with low-dose allopurinol (ThiLDA)-a prospective clinical one-way crossover trial. *Eur. J. Clin. Pharmacol.*, **75**, 1669–

1674 (2019).
19) Kakuta Y, Naito T, Onodera M, Kuroha M, Kimura T, Shiga H, Endo K, Negoro K, Kinouchi Y, Shimosegawa T. NUDT15 R139C causes thiopurine-induced early severe hair loss and leukopenia in Japanese patients with IBD. *Pharmacogenomics J.*, **16**, 280–285 (2016).
20) Wright DF, Stamp LK, Merriman TR, Barclay ML, Duffull SB, Holford NH. The population pharmacokinetics of allopurinol and oxypurinol in patients with gout. *Eur. J. Clin. Pharmacol.*, **69**, 1411–1421 (2013).
21) Broekman M, Coenen MJH, Wanten GJ, van Marrewijk CJ, Klungel OH, Verbeek ALM, Hooymans PM, Guchelaar HJ, Scheffer H, Derijks LJJ, Wong DR, de Jong DJ. Risk factors for thiopurine-induced myelosuppression and infections in inflammatory bowel disease patients with a normal TPMT genotype. *Aliment. Pharmacol. Ther.*, **46**, 953–963 (2017).
22) Derijks LJ, Gilissen LP, Engels LG, Bos LP, Bus PJ, Lohman JJ, van Deventer SJ, Hommes DW, Hooymans PM. Pharmacokinetics of 6-thioguanine in patients with inflammatory bowel disease. *Ther. Drug Monit.*, **28**, 45–50 (2006).
23) Kiszka-Kanowitz M, Theede K, Mertz-Nielsen A. Randomized clinical trial: a pilot study comparing efficacy of low-dose azathioprine and allopurinol to azathioprine on clinical outcomes in inflammatory bowel disease. *Scand. J. Gastroenterol.*, **51**, 1470–1475 (2016).
24) Friedman AB, Brown SJ, Bampton P, Barclay ML, Chung A, Macrae FA, McKenzie J, Reynolds J, Gibson PR, Hanauer SB, Sparrow MP. Randomised clinical trial: efficacy, safety and dosage of adjunctive allopurinol in azathioprine/mercaptopurine nonresponders (AAA Study). *Aliment. Pharmacol. Ther.*, **47**, 1092–1102 (2018).