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ORIGINAL ARTICLE

Influence of allopurinol on thiopurine associated toxicity: A retrospective population-based cohort study

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Aims: Thiopurines are important for treating inflammatory bowel disease, but are often discontinued due to adverse effects. Concomitant use of allopurinol might lower the risk of these unwanted effects, but large studies in the general population are lacking. The aims of this study were to evaluate rates of hepatotoxicity, myelotoxicity, pancreas toxicity and therapy persistence in adult thiopurine users with or without allopurinol.

Methods: A retrospective population-based cohort study was conducted within current thiopurine users (Clinical Practice Research Datalink). Among these patients, co-use of allopurinol was compared to non-use. Hazard ratios (HRs) for hepatotoxicity, myelotoxicity and pancreatitis were derived using time-dependent Cox proportional hazards models, and were adjusted for potential confounders. Persistence of thiopurine use was evaluated using Log-rank statistics.

Results: Patients using thiopurines (n = 37 360) were identified of which 1077 were concomitantly taking allopurinol. A 58% decreased risk of hepatotoxicity was observed in those concomitantly taking allopurinol (HR 0.42; 95% CI 0.30–0.60; NNT 46). Rate of myelotoxicity (HR 0.96; 95% CI 0.89–1.03) was not influenced. Risk of pancreatitis was increased (HR 3.00; 95% CI 1.01–8.93; NNH 337), but was only seen in those with active gout (suggesting confounding by indication). Finally, allopurinol co-users were able to maintain thiopurine therapy over twice as long as those not on allopurinol (3.9 years *vs*. 1.8 years, $P < 0.0001$).

Conclusion: In thiopurine users, allopurinol is associated with a 58% reduced risk of hepatotoxicity. In addition, thiopurine persistence was prolonged by 2.1 years in allopurinol users. These data support the use of allopurinol in individuals requiring thiopurine therapy.

KEYWORDS

allopurinol, hepatotoxicity, myelotoxicity, pancreas toxicity, thiopurines

† Deceased.

Dr Arief Lalmohamed was principal investigator and takes full responsibility for the integrity of the study.

1 | INTRODUCTION

Thiopurines as a class include azathioprine, mercaptopurine and thioguanine, and are widely used in the treatment of autoimmune diseases, especially in inflammatory bowel disease (IBD).[1,2] Thiopurines were recommended for rheumatoid arthritis (RA) too, until the 2013 update of the EULAR recommendations.[3] In IBD, thiopurines are proven to be effective in maintaining remission, both in ulcerative colitis[2] and Crohn's disease.[1] Yet, up to 60% of patients discontinue thiopurine therapy within 5 years either because of insufficient clinical response or due to adverse events.[4] Some of these adverse events, such as hepatotoxicity,[5,6] myelotoxicity[7] and pancreatitis,[8] are potentially life-threatening.

Azathioprine and mercaptopurine are metabolized to 6-thioguanine nucleotides (6-TGN), which include 6-thioguanine monophosphate (6-TGMP), 6-thioguanine diphopsphate (6-TGDP) and 6-thioguanine triphosphate (6-TGTP). The therapeutic range of 6-TGN is 230–450 pmol/8 × 10^8 erythrocytes (Lennard method) or 600–1200 pmol/8 × 10^8 erythrocytes (Dervieux method) and hepatotoxicity correlated with elevated 6-MMPR levels (>5700 pmol/8 × 10^8 erythrocytes) for both the Lennard and Dervieux methods.[9,10] 6-TGTP is primarily responsible for the immunosuppressant effect and possibly for myelotoxicity.[11] Myelotoxicity can also occur in patients with high concentrations of 6-MMPR, due to inhibition of *de novo* purine synthesis.[12] Nevertheless, high 6-MMPR concentrations are primarily associated with hepatotoxicity.[10] Therefore, maintaining adequate and non-toxic levels of these metabolites is essential for clinical effectiveness. However, pharmacokinetic studies have shown that up to 30% of patients preferentially metabolize thiopurines towards the hepatotoxic 6-MMPR rather than 6-TGN (so-called shunters).[13–15]

Adding allopurinol to thiopurine therapy has been described to improve the risk–benefit ratio of this medication in shunters, as allopurinol promotes metabolism of thiopurines towards 6-TGN metabolites rather than hepatotoxic 6-MMPR metabolites. Normally, this combination is contraindicated, certainly without dose adjustment. Current guidelines therefore state that the thiopurine dose should be reduced by 66–75% when concomitantly using allopurinol. The usual dose of allopurinol used for this purpose is 100 mg/day. However, the effectiveness of this approach in preventing hepatotoxicity has only been studied in relatively small single-centre populations from IBD clinics, while the impact on other toxicity parameters (e.g. myelotoxicity) and long-term therapy persistence was not addressed in depth.[4,16–19]

Therefore, the aims of this study were to evaluate the frequency of side effects and the duration of therapy persistence in patients using thiopurines with or without the coadministration of allopurinol in a large general population.

What is already known about this subject

- Thiopurines are often discontinued due to adverse effects, such as hepatotoxicity and myelotoxicity.
- Adding allopurinol might reduce these unwanted negative outcomes of thiopurines. Normally this is a contraindication; however, by carefully reducing the thiopurine dose to 66–75% of the original prescription, this combination might improve the safety profile of thiopurine, especially in shunters.
- Large studies in a general population describing the potential beneficial effect of adding allopurinol are not available.

What this study adds

- Concomitant use of allopurinol in thiopurine users is associated with a 58% reduced hepatotoxicity risk.
- Myelotoxicity risk was not affected by co-use of allopurinol.
- Duration of thiopurine therapy (i.e. persistence) was over twice as long in individuals taking thiopurines combined with allopurinol as those who were taking thiopurines only.

2 | METHODS

2.1 | Data source

Data were retrieved from the Clinical Practice Research Datalink (CPRD). The CPRD is the world's largest GP-based database, situated in the United Kingdom, containing anonymous medical records from general practices, representing 16.7% of the British population. The data recorded in the CPRD contains diagnoses, prescription data, laboratory data, demographic information, clinical events, specialist referrals and related major outcomes.[20] The CPRD database has a high level of validity and completeness.[21] Drug/molecular target nomenclature were used conform to the IUPHAR/BPS Guide to PHARMACOLOGY.[22,23] This protocol has been approved by the Independent Scientific Advisory Committee 19_032R of the CPRD.

2.2 | Study population

All adults with at least one prescription for a thiopurine (azathioprine or mercaptopurine), between 1 January 1987 and 31 December 2018 were selected. Thioguanine use was not included in the study population, as this thiopurine is not metabolized towards 6-MMPR. The date of first thiopurine prescription was defined as the start of follow-up. All patients were required to have at least 1 year of valid data collection period prior to the first prescription. For the 'valid data collection period', we utilized the Up-to-Standard (UTS) technique by CPRD. A practice is deemed UTS if it meets the CPRD practice-based quality marker, which is based on continuous and complete recording of patient data. Hence, 'valid data collection period' comprises only practices within their UTS time window.[24] Follow-up ended at the end of data collection, date of transfer of the patient out of the practice area, or the patient's death, whichever came first.

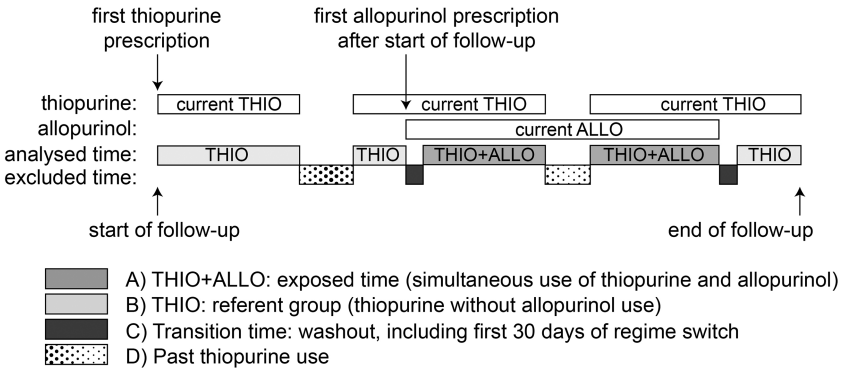

FIGURE 1 Timeline of an example thiopurine user

2.3 | Exposure

During follow-up, for each patient four time windows of usage patterns could potentially be identified, of which two were analysed (see example patient in Figure 1).

- THIO + ALLO: exposed time (simultaneous use of thiopurine and allopurinol, analysed)
- THIO: reference group (thiopurine without allopurinol use, analysed)
- Transition time: washout, including first 30 days of regime switch (not analysed)
- Past thiopurine use: (not analysed)

In order to assess these patterns, thiopurine prescriptions were used. Thiopurine use started with a prescription for thiopurine and ended if no new repeat prescription occurred within 30 days of the end of use. Afterwards, the patient was classified as a non-user, but could be classified as a thiopurine user again if a new prescription occurred. Allopurinol use was assessed using the same method. The transition period (i.e., the initial period of co-use) was set at 30 days, to take into account potential carry-over effects, primarily due to the lag between the occurrence of myelo- and hepatotoxic effects. This transition period was excluded from the main analysis. In a sensitivity analysis, the length of this transition period was changed to 15 and 60 days. Within the group of allopurinol users, all patients with high thiopurine doses (azathioprine equivalent > 100 mg daily) were excluded. This implies inadequate anticipation of the interaction between allopurinol and thiopurines, as current guidelines state that the thiopurine dose should be reduced by 66–75% when concomitantly using allopurinol.[25,26]

2.4 | Outcomes

Hepatotoxicity was the primary outcome of interest, and was defined as having an abnormal liver function test [≥3 times the upper limit of normal ranges for either alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)].[27] Liver injury case ascertainment based on primary care liver test results has been validated in CPRD before and demonstrated excellent case ascertainment rates.[28]

Secondary study outcomes included myelotoxicity: platelet count < 150 000 platelets/μl and/or leukocyte counts < 4000/μl;[29,30] pancreas toxicity: lipase and/or amylase ≥ 3 times the upper limit of normal ranges;[31] combined toxicity: any of the above unintended outcomes taken together. Finally, the duration of therapy continuation (i.e. therapy persistence) of thiopurines was analysed.

2.5 | Potential confounding factors and effect modifiers

Potential confounders for hepatotoxicity, myelotoxicity and pancreas toxicity were assessed at baseline (e.g. at the start of follow-up). These risk factors included: alcohol use (current, previous, never, unknown), body mass index (BMI, <20 kg/m^2, 20–25 kg/m^2, >25 kg/m^2), age, gender, smoking and use of certain types of drugs associated with any of the adverse events of interest (shown in Table 1) within 3 months before start of follow-up. Drugs associated with hepatotoxicity were grouped based on their underlying mechanism for hepatic injury.[32] Additionally, for pancreas toxicity as the outcome, a history of gallstones and pancreatitis-associated drugs were included.[33] For BMI, alcohol use and smoking status, the most recent record was used. Age was assessed as a time-dependent variable. In a sensitivity analysis, we used multiple imputation with chained equation methods to deal with missing information on smoking status, alcohol use and body mass index, as described by others.[34]

2.6 | Data analysis

Crude and adjusted hazard ratios (HR) were calculated for hepatotoxicity, myelotoxicity, pancreas toxicity and combined toxicity, comparing allopurinol versus no allopurinol within thiopurine users. For this purpose, time-dependent Cox proportional hazards models were used (SAS version 9.4; PHREG procedure). All analyses were fully adjusted for all of the potential confounders. To investigate potential effect modifiers, the main analyses were stratified by the general risk factors mentioned under 'potential confounders'. Wald tests were used to assess statistical interactions. Finally, therapy persistence of thiopurines was visualized for allopurinol- and non-users using Kaplan Meier plots and tested using Log-rank statistics.

TABLE 1 Baseline characteristic of allopurinol users and matched non-users among current thiopurine users

	Thiopurine users			
	Allopurinol		No allopurinol	
Characteristic	*n* = 1077		*n* = 36 283	
Follow-up in years (mean, SD)	3.6	(5.5)	3.5	(4.1)
Females	367	(34%)	19 859	(55%)
Age in years (mean, SD)	59	(16.9)	48	(19.5)
BMI in kg/m^2 (mean, SD)	28	(5.5)	26	(5.8)
Unknown	90	(8%)	4228	(12%)
Drinking status				
Non-drinker	212	(20%)	8391	(23%)
Drinker	741	(69%)	22 267	(61%)
Unknown	124	(12%)	5625	(16%)
Smoking status				
Non-smoker	566	(53%)	18 354	(51%)
Ex-smoker	290	(27%)	8060	(22%)
Smoker	192	(18%)	8343	(23%)
Unknown	29	(3%)	1526	(4%)
Thiopurine indication				
Inflammatory bowel disease (IBD)	583	(54%)	21 420	(59%)
Rheumatic disease	139	(13%)	6307	(17%)
Other/unknown	355	(33%)	8556	(24%)
Thiopurine drug				
Azathioprine	969	(90%)	33 380	(92%)
Daily dose in mg (median, IQR)	50	(50–100)	100	(50–100)
Mercaptopurine	108	(10%)	2903	(8%)
Daily dose in mg (median, IQR)	75	(50–100)	100	(100–100)
Allopurinol daily dose in mg (median, IQR)	100	(100–300)	N/A	
Drugs use within 6 months prior to thiopurine use associated with outcome parameters				
Hepatocellular (elevated ALT)[a]	638	(59%)	18 926	(52%)
Mixed (elevated ALP + elevated ALT)[b]	230	(21%)	4740	(13%)
Cholestatic (elevated ALP + elevated TBL)[c]	203	(19%)	6760	(19%)
Drugs associated with pancreas toxicity[d]	465	(43%)	13 216	(36%)

Abbreviations: IQR, interquartile range; ALT, alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin level.
[a]Hepatocellular (elevated ALT): acarbose, acetaminophen, allopurinol, amiodarone, baclofen, buproprion, fluoxetine, HAART drugs, isoniazid, ketoconazole, lisinopril, losartan, methotrexate, omeprazole, paroxetine, pyrazinamide, rifampin, risperidone, sertraline, statins, tetracyclines, trazodone, trovafloxacin and valproic acid.
[b]Mixed (Elevated ALP + Elevated ALT): amitriptyline, azathioprine, captopril, carbamazepine, clindamycin, cyproheptadine, enalapril, flutamide, nitrofurantoin, phenobarbital, phenytoin, sulfonamides, trazodone, trimethoprim–sulfamethoxazole and verapamil.
[c]Cholestatic (Elevated ALP + Elevated TBL): amoxicillin-clavulanic acid, chlorpromazine, clopidogrel, erythromycins, irbesartan, mirtazapine, phenothiazines, terbinafine and tricyclics.
[d]Drugs associated with pancreas toxicity: didanosine, valproic acid, angiotensin-converting-enzyme inhibitors and mesalazine.

3 | RESULTS

Baseline characteristics of allopurinol users and non-users among individuals taking thiopurines are shown in Table 1. A total of 1077 allopurinol users and 36 283 non-allopurinol users with a median follow-up of 3.8 years were identified. Median age was higher in the allopurinol group (54 years) compared with control subjects (48 years). For allopurinol users, the dominant gender was males (66%), whereas gender was more equally distributed in non-users. Within the allopurinol group 90% were azathioprine users and 10% were taking mercaptopurine. These proportions did not differ substantially between allopurinol users and non-users. Median azathioprine and mercaptopurine dose in the allopurinol group was respectively 50 mg and 75 mg daily, and was, as expected, lower than in the non-allopurinol group.

TABLE 2 Risk of thiopurine related toxicity with allopurinol use versus no allopurinol use within thiopurine users

	Thiopurine use					
	No allopurinol		Allopurinol			
	N events	IR[a]	N events	IR[a]	Crude HR (95% CI) Allopurinol versus no allopurinol	Adj HR (95% CI)
Hepatotoxicity[b]	1863	149	32	65	0.42 (0.29–0.59)	0.42 (0.30–0.60)
Myelosuppression[c]	27 856	3957	801	4108	1.04 (0.97–1.12)	0.96 (0.89–1.03)
Leukopenia	10 001	971	314	842	0.81 (0.73–0.91)	0.92 (0.82–1.03)
Thrombocytopenia	4726	404	186	446	1.08 (0.93–1.25)	0.94 (0.81–1.09)
Erythrocytopenia	15 900	2137	358	2170	1.05 (0.94–1.16)	1.03 (0.93–1.15)
Pancreatitis[d]	27	2.1	4	7.9	3.22 (1.12–9.27)	3.00 (1.01–8.93)
Combined toxicity[e]	39 057	6499	993	5773	0.90 (0.84–0.96)	0.87 (0.82–0.93)

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; N, number of adverse events.
[a]IR expressed as incidence rate per 10 000 person years.
[b]Adjusted for age, gender, calendar year, BMI, alcohol use, smoking status and drugs associated with liver toxicity in the previous 3 months.
[c]Adjusted for age, gender, calendar year, BMI, alcohol use and smoking status.
[d]Adjusted for age, gender, calendar year, BMI, alcohol use, smoking status and drugs associated with pancreatitis in the previous 3 months.
[e]Adjusted for age, gender, calendar year, BMI, alcohol use, smoking status and drugs associated with liver toxicity/pancreatitis and antibiotics in the previous 3 months.

Within thiopurine users, hepatotoxicity risk was significantly reduced by 58% in those taking allopurinol concomitantly, versus individuals who were not (crude HR 0.42; 95% CI 0.29–0.59, adjusted (adj.) HR 0.42; 95% CI 0.30–0.60; Table 2). The sensitivity analysis using multiple imputation yielded similar results (liver disease, HR 0.42; 95% CI 0.29–0.60). Corresponding absolute risks were reduced from 5.13% to 2.97% resulting in a number needed to treat of 46. Rate of risk reduction was greatest in older subjects (35–65 years: adj. HR 0.40, 95% CI 0.25–0.63; >65 years: adj. HR 0.28, 95% CI 0.12–0.62), whereas no trend could be observed in subjects aged 18–34 years old (adj. HR 0.99, 95% CI 0.37–2.70). Although the HR for females did not reach statistical significance (HR for females: 0.57, 95% CI 0.29–1.09), no statistical interaction between females and males was observed using Wald statistics. In a sensitivity analysis, similar risk estimates were found when the transition period (washout time window) was set at 15 or 60 days (instead of 30 days), demonstrating robust findings.

Rates of myelotoxicity were not significantly different between both groups, adj. HR 0.96 (95% CI 0.89–1.03; Table 2). The same was true when looking at subtypes of myelotoxicity: rates of leukopenia adj. HR 0.92 (95% CI 0.82–1.03), thrombocytopenia HR 0.94 (95% CI 0.81–1.09), and erythrocytopenia HR 1.03 (95% CI 0.93–1.15) were all similar between those taking allopurinol *vs*. subjects who were not.

On the other hand, pancreatitis risk was significantly increased in allopurinol users, yielding an adjusted HR of 3.00 (95% CI 1.01–8.93; NNH 337), but this analysis was based on 31 events only (Table 2). Within allopurinol users, absolute incidence rates per 10 000 person years of pancreatitis were 7.9, as compared to 65 for hepatotoxicity. All of the 31 allopurinol patients experiencing pancreatitis had elevated serum urate levels (>6 mg/dL), suggesting that allopurinol was prescribed for gout and not for modifying thiopurine metabolism.[35] This was also reflected by the prescribed dose: the majority of patients received a higher dose of allopurinol (>100 mg) which is typical for gout.

Looking at all of these unwanted events combined, a lowered combined risk for the adverse events studies was found in patients on allopurinol adj. HR 0.87 (95% CI 0.82–0.93). Allopurinol users were also able to continue thiopurine therapy over twice as long as subjects not taking allopurinol ($P < 0.0001$; Figure 2). After 5 years, 43.3% remained on thiopurines (95% CI 40.3–46.2) compared to 24.2% of those who were not on allopurinol (95% CI 23.8–24.7%). In addition, median duration of thiopurine therapy was substantially longer in those taking allopurinol (3.88 years) compared to those not on allopurinol (1.83 years).

4 | DISCUSSION

In this large cohort of thiopurine users, allopurinol use was associated with a 58% significantly reduced risk of hepatotoxicity with a number

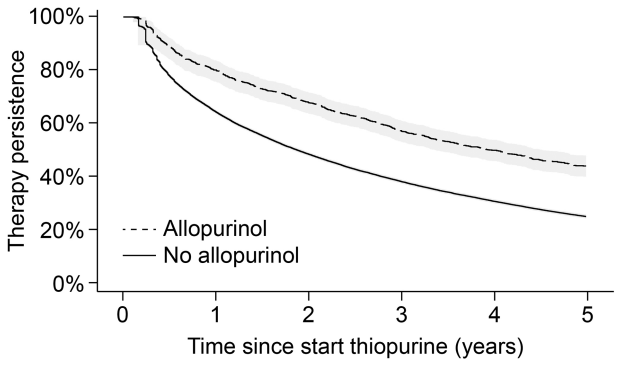

FIGURE 2 Kaplan–Meier curves of thiopurine therapy persistence of allopurinol-users and non-users ($P < 0.0001$)

needed to treat of 46. Looking at all major thiopurine associated adverse events together, allopurinol was also associated with significantly fewer side effects. Finally, allopurinol users remained on their thiopurine therapy substantially longer than those not taking allopurinol.

This is the largest study investigating the intended use of the drug–drug interaction between thiopurines and allopurinol in a general population. These results are in line with outcomes from other studies with smaller sample sizes.[36–38] Pavlidis *et al*. investigated thiopurine users who developed hepatotoxicity. In 11 of 14 patients (79%) commencing allopurinol, hepatotoxicity resolved.[37] Other studies reported similar results: 9 out of 11 patients[38] (82%) and 25 out of 30 patients[36] (83%) abrogated hepatotoxicity after starting allopurinol with concurrent thiopurine use. However, these studies tested this beneficial effect of allopurinol in a clinical setting. Moreover, these studies lacked a comparator group (i.e., it is unclear whether hepatotoxicity would have resolved without allopurinol).

The most plausible explanation of these findings lies in the pharmacokinetic interaction between allopurinol and thiopurines. High blood levels of 6-MMPR are associated with an increased risk of hepatotoxicity,[10] whereas low blood concentrations of 6-TGN are linked to poor therapeutic response.[39] Allopurinol increases 6-TGN levels at the expense of 6-MMPR exposure.[40–42] This should translate into better clinical outcomes (e.g. lower risks of hepatotoxicity and higher therapy persistence), and we here demonstrate this in a large outpatient setting.

Although absolute rates were low, the increased risk of pancreatitis requires further exploration. Based on the high serum uric acid level (>6 mg/dL) that was found in all our patients on allopurinol who had this complication, we suggest that they had in fact another underlying disease, gout, which is known to be associated with pancreatitis.[43–45] Indeed, gout is known to have a higher disease burden.[46] It is likely that allopurinol was prescribed for gout in the current study given the median dose of 300 mg. Another possible explanation, albeit highly speculative, is that alternative metabolites are formed by allopurinol and these specific metabolites might be associated with pancreatitis. However, no supporting data exist.

The strengths of this study include its large sample size, routine access to laboratory services (which enabled us to look at hepatotoxicity in a detailed manner) and a large duration of follow-up. This study had some limitations, however. Firstly, the underlying indication could not be identified in roughly a third of the patients, although it is likely that among these patients IBD remains the primary indication as reflected by the NICE guidelines.[47,48] Also, thiopurines have never been the first choice in rheumatic disease and were no longer recommended in the last revision of the EULAR guidelines.[3] Nevertheless, a small proportion of our study population did use thiopurines for this indication. Yet, we expect that the underlying diagnosis does not influence the effect of allopurinol as this is driven mainly by a drug–drug interaction independent of patient population.

Secondly, limited data were available on alternative strategies to lower the risk on thiopurine-associated toxicity such as switching to thioguanine[49] or phenotyping TPMT activity. Indeed, in the current study, the number of patients using thioguanine was too low to compare to the addition of allopurinol to azathioprine or 6-mercaptopurine. Similarly, we had no data on TPMT activity. Some studies suggested that altered TPMT activity may be associated with therapy failure and/or myelosuppression,[50,51] while other studies could not confirm this association.[52,53] Therefore, the place of allopurinol addition *vs*. alternative strategies to deal with thiopurine-related toxicity remains to be elucidated.

Finally, it was not possible to assess the therapeutic efficacy of thiopurine use in more detail: IBD disease scores were unavailable, there was no access to endoscopic data, and no data on step up therapy (e.g. TNF-alpha blockers such as infliximab). However, we were able to identify substantially longer therapy persistence of thiopurines among allopurinol users suggestive of a longer duration of the therapeutic effect in those patients taking thiopurines together with allopurinol.

In conclusion, allopurinol use was associated with a 58% reduced risk of hepatotoxicity in thiopurine users (NNT 46), while rates of myelotoxicity were not influenced. Although rates of pancreatitis were increased among allopurinol users, this seemed to be driven by the underlying disease rather than the drug itself. Individuals on allopurinol continued their thiopurine therapy for more than twice the length of time, and combined thiopurine toxicity was reduced by 13%. These results support the safety of concomitant use of allopurinol in individuals dependent on thiopurine therapy.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

J.P.A.H. and A.L. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J.P.A.H., A.G.G.E., E.M.M. and A.L. were responsible for the study concept and design. J.P.A.H. and A.L. acquired the data, which were analysed and interpreted by all the authors. The manuscript was drafted by A.L. and J.P.A.H. All authors were responsible for the critical revision of the manuscript for important intellectual content.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available through the CPRD office (license required).

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