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

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Introduction

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, however large studies in the general population are lacking.

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. Data was derived from the Clinical Practice Research Datalink. Patients with a thiopurine prescription were identified. 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

Patient using thiopurines (N=37,360) were identified of which 1,077 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 which is associated with pancreatitis, suggesting confounding by indication. Results are shown in table 1. Finally, allopurinol co-users were able to maintain thiopurine therapy over twice as long as those not on allopurinol (3.9 years versus 1.8 years, P<0.0001) as shown in figure 1.

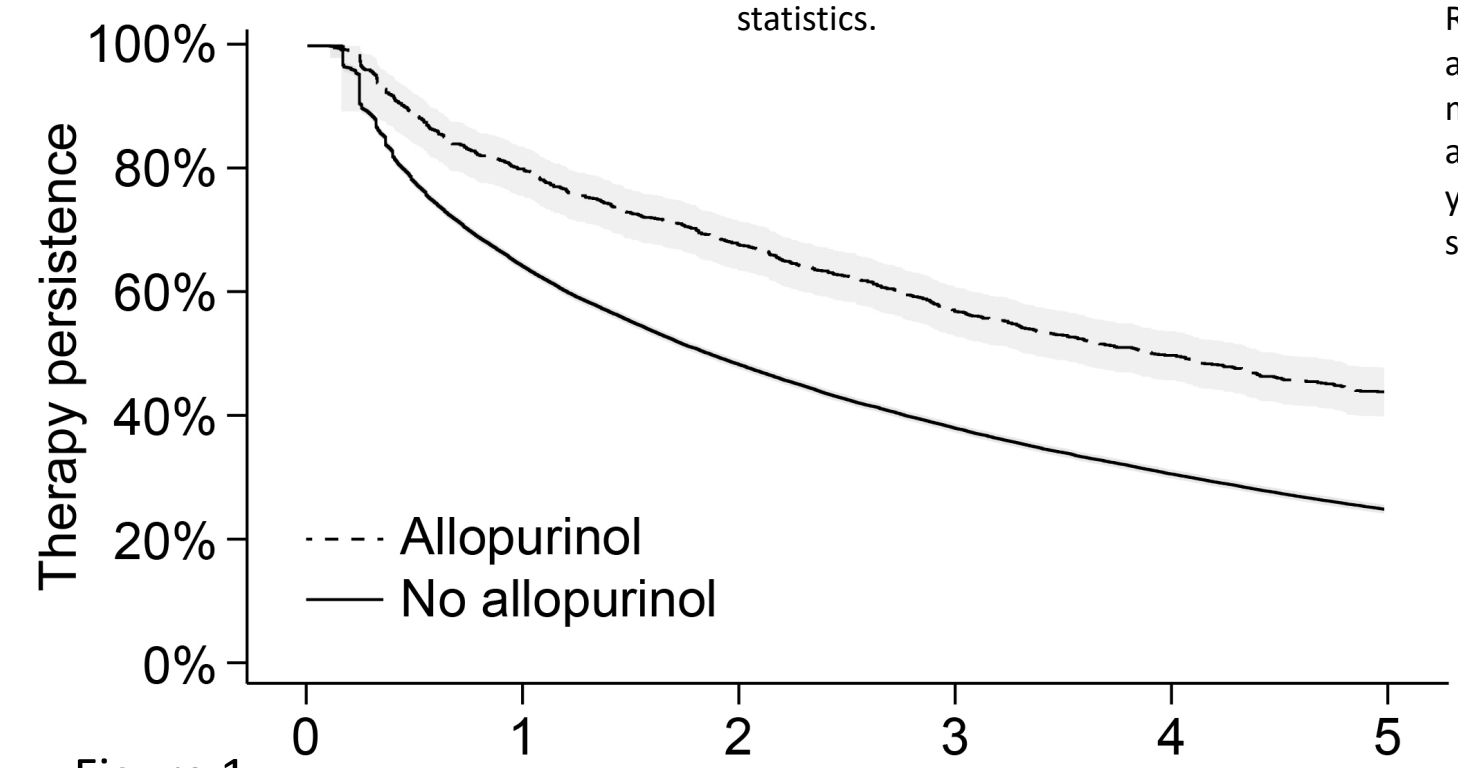

Figure 1.

Table 1. Risk of thiopurine related toxicity with allopurinol use versus no allopurinol use within thiopurine users

	No ALLO	ALLO		
	Incidence rate	**Incidence rate**	**Crude HR (95% CI)**	**Adj HR (95% CI)**
			Allopurinol vs no allopurinol	Allopurinol vs no allopurinol
Hepatotoxicity	149	65	0.42 (0.29-0.59)	0.42 (0.30-0.60)
Myelosuppression	3.957	4.108	1.04 (0.97-1.12)	0.96 (0.89-1.03)
Pancreatitis	2.1	7.9*	3.22 (1.12-9.27)	3.00 (1.01-8.93)
Combined toxicity	6.499	5.773	0.90 (0.84-0.96)	0.87 (0.82-0.93)

*all these patients had gout

Conclusions

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.

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