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

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Background: Thiopurines are important for treating inflammatory bowel disease, but are often discontinued due to adverse effects. Through a pharmacokinetic interaction, concomitant use of allopurinol might lower the risk of these unwanted effects, but 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 (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 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 (the underlying allopurinol indication). Finally, allopurinol co-users were able to maintain thiopurine therapy more than twice as long as those not on allopurinol (3.9 years versus 1.8 years, P<0.0001).

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.

Keywords: Thiopurines; allopurinol; hepatotoxicity; myelotoxicity; pancreas toxicity