A QSP approach to predict clinical outcomes of thiopurine therapy in inflammatory bowel disease

Vijay K. Siripuram1*, Daniel F.B. Wright1, Murray L. Barclay2, Stephen B. Duffull1

1 Otago Pharmacometrics Group, School of Pharmacy, University of Otago, New Zealand 2 Departments of Gastroenterology and Clinical Pharmacology, Christchurch Hospital, New Zealand

Objectives: To explore the enzyme activities required to produce plausible systems model predictions of 6-thioguanine nucleotides (TGN) and 6-methyl mercaptopurine (MMP) concentrations in red blood cells (RBC units: pmol/8x10^8 RBCs) under different clinical scenarios in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine.

Methods: A systems model for thiopurine metabolism was developed based on intracellular purine synthesis pathways (submitted to CPT: PSP) [Figure 1]. This model was used to simulate values of metabolite concentrations with reference to 3 different clinical scenarios commonly observed in patients treated with standard doses of thiopurines: i) normal patients (235 < TGN concentration < 450; MMP concentrations < 5700), ii) those presenting with myelotoxicity (TGN concentrations > 450) and iii) hepatotoxicity with thiopurine resistance (aka “shunters”) (MMP concentrations > 5700 and TGN concentrations < 235). Each of these scenarios represents an unknown difference in enzymatic activity. All simulations were performed using MATLAB (R2015a, Math Works Inc).

Results: Scenario (i), was obtained by calibrating the activities of several enzymes involved in the thiopurine metabolic pathway (See figure-1) and the reference activities were used as starting point to perform perturbations for the remaining scenarios. Scenario, (ii) was obtained by down-regulation of TPMT activity, (iii) was obtained by either up-regulation of TPMT activity or down-regulation of HGPRT or IMPDH and/or GMPS activities.

Conclusions: Thiopurine metabolism is complex and poorly understood despite over 50 years of clinical experience in dosing. The proposed systems model has potential to provide insight into future clinical study design to assess some of these issues.