HHS Public Access

Author manuscript

Br J Clin Pharmacol. Author manuscript; available in PMC 2024 October 01.

Published in final edited form as:

Br J Clin Pharmacol. 2023 October ; 89(10): 2964–2976. doi:10.1111/bcp.15792.

Population Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics Modeling of Oxypurinol in Hmong Adults with Gout and/or Hyperuricemia

Ya-Feng Wen, Pharm.D.[1], **Richard C. Brundage, Pharm.D., Ph.D.**[1], **Youssef M. Roman, Pharm.D., Ph.D.**[2], **Kathleen A. Culhane-Pera, M.D., M.A.**[3], **Robert J. Straka, Pharm.D., FCCP**[1]

[1]Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA

[2]Department of Pharmacotherapy & Outcomes Science, School of Pharmacy, Virginia Commonwealth University, Richmond, VA 23298, USA

[3]Minnesota Community Care, St. Paul, MN 55107, USA

Abstract

Aim: Quantify identifiable sources of variability, including key pharmacogenetic variants in oxypurinol pharmacokinetics and their pharmacodynamic effect on serum urate.

Methods: Hmong participants (n=34) received 100 mg allopurinol twice daily for 7 days followed by 150 mg allopurinol twice daily for 7 days. A sequential population pharmacokinetic pharmacodynamics (PKPD) analysis with non-linear mixed-effects modeling was performed. Allopurinol maintenance dose to achieve target SU was simulated based on the final PKPD model.

Results: A one-compartment model with first order absorption and elimination best described the oxypurinol concentration-time data. Inhibitory of SU by oxypurinol was described with a direct inhibitory Emax model using steady-state oxypurinol concentrations. Fat-free body mass, estimated creatinine clearance and *SLC22A12* rs505802 genotype (0.32 per T allele, 95%CI 0.13, 0.55) were found to predict differences in oxypurinol clearance. Oxypurinol concentration required to inhibit 50% of xanthine dehydrogenase activity was affected by *PDZK1* rs12129861 genotype (−0.27 per A allele, 95%CI −0.38, −0.13). Most individuals with both *PDZK1*

Corresponding Author: Robert J. Straka, Experimental and Clinical Pharmacology, University of Minnesota College of Pharmacy, 308 Harvard St SE, Minneapolis, MN 55455, strak001@umn.edu.

The authors confirm that the Principal Investigator for this paper is Robert J. Straka and that he had direct clinical responsibility for patients.

Author Contribution: *Conceptualization*: Y.W., R.C.B., and R.J.S. *Investigation and methodology*: Y.W., R.C.B., Y.M.R., K.A.C-P., and R.J.S. *Data Analysis*: Y.W. and R.C.B. *Funding Acquisition*: K.A.C-P. and R.J.S. *Writing – Original Draft Preparation*: Y.W. *Writing – Review & Editing*: Y.W., R.C.B., Y.M.R., K.A.C-P., and R.J.S. *Supervision*: R.C.B. and R.J.S. All authors approved the final version of the manuscript.

Conflict of interest disclosure: All listed authors declare no conflicts of interest.

Ethics approval: This study was approved by the Human Research Protection Program at the University of Minnesota IRB (# 1408M53223).

Patient consent: Consent was obtained for all the study participants prior to any study related activities.

ClinicalTrials.gov **Identifier**: NCT02371421

rs12129861 AA and *SLC22A12* rs505802 CC genotypes achieve target SU (with at least 75% success rate) with allopurinol below the maximum dose, regardless of renal function and body mass. In contrast, individuals with both *PDZK1* rs12129861 GG and *SLC22A12* rs505802 TT genotypes would require more than the maximum dose, thus selecting alternative medications.

Conclusion: The proposed allopurinol dosing guide uses individuals' fat-free mass, renal function, and *SLC22A12* rs505802 and *PDZK1* rs12129861 genotypes to achieve target SU.

Keywords

allopurinol; gout; population pharmacokinetics; NONMEM; pharmacometrics

INTRODUCTION

Allopurinol is the first-line urate-lowering therapy (ULT) to prevent gout by lowering serum urate (SU) to a target of 6 mg/dL in all patients who can tolerate the medication.[1] Despite the availability of other agents with similar and newer mechanism of actions, allopurinol remains the most widely used agent to manage chronic hyperuricemia and gout worldwide.[2] The treat-to-target SU level approach instead of a fixed dose ULT strategy has been recommended by American College of Rheumatology and other organizations.[3–5] This approach is supported by an open-label, randomized controlled trial demonstrating that dose escalation resulted in 69% of patients with gout achieved target SU[6] comparing to only 20–50% of patients achieve target SU with fixed allopurinol dose.[7] Patients who typically fail to achieve SU targets include those who have high SU (>9 mg/dL), moderate-to-severe chronic kidney disease (stage ≥3), or urolithiasis. Patients with aforementioned conditions have a greater risk for gout flares and tophi formation.[8,9] Additionally, hyperuricemia (defined as SU ≥6.8 mg/dL) is strongly associated with other chronic conditions, including hypertension,[10,11] type 2 diabetes mellitus,[12] metabolic syndrome,[13] cardiovascular diseases[14] and dyslipidemia with elevated low-density lipoprotein cholesterol and hypertriglyceridemia.[15]

To optimize allopurinol use, several strategies have been proposed. One approach projects an allopurinol maintenance dose based on creatinine clearance (CrCL).[16] However, this approach was developed with the specific goal to avoid the allopurinol-induced severe cutaneous adverse reaction (SCAR) and not to achieve target SU. This approach may be sensible because impaired renal function correlated with the development and poor prognosis of allopurinol induced SCAR.[17–19] Given this CrCL-based dose approach, it is understandable that only 19% of patients achieved target SU.[20] Starting allopurinol dose based on estimated glomerular filtrate rate (eGFR) has been proposed.[21] Similarly, the goal was to prevent allopurinol-induced SCAR, with the authors asserting that the starting dose, not the maintenance dose, correlated with the incidence of allopurinol-induced SCAR. Stamp et al[21] reported that dose titration is often required to achieve target SU in patients who tolerate allopurinol. An approach that encourages safe targeting of optimal allopurinol dosage to achieve target SU remains elusive. This situation creates a gap in tools that specifically address the goal of dose optimization with the intended purpose of mitigating acute and chronic complications associated with hyperuricemia and gout.

Genome-wide association studies (GWAS) provide insights on how single nucleotide polymorphisms (SNPs) in key transporter genes can impact treatment outcomes. The ABCG2 (BCRP) rs2231142C>A is associated with SU-lowering response to allopurinol[22–25] and has been suggested as a guide to improve drug dosage and/or selection by identifying patients in need of alternate therapeutic approaches.[26] The SLC22A12 (URAT1) rs505802C>T is not only associated with the risk of hyperuricemia,[27] but also importantly associated with the exposure of serum oxypurinol, the active metabolite of allopurinol.[28] These two transporters, BRCP and URAT1, may prove to be important when identifying genomic based sources of variability in response to allopurinol.

Several population pharmacokinetics (PK)[29–31] and pharmacokinetic-pharmacodynamic (PKPD)[32–35] models have been developed. Despite these models identifying that body mass, renal function, and concomitant medications, including diuretics and uricosurics, are important factors, none of the studies illustrated a strong association between SNPs and either PK or PD parameters for oxypurinol. Majority of the aforementioned studies investigated the impact of rs2231142C>A (Q141K) which is sensible due to such missense variants of *ABCG2* could decrease oxypurinol renal excretion and thereby lead to higher serum oxypurinol and greater SU-lowering effect[22] and multiple observational studies have also suggested a strong association between this variant and SU-lowering response to allopurinol.[22–25] Furthermore, most of the studied populations are of European descent. It is, however, plausible that other genetic variants may play important roles in modulating PKPD of allopurinol in populations with different ethnic background.

The aims of this project were to (1) develop a population PKPD model to characterize the relationship between serum oxypurinol and SU, (2) quantify the effects of relevant clinical characteristics and SNPs identified from GWAS on the PKPD effects for oxypurinol, and (3) predict the allopurinol maintenance dose to achieve target SU of <6 mg/dL.

METHODS

Patients and study design

Data from a prospective, open-labeled, genetically-guided, pilot study, ***G****enetics* ***O****f Hyper****U****ricemia and Gout* ***T****herapy in* ***H****mong (GOUT-H*) (clinicaltrial.gov, NCT02371421) were analyzed. This study was approved by the Human Research Protection Program at the University of Minnesota Institutional Review Board (IRB #1408M53223). Detailed study design was described in previous publication.[28] Briefly, 34 Hmong participants with gout and/or hyperuricemia were screened at the screening visit and enrolled in the study based on the eligibility. After 7 days of allopurinol or febuxostat washout (baseline visit), all the participants took allopurinol 100 mg twice daily for 7 days followed by 150 mg twice daily for 7 days. At the follow-up visit (2 weeks after the baseline visit), participants took the final dose of allopurinol.

Blood samples were collected at the screening, baseline, and follow-up visits to measure SU and serum creatinine after overnight fasting for 10 hours. Additionally, blood and urine samples were collected at 0, 2, 4, and 6-hours post-allopurinol dose at the follow-up visit to measure oxypurinol concentrations.

Oxypurinol and urate assay

Urate concentrations were measured using a Roche COBAS 6000 chemistry analyzer (Roche Diagnostics, Indianapolis, IN) using the enzymatic method with a limit detection of 0.2 mg/dL. The inter-assay coefficient of variation was 1.3% at 5.50 mg/dL and 2.0% at 9.67 mg/dL. Oxypurinol concentrations were measured as described in previous publication.[28] None of the SU, serum oxypurinol, and urine oxypurinol concentrations were below the limit of quantification.

Pharmacogenetic testing

Genomic DNA was purified and extracted from saliva samples collected using ORAgene DISCOVER kits (OGR-500, DNA Genotek Inc., Ottawa, ON, Canada) with QIAamp DNA Kit (Qiagen Inc., Germantown, MD, USA) per the manufacturer's protocol. Nine SNPs were genotyped using the iPLEX Gold method (iPLEX Application, Agena, San Diego, CA, USA). Functionality of each gene and supporting evidence for inclusion were described previously[22,27,28,36–38] and are summarized in Supplementary Table S1.

Population PK model

The population analysis for oxypurinol PK was conducted using the nonlinear mixed effects modeling program, NONMEM version 7.4 (ICON Development Solutions, LC, Ellicott City, MD) with the first order conditional estimation method with interaction. Exploratory analyses and diagnostic plots were performed with R and Perl-speaks-NONMEM (PsN) version 5.2.6.[39] One and two compartmental PK models with linear elimination and first-order absorption models with and without a time lag were explored. Model derived values of the combined absorption and formation rate constant (K_{fm}), apparent clearance (CL/f_m) and apparent volume (V/f_m) for oxypurinol were estimated, where f_m represents the fraction of allopurinol dose available as oxypurinol systemically.

The between subject variability (BSV) was assumed to follow a log-normal distribution, described as follow:

$$\theta_{ip} = \theta_{\mu p}\exp(\eta_{ip})$$

where θ_{ip} is the p^{th} model parameter θ for the i^{th} individual; $\theta_{\mu p}$ is the population mean of the p^{th} model parameter θ; and η_{ip} is a random variable that represents the deviation from the mean of the p^{th} parameter for the i^{th} individual; the collection of η_{ip} are assumed to have a mean of zero and variance ω^2. The variance ω^2 of BSV was calculated as a percentage of coefficient of variation (%CV) using the following equation:

$$CV(\%) = \sqrt{\exp\left(\omega^2\right) - 1} \times 100\%$$

The residual unexplained error including additive, proportional, and combined errors were tested.

Population PKPD model

After the final PK model was established, the PKPD model was analyzed with a sequential approach using individual pharmacokinetic parameters with the standard error (IPPSE) method.[40,41] Steady-state oxypurinol concentration was linked to the PD model using a direct effect Emax model was tested, using the following equation:

$$Oxypurinol_{ss}(mg/L) = \frac{150mg}{CL/f_m(L/h) \times 12(h)}$$

$$Post\ treatmnt\ SU(mg/dL) = BL_{urate}(mg/dL) - \frac{I_{max}\ \ (mg/dL) \times oxypurinol_{ss}^{\gamma}(mg/L)}{IC_{50}^{\gamma}(mg/L) + oxypurinol_{ss}^{\gamma}(mg/L)}$$

where oxypurinol$_{ss}$ is the serum oxypurinol concentration at steady-state; BL_{urate} is the baseline SU; I_{max} is the maximum inhibitory effect of oxypurinol on xanthine dehydrogenase to inhibit urate production; IC_{50} is the oxypurinol concentration required to inhibit 50% of the activity of xanthine dehydrogenase; γ is the Hill coefficient for the sigmoid Emax model. The PKPD structural model is depicted in Figure 1.

Covariate model development

Demographics, clinical factors, concomitant medications, and genetic variants were evaluated for their influence on the parameters of PK and PD models. The selection of covariates for testing was based on previous significant findings[29,30,33,35,42] and biological plausibility.

Demographic covariates included gender, total body weight (TBW), adjusted body weight (AJBW), and fat-free mass (FFM).[43] Renal function was tested as standardized CrCL, estimated from the Cockcroft–Gault equation then normalized to a standard CrCL of a 70 kg human (calculated as observed CrCL*70/ideal body weight) to decorrelate the weight effect on CrCL. Concomitant medications were tested based on participants' self-reported information. These included drugs that lower SU: losartan,[44] HMG-CoA reductase inhibitors (particularly, atorvastatin),[45,46] and calcium channel blockers[47]; and drugs that increase SU: angiotensin converting enzyme inhibitors, angiotensin receptor blockers (but not including losartan), beta-blockers, diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs).[47] In addition to testing the effect of each medication type, two categories were also tested: drugs that lower SU and drugs that increase SU.

Nine SNPs related to SU levels or risks of gout development (Supplementary Table S1) were tested. An additive genetic model was assumed for the effect of SNPs on the PKPD parameters.

A stepwise covariant modeling (SCM) approach using the PsN toolkit with the forward and backward thresholds at $p < 0.05$ and $p < 0.01$, respectively was used for selecting covariates that contributed to the CL/f_m and V/f_m for the PK model, and BL_{urate}, I_{max}, and IC_{50} for the PD model. The significance of inclusion and elimination of each covariate was tested based on likelihood ratio test that follows the χ^2 distribution.

Model selection and qualification

Model selection was dependent on several criteria, including the χ^2 (likelihood ratio) test, goodness of fit (GOF) plots. Visual predictive check (VPC) plots (1000 simulations) stratified for significant covariates was used for model qualification. Sampling importance resampling (SIR) procedure[48] with five iterations with 1,000, 1,000, 1,000, 2,000, and 2,000 samples (M) and 200, 400, 500, 1,000, and 1,000 resamples (m) were performed to assess precision of the final parameter estimates using PsN. Model development, diagnostics, and graphing were using functions within PsN, Pirana[49] and R software (version 4.1.0)[50].

Simulations to predict allopurinol maintenance dose

Simulation was performed to examine the impact of important covariates on the serum oxypurinol and urate concentration. Different dosing strategies under a combination of significant covariates in the final PKPD model to achieve target SU of < 6mg/dL were performed for 1000 simulations for a total of 91,584 virtual patients. The distribution of PKPD model parameters were based on the final PKPD model. The model identified maintenance dose was the lowest dose that could achieve the target SU <6mg/dL in at least 75% of the cases. Simulation considerations were based on previous publication[33] with a few exceptions. First, the maintenance dose of allopurinol was considered from 50 to 800 mg/day because a maximum of 800 mg/day was approved by the US FDA. Second, creatinine clearance was simulated between 15 to 120 mL/min in 1 mL/min increment then stratified into 15–30 mL/min, 30–60 mL/min, and ≥ 60 mL/min categories. Third, FFM between 50 to 100 kg with 10 kg increment was considered. The impact of *SLC22A12* rs505802 CC, CT, TT genotypes on oxypurinol CL/f_m and the impact of *PDZK1* rs12129861 GG, GA, and AA genotypes on IC_{50} were considered (see Result section for the rationale for the selection of these covariates). Simulations were performed using R software (version 4.1.0)[50].

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20[51].

RESULTS

Participant characteristics

The 34 participants' demographics characteristics, clinical features, and self-reported concomitant medications collected at the baseline visit are described in Table 1. Notably, there were only 3 women, and only 1 participant with normal weight, based on the World Health Organization's Asian criteria-based body-mass index (BMI).[52] The dataset included 136 serum oxypurinol, 87 urine oxypurinol, and 102 serum urate concentrations. No genotype information was missing for the 9 SNPs tested. Genotype information and distributions are presented in Supplemental Table 1.

Final PK model

A one compartment PK model with first order absorption/conversion and elimination with proportional residual error model provided the best fit to the observed serum oxypurinol-time data. Using a two-compartment PK model or other residual error models provided similar fits, so the simpler model was retained. Covariance between BSV for CL/f_m and V/f_m was tested but this resulted in similar BSV estimates; therefore, the covariance was not included.

Model development steps for the oxypurinol PK model are summarized in Supplemental Table 2. The final model included FFM on CL/f_m and V/f_m allometric scaled using the theoretical value (0.75 for CL/f_m and 1 for V/f_m), renal function using estimated CrCL, and *SLC22A12* rs505802C>T. Using TBW as a covariate on CL/f_m improved the model fit but failed to improve the fit when used as covariate on V/f_m. On the other hand, using either AJBW or FFM as a covariate on both CL/f_m and V/f_m improved the fit. The selection of FFM as a covariate instead of AJBW was based on previous findings that FFM was also found to be a significant covariate.[30,33] HMG-CoA reductase inhibitors and drugs that decrease SU reduced CL/f_m by about 48% and 30%, respectively, but the effect was not statistically significant in the SCM step (Supplemental Table 2). In addition to *SLC22A12* rs505802C>T as a covariate on CL/f_m, *CARMIL1* rs742132A>G and *PDZK1* rs12129861G>A were found to be significant during the forward selection step but were excluded during backward elimination step. The combined absorption and formation rate constant (K_{fm}) and its BSV were fixed to initial estimates (which is similar to the value, 0.92 h^{-1} reported in the literature[53]) due to insufficient data to support the parameter estimates and high shrinkage.[54]

The BSV in CL/f_m decreased from 42.8% to 28.3%, and V/f_m decreased from 40.7% to 32.4% after including significant covariates. The results of the base and final (including covariate) PK models are summarized in Table 2, and the final estimates for CL/f_m and V/f_m for oxypurinol are given by:

$$CL/f_m(L/h) = 1.05(L/h) \times \left(\frac{standardized\ CrCL(mL/min)}{100(mL/min)}\right)^{0.45} \times \left(\frac{FFM(kg)}{70(kg)}\right)^{0.75} \times (\mathbf{1} \text{ for } SLC22A12 \text{ rs505802 CC, } \mathbf{1.32} \text{ for CT and } \mathbf{1.64} \text{ for TT})$$

$$V/f_m(L) = 59.3(L) \times \left(\frac{FFM(kg)}{70(kg)}\right)^{1}$$

To estimate the renal and non-renal CL/f_m of oxypurinol, a PK model with both serum and urine oxypurinol data was fitted. The renal CL/f_m was 0.77 L/h (77%) and non-renal CL/f_m was 0.23 L/h (23%) (Supplemental Table 3). Similar to the PK model with serum oxypurinol, the estimated CrCL and *SLC22A12* rs505802C>T were found to be significant with renal CL/f_m. NSAIDs, *CARMIL1* rs742132A>G, and *SLC2A9* rs1014290C>T were found to be significant in the forward selection step but not in the backward elimination step on renal CL/f_m. No covariates were found to be significant with non-renal CL/f_m.

Final PD model

A direct effect Emax model with BL_{urate}, I_{max}, and IC_{50} with additive residual error model provided an adequate model to the SU data. The Hill coefficient could not be demonstrated to be different from 1.0 and was subsequently fixed to unity. The BSV for I_{max}, and IC_{50} was fixed to estimates from the base model due to insufficient data to estimate the precision of these parameters and high shrinkage in the final model.[54]

Model development steps for the PD model are summarized in Supplemental Table 4. The final model included estimated CrCL on BL_{urate} and *PDZK1* rs12129861G>A on IC_{50}. The results of the base and final (including covariate) PD models are summarized in Table 2, and the final estimates for SU response are given by:

$$Serum\ urate(mg/dL) = 9(mg/dL) \times \left(\frac{CrCL(mL/min)}{100(mL/min)}\right)^{-0.175} - \frac{7.6(mg/dL) \times oxypurinol_{ss}(mg/L)}{IC_{50}(mg/L) + oxypurinol_{ss}(mg/L)}$$

IC_{50} = 17.6 for *PDZK1* rs12129861 GG, 12.8 for GA and 8.1 for AA

Model evaluation

The median parameter estimates with its 95%CI using SIR were comparable to the parameter estimate for the final PKPD models suggesting the PKPD model is stable (Table 2). The covariance step for base and final models presented in Table 2 and Supplementary Table 3 was successful but the results were not shown because SIR provided a better estimate for the precision of parameters. The GOF plots for the final PKPD models also showed no visual or statistical bias for the model prediction (Figure 2).

The VPC plot was stratified by *SLC22A12* rs505802C>T for the PK model and stratified by *PDZK1* rs12129861G>A for the PD model, presented in Figure 3A. The VPC for the serum oxypurinol showed the median, 5th, and 95th percentiles of the model predicted serum oxypurinol concentrations followed the observed data in *SLC22A12* rs505802 CC and CT genotypes. Due to the small sample size in TT genotype group, the 95%CI of the predicted oxypurinol concentrations overlapped and the small sample size limited the utility of VPC. The VPC plots for the PD model showed some inadequacy in capturing SU at the screening visit (time between −40 to 0 days) in *PDZK1* rs12129861 GG genotype group. Nonetheless, the predicted SU followed the observed SU data well at the baseline and the follow-up visits in all three genotype groups (Figure 3B).

Allopurinol maintenance dose prediction

Table 3 presents the predicted allopurinol daily maintenance dose to achieve serum urate of <6 mg/dL with 75% of success rate. In general, individuals with lower FFM or higher CrCL require lower allopurinol dose. Individuals with *SLC22A12* rs505802 T allele or *PDZK1* rs12129861 G allele require a higher allopurinol dose. Individuals with chronic kidney disease (CrCL <60 mL/min) who carry both *SLC22A12* rs505802 TT and *PDZK1* rs12129861 GG genotypes require a higher than maximum dose, and hence would be candidates for alternative medications.

DISCUSSION

Allopurinol is the first-line ULT; however, many patients fail to achieve target SU on allopurinol. We developed a population PKPD model and identified the importance of clinical variables on the PKPD parameters in Hmong participants with gout and/or hyperuricemia. Body mass (FFM), renal function (estimated CrCL), and *SLC22A12* rs505802C>T are key determinants to the PK of oxypurinol. Baseline SU, estimated CrCL, and *PDZK1* rs12129861G>A are important covariates to the PD of oxypurinol. When determining the minimum allopurinol maintenance dose to achieve target SU, all of the aforementioned clinical factors need to be considered.

The final estimated population oxypurinol clearance [CL/f_m of 1.05 L/h (95%CI 0.88–1.31)] was similar to a previous study (1.32 L/h)[33] where the study participants had similarly estimated CrCL (70 mL/min versus 87 mL/min in GOUT-H). The final estimated population oxypurinol volume of distribution [V/f_m of 59.3 L (95%CI 51.3–71.9)] was higher than the aforementioned study (41.6 L), possibly due to the older mean age of participants in their study (60-year-old versus 43-year-old in GOUT-H) and their approach to adjust for body mass (TBW versus FFM in GOUT-H). Given that the plasma protein binding for oxypurinol is negligible, the distribution of oxypurinol is similar to water content.[55] Since elderly typically have 10–15% less total body water compared to younger individuals,[56] the higher observed volume of oxypurinol (V/f_m) in our population is expected.

The final estimated population parameters for the PD model (BL_{urate}: 9 mg/dL, I_{max}: 7.6 mg/dL, IC_{50}: 17.6 mg/L) were similar to participants with gout and/or hyperuricemia (BL_{urate}: 8.5 mg/dL or 0.511 mmol/L, I_{max}: 6.87 mg/dL or 0.409 mmol/L, IC_{50}: 14.1 mg/L or 83.9 μmol/L)[33] but different from the healthy participants (BL_{urate}: 4.6 mg/dL, I_{max}: 1 mg/dL, IC_{50}: 2.59 mg/L).[35] Higher I_{max} value observed in patients with hyperuricemia suggests the maximum SU lowering effect of allopurinol depends on the baseline SU level. The considerably higher IC_{50} in patients with gout and/or hyperuricemia indicates that a higher dose of allopurinol to achieve the same effect compared to non-hyperuricemic adults. This is likely due to the competitive inhibition of SU on xanthine dehydrogenase.

Similar to previous findings[30,33], we found that FFM predicts oxypurinol clearance and volume of distribution better than TBW. Since the majority of our study participants were either overweight or obese, FFM approximates the lean body weight better[43] and better reflects the true volume of distribution of oxypurinol. Renal function also plays a critical role in both PK and PD of oxypurinol, which has been demonstrated in previous population PKPD analyses and clinical studies.[57–59] Contrary to a clinical observation that a lower allopurinol dose is needed to achieve target SU in patients with renal impairment (CrCl≤60 ml/min) compared with patients with CrCl >60 ml/min,[57] we predicted that a higher allopurinol dose is required in patients with renal impairment. Although estimated CrCL is positively associated with both CL/f_m and BL_{urate} in the PKPD model, the overall contribution of renal function is larger in BL_{urate}. This observation was consistent with previous published PKPD model[33] where a higher allopurinol dose was required in patients with renal impairment compared to those without renal impairment if patients were

taking diuretics. This relationship, which would appear to be counterintuitive, is likely under-appreciated by clinicians and clinical pharmacologists.

Drugs that may impact SU were not important factors in the final PKPD model. This contrasts with other studies that clearly demonstrated that people taking diuretics have a 25–30% lower oxypurinol clearance compared to those not taking diuretics.[29,30,33] We did not observe this relationship in our study, likely due to our modest count of participants (n=4) who were taking various diuretics (hydrochlorothiazide, triamterene/hydrochlorothiazide, furosemide, and bumetanide). The association of loop, thiazide, and thiazide-like (but not potassium-sparing) diuretics with increased SU and higher incidence of gout, are well documented from both clinical observations[60–63] and *in vitro* studies[64–66]. The proposed mechanisms for this observation includes either inhibition of urate efflux transporters, such as MRP4 (*ABCC4*)[65] and NPT1 (*SLC17A1*)[66], or increased urate reabsorption secondary to extracellular fluid volume depletion from diuresis.[64] On the other hand, the evidence of how diuretics impact the PK of oxypurinol is less clear with some previous studies implicating loop diuretics, particularly furosemide, to be associated with increased plasma oxypurinol concentrations.[57,67] Despite not being statistically significant, we found that patients taking HMG-CoA reductase inhibitors were associated with 52% decrease in oxypurinol CL/f_m. The majority of the participants were taking atorvastatin (4/5, 80%), which suggests the potential impact of atorvastatin on the clearance of oxypurinol.[45,46]

SLC22A12 rs505802C>T was found to be a key determinant of oxypurinol clearance CL/f_m. This association is plausible because oxypurinol undergoes extensive reabsorption through URAT1 encoded by *SLC22A12*,[68] such that URAT1 dysfunction would impact the disposition of oxypurinol. Although the association between *ABCG2* rs2231142C>A and SU-lowering response to allopurinol has been established in GWAS and replicated in other observational studies,[22–25] no studies have shown a clear association between this SNP (rs2231142) and the PK parameters of allopurinol or oxypurinol. However, we cannot rule out the importance of *ABCG2* rs2231142C>A, particularly in patients with extrarenal underexcretion hyperuricemia. Since a larger portion of the GOUT-H Hmong participants were overproduction hyperuricemia, instead of extrarenal underexcretion hyperuricemia,[28] the impact of *ABCG2* rs2231142C>A may be diminished in our study population.

An interesting finding was the impact of *PDZK1* rs12129861G>A on IC_{50} in the inhibitory E_{max} model of oxypurinol. Of note, it is possible that *PDZK1* rs12129861G>A may impact I_{max} given similar magnitude reduction in objective function value (OFV). However, the genetic effect on the folding protein is more likely to affect the drug binding affinity and thus impact the potency (IC_{50}) rather than affecting the maximal effect (I_{max}). PDZK1 is a key component of urate-transporting molecular complex for URAT1 and OAT4.[69,70] The *PDZK1* rs12129861 A allele was also associated with a lower SU level[27] and a decrease risk of gout.[71,72] We found individuals with AA genotype have almost half of the IC_{50} as GG genotype (8.1 versus 17.6 mg/L) suggesting a higher affinity of oxypurinol with individuals with AA genotype. However, since this SNP is in the upstream region of *PDZK1*, a causal SNP has yet to be determined; a mechanistic study needs to be performed to elucidate the impact of PDZK1 on oxypurinol SU-lowering effect.

Limitations

A number of limitations should be noted. First, the small sample size (n=34) limits the ability to identify important covariates that could further explain the BSV in PKPD parameters of oxypurinol. In addition, the SCM with modest type I error control for the forward (p <0.05) and backward steps (p <0.01) with multiple testing may result in false positive findings given the limited number of participants.[73] For example, the exponent of CrCL on baseline SU was −0.18 (95%CI −0.33, −0.036) suggesting CrCL was not a major determinant of SU despite a significant reduction in OFV when including CrCL in the model (Supplementary Table 4). However, the inclusion of renal function on SU was mainly driven by the physiology given more than 2/3 of serum urate is eliminated by kidney. In addition, the significant association between *SLC22A12* rs505802 genotype and oxypurinol clearance, and *PDZK1* rs12129861 genotype with IC_{50} in this population but not in other populations highlight the importance of including diverse populations in clinical studies. In other words, these observations may be unique to the Hmong population studied. Secondly, PK sampling scheme only covered half of the dosing interval that may negatively impact the accuracy of oxypurinol PK parameters estimate. This was a design feature suggested by the Hmong Genomics Board based on respecting the practical limitations of our participants. Given oxypurinol likely exhibits one compartmental PK behavior that is in concordance with previous studies[29,30,33,35] and the maximum oxypurinol concentration observed in our study was at 2 hours, these provide confidence in our estimates. Thirdly, although we identified *SLC22A12* rs505802 and *PDZK1* rs12129861 are key determinants for PKPD response of oxypurinol, these SNPs are in the non-coding region, thus the causal SNPs for the differences observed in CL/f_m and IC_{50} among individuals with different genotypes require further investigation. Forth, the imprecision of the PD parameters, such as IC_{50} and CrCL exponent on baseline SU, was larger than the PK parameters. In addition, the BSV for IC_{50} was fixed at a large value based on initial model fitting due to limited data available. These factors should be considered when interpreting simulation results and be aware that the actual variability will be higher than the prediction as the simulations were based on typical values.

Due to the intentional inclusion of southeast Asians of Hmong ancestry, we caution overinterpretation of the findings of this study to other populations. This caution is based both from the perspective of limited information concerning what is known about the relative role of renal function and uric acid disposition in this population relative to others as well as the observed differences in the prevalence of allele frequencies found in Hmong relative to other southeast Asian populations or populations of non-southeast Asian ancestry. As this was a pilot study in this unique population, the proposed allopurinol maintenance dose to achieved target SU requires validation in a prospective clinical study in a larger Hmong population.

CONCLUSION

In summary, we developed a population PKPD model for oxypurinol in Hmong participants with gout and/or hyperuricemia who take allopurinol. Body mass and renal function are key determinants for oxypurinol clearance and baseline SU, which aligns with previous findings.

We also identified SNPs that can impact the oxypurinol clearance and its SU-lowering effect, which could have clinical importance. Considering all the important covariates, we propose a maintenance dose scheme of allopurinol to achieve target SU in the Hmong population that could help to better manage gout in this population, which exhibits a high prevalence of gout.[74,75] The validity of this dosing scheme will require further study. However, we believe this study represents an important step in demonstrating the value of clinical trials including unique, under-represented populations who are at high risk for clinical consequences from hyperuricemia and gout and could benefit from effective ULT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment:

The authors wish to thank the support from all the Hmong participants, the Hmong GOUT-H Research Board, and Minnesota Community Care.

Funding:

This work was supported by the University of Minnesota, Office of Community Engagement of the Clinical and Translational Science Institute for its funding via 2014 Collaborative Pilot Grants No. 22556 and National Center for Advancing Translational Sciences of the National Institutes of Health Award Number UL1TR000114. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data availability:

Raw data is not available to the public due to lack of patient consent for data sharing. NONMEM control files for pharmacokinetics and pharmacodynamics modeling and R script for allopurinol dose simulation are available in the supplemental text 1–4.

Abbreviations

AJBW	adjusted body weight
BL_{urate}	baseline serum urate
BSV	between subject variability
CL/f_m	apparent clearance
CrCL	creatinine clearance
CV	coefficient of variation
FFM	fat-free mass
f_m	the fraction of allopurinol dose available as oxypurinol systemically
γ	the Hill coefficient for the sigmoid Emax model

GOF	goodness of fit
GOUT-H	**G**enetics **O**f Hyper**U**ricemia and Gout **T**herapy in **H**mong
GWAS	Genome-wide association studies
IC_{50}	the oxypurinol concentration required to inhibit 50% of the activity of xanthine dehydrogenase
I_{max}	the maximum inhibitory effect of oxypurinol on xanthine dehydrogenase to inhibit urate production
IPPSE	individual pharmacokinetic parameters with the standard error
K_{fm}	rate constant
NSAIDs	non-steroidal anti-inflammatory drugs
$\textbf{Oxypurinol}_{ss}$	the serum oxypurinol concentration at steady-state
PK	pharmacokinetics
PKPD	pharmacokinetic-pharmacodynamic
SCAR	severe cutaneous adverse reaction
SCM	stepwise covariant modeling
SIR	sampling importance resampling
SNPs	single nucleotide polymorphisms
SU	serum urate
TBW	total body weight
ULT	urate-lowering therapy
V/f_m	apparent volume
VPC	visual predictive check

References

1. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis & Rheumatology. 2020/05/10 2020;n/a(n/a)doi:10.1002/art.41247
2. Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. Lancet. May 15 2021;397(10287):1843–1855. doi:10.1016/S0140-6736(21)00569-9 [PubMed: 33798500]
3. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis care & research. Oct 2012;64(10):1431–1446. doi:10.1002/acr.21772 [PubMed: 23024028]

4. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Annals of the rheumatic diseases. Jan 2017;76(1):29–42. doi:10.1136/annrheumdis-2016-209707 [PubMed: 27457514]
5. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology. Aug 2007;46(8):1372–4. doi:10.1093/rheumatology/kem056a [PubMed: 17522099]
6. Stamp LK, Chapman PT, Barclay ML, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. Annals of the rheumatic diseases. Sep 2017;76(9):1522–1528. doi:10.1136/annrheumdis-2016-210872 [PubMed: 28314755]
7. Khanna P, Hagerty D, Mischler R, Morlock R. FRI0397 Adherence to EULAR recommendations for the treatment of GOUT. Annals of the rheumatic diseases. 2014;71(Suppl 3):448–449. doi:10.1136/annrheumdis-2012-eular.2854
8. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis and rheumatism. Jun 15 2004;51(3):321–5. doi:10.1002/art.20405 [PubMed: 15188314]
9. Dalbeth N, House ME, Horne A, Taylor WJ. Reduced creatinine clearance is associated with early development of subcutaneous tophi in people with gout. BMC musculoskeletal disorders. Dec 21 2013;14:363. doi:10.1186/1471-2474-14-363 [PubMed: 24359261]
10. Feig DI. Hyperuricemia and hypertension. Advances in chronic kidney disease. Nov 2012;19(6):377–385. doi:10.1053/j.ackd.2012.05.009 [PubMed: 23089272]
11. Kuwabara M, Hisatome I, Niwa K, et al. Uric Acid Is a Strong Risk Marker for Developing Hypertension From Prehypertension: A 5-Year Japanese Cohort Study. Hypertension. Jan 2018;71(1):78–86. doi:10.1161/HYPERTENSIONAHA.117.10370 [PubMed: 29203632]
12. Sluijs I, Beulens JW, van der AD, Spijkerman AM, Schulze MB, van der Schouw YT. Plasma uric acid is associated with increased risk of type 2 diabetes independent of diet and metabolic risk factors. The Journal of nutrition. Jan 2013;143(1):80–85. doi:10.3945/jn.112.167221 [PubMed: 23173177]
13. Chen LY, Zhu WH, Chen ZW, et al. Relationship between hyperuricemia and metabolic syndrome. Journal of Zhejiang University Science B. Aug 2007;8(8):593–8. doi:10.1631/jzus.2007.B0593 [PubMed: 17657863]
14. Mehmet Kanbay MS, Baris Afsar, et al. The role of uric acid in the pathogenesis of human cardiovascular desease. Heart. 2013;99:759–756. [PubMed: 23343689]
15. Jensen T, Niwa K, Hisatome I, et al. Increased Serum Uric Acid over five years is a Risk Factor for Developing Fatty Liver. Sci Rep. Aug 6 2018;8(1):11735. doi:10.1038/s41598-018-30267-2 [PubMed: 30082907]
16. Hande KR, Noone RM, Stone WJ. Severe Allopurinol Toxicity: Description and Guidelines for Prevention in Patients with Renal Insufficiency. The American journal of medicine. 1984;76:47–56.
17. Chung WH, Chang WC, Stocker SL, et al. Insights into the poor prognosis of allopurinol-induced severe cutaneous adverse reactions: the impact of renal insufficiency, high plasma levels of oxypurinol and granulysin. Annals of the rheumatic diseases. Dec 2015;74(12):2157–2164. doi:10.1136/annrheumdis-2014-205577 [PubMed: 25115449]
18. Yang CY, Chen CH, Deng ST, et al. Allopurinol Use and Risk of Fatal Hypersensitivity Reactions: A Nationwide Population-Based Study in Taiwan. JAMA Intern Med. Sep 2015;175(9):1550–7. doi:10.1001/jamainternmed.2015.3536 [PubMed: 26193384]
19. Hung SL, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. P Natl Acad Sci USA. Mar 15 2005;102(11):4134–4139. doi:10.1073/pnas.0409500102
20. Dalbeth N, Kumar S, Stamp L, Gow P. Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. J Rheumatol. Aug 2006;33(8):1646–50. [PubMed: 16783857]

21. Stamp LK, Taylor WJ, Jones PB, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. Arthritis and rheumatism. Aug 2012;64(8):2529–36. doi:10.1002/art.34488 [PubMed: 22488501]
22. Wen CC, Yee SW, Liang X, et al. Genome-wide association study identifies ABCG2 (BCRP) as an allopurinol transporter and a determinant of drug response. Clin Pharmacol Ther. May 2015;97(5):518–525. doi:10.1002/cpt.89 [PubMed: 25676789]
23. Roberts RL, Wallace MC, Phipps-Green AJ, et al. ABCG2 loss-of-function polymorphism predicts poor response to allopurinol in patients with gout. Pharmacogenomics J. Mar 2017;17(2):201–203. doi:10.1038/tpj.2015.101 [PubMed: 26810134]
24. Wallace MC, Roberts RL, Nanavati P, et al. Association between ABCG2 rs2231142 and poor response to allopurinol: replication and meta-analysis. Rheumatology. Apr 1 2018;57(4):656–660. doi:10.1093/rheumatology/kex467 [PubMed: 29342288]
25. Brackman DJ, Yee SW, Enogieru OJ, et al. Genome-Wide Association and Functional Studies Reveal Novel Pharmacological Mechanisms for Allopurinol. Clin Pharmacol Ther. Sep 2019;106(3):623–631. doi:10.1002/cpt.1439 [PubMed: 30924126]
26. Wright DFB, Dalbeth N, Phipps-Green AJ, et al. The impact of diuretic use and ABCG2 genotype on the predictive performance of a published allopurinol dosing tool. British journal of clinical pharmacology. May 2018;84(5):937–943. doi:10.1111/bcp.13516 [PubMed: 29341237]
27. Kolz M, Johnson T, Sanna S, et al. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. PLoS Genet. Jun 2009;5(6):e1000504. [PubMed: 19503597]
28. Roman YM, Culhane-Pera K, Lo M, et al. The Impact of rs505802 for *SLC22A12* on Oxipurinol and Uric Acid Disposition in Hmong Patients on Allopurinol from the Genetics of Hyperuricemia Therapy in Hmong (GOUT-H) Study. Clinical Pharmacology & Therapeutics. 2017;101(S1;PI-110):S5–S99. doi:10.1002/cpt.570
29. Stocker SL, McLachlan AJ, Savic RM, et al. The pharmacokinetics of oxypurinol in people with gout. British journal of clinical pharmacology. Sep 2012;74(3):477–89. doi:10.1111/j.1365-2125.2012.04207.x [PubMed: 22300439]
30. 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. Jul 2013;69(7):1411–21. doi:10.1007/s00228-013-1478-8 [PubMed: 23475133]
31. Pilon MO, Leclair G, Oussaid E, et al. An association study of ABCG2 rs2231142 on the concentrations of allopurinol and its metabolites. Clin Transl Sci. Jun 10 2022;doi:10.1111/cts.13318
32. Graham GG, Kannangara DR, Stocker SL, et al. Understanding the dose-response relationship of allopurinol: predicting the optimal dosage. British journal of clinical pharmacology. Dec 2013;76(6):932–8. doi:10.1111/bcp.12126 [PubMed: 23590252]
33. Wright DF, Duffull SB, Merriman TR, Dalbeth N, Barclay ML, Stamp LK. Predicting allopurinol response in patients with gout. British journal of clinical pharmacology. Feb 2016;81(2):277–89. doi:10.1111/bcp.12799 [PubMed: 26451524]
34. Kannangara DRW, Graham GG, Wright DFB, et al. Individualising the dose of allopurinol in patients with gout. British journal of clinical pharmacology. Sep 2017;83(9):2015–2026. doi:10.1111/bcp.13307 [PubMed: 28417592]
35. Vora B, Brackman DJ, Zou L, et al. Oxypurinol pharmacokinetics and pharmacodynamics in healthy volunteers: Influence of BCRP Q141K polymorphism and patient characteristics. Clin Transl Sci. Jul 2021;14(4):1431–1443. doi:10.1111/cts.12992 [PubMed: 33931953]
36. Kottgen A, Albrecht E, Teumer A, et al. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. Nat Genet. Feb 2013;45(2):145–154. doi:10.1038/ng.2500 [PubMed: 23263486]
37. Okada Y, Sim X, Go MJ, et al. Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. Nat Genet. Aug 2012;44(8):904–9. doi:10.1038/ng.2352 [PubMed: 22797727]

38. Vitart V, Rudan I, Hayward C, et al. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. Nat Genet. Apr 2008;40(4):437–42. doi:10.1038/ng.106 [PubMed: 18327257]
39. Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. Sep 2005;79(3):241–57. doi:10.1016/j.cmpb.2005.04.005 [PubMed: 16023764]
40. Lacroix BD, Friberg LE, Karlsson MO. Evaluation of IPPSE, an alternative method for sequential population PKPD analysis. J Pharmacokinet Pharmacodyn. Apr 2012;39(2):177–93. doi:10.1007/s10928-012-9240-x [PubMed: 22270323]
41. Zhang L, Beal SL, Sheinerz LB. Simultaneous vs. sequential analysis for population PK/PD data II: robustness of methods. J Pharmacokinet Pharmacodyn. Dec 2003;30(6):405–16. doi:10.1023/b:jopa.0000012999.36063.4e [PubMed: 15000422]
42. Stocker SL, Graham GG, McLachlan AJ, Williams KM, Day RO. Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in patients with gout. J Rheumatol. May 2011;38(5):904–910. doi:10.3899/jrheum.101160 [PubMed: 21285173]
43. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clinical pharmacokinetics. 2005;44(10):1051–65. doi:10.2165/00003088-200544100-00004 [PubMed: 16176118]
44. Enomoto A, Kimura H, Chairoungdua A, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. Nature. May 23 2002;417(6887):447–52. doi:10.1038/nature742 [PubMed: 12024214]
45. Milionis HJ, Kakafika AI, Tsouli SG, et al. Effects of statin treatment on uric acid homeostasis in patients with primary hyperlipidemia. American heart journal. Oct 2004;148(4):635–40. doi:10.1016/j.ahj.2004.04.005 [PubMed: 15459594]
46. Kose E, An T, Kikkawa A, Matsumoto Y, Hayashi H. Effects on serum uric acid by difference of the renal protective effects with atorvastatin and rosuvastatin in chronic kidney disease patients. Biol Pharm Bull. 2014;37(2):226–31. doi:10.1248/bpb.b13-00418 [PubMed: 24492719]
47. Choi HK, Soriano LC, Zhang Y, Rodriguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. BMJ. 2012;344:d8190. doi:10.1136/bmj.d8190 [PubMed: 22240117]
48. Dosne AG, Bergstrand M, Harling K, Karlsson MO. Improving the estimation of parameter uncertainty distributions in nonlinear mixed effects models using sampling importance resampling. J Pharmacokinet Pharmacodyn. Dec 2016;43(6):583–596. doi:10.1007/s10928-016-9487-8 [PubMed: 27730482]
49. Keizer RJ, Karlsson MO, Hooker A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT Pharmacometrics Syst Pharmacol. Jun 26 2013;2:e50. doi:10.1038/psp.2013.24 [PubMed: 23836189]
50. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing; 2021.
51. Alexander SP, Christopoulos A, Davenport AP, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: G protein-coupled receptors. Br J Pharmacol. Oct 2021;178 Suppl 1:S27–S156. doi:10.1111/bph.15538 [PubMed: 34529832]
52. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. Jan 10 2004;363(9403):157–63. doi:10.1016/S0140-6736(03)15268-3 [PubMed: 14726171]
53. Wright DF, Doogue MP, Barclay ML, et al. A population pharmacokinetic model to predict oxypurinol exposure in patients on haemodialysis. Eur J Clin Pharmacol. Jan 2017;73(1):71–78. doi:10.1007/s00228-016-2133-y [PubMed: 27683090]
54. Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. AAPS J. Sep 2009;11(3):558–69. doi:10.1208/s12248-009-9133-0 [PubMed: 19649712]
55. Turnheim K, Krivanek P, Oberbauer R. Pharmacokinetics and pharmacodynamics of allopurinol in elderly and young subjects. British journal of clinical pharmacology. Oct 1999;48(4):501–9. doi:10.1046/j.1365-2125.1999.00041.x [PubMed: 10583019]

56. Andres TM, McGrane T, McEvoy MD, Allen BFS. Geriatric Pharmacology: An Update. Anesthesiol Clin. Sep 2019;37(3):475–492. doi:10.1016/j.anclin.2019.04.007 [PubMed: 31337479]
57. Stamp LK, Barclay ML, O'Donnell JL, et al. Relationship between serum urate and plasma oxypurinol in the management of gout: determination of minimum plasma oxypurinol concentration to achieve a target serum urate level. Clin Pharmacol Ther. Sep 2011;90(3):392–8. doi:10.1038/clpt.2011.113 [PubMed: 21796116]
58. Stamp LK, Chapman PT, Barclay M, et al. Relationships Between Allopurinol Dose, Oxypurinol Concentration and Urate-Lowering Response-In Search of a Minimum Effective Oxypurinol Concentration. Clin Transl Sci. Jan 2020;13(1):110–115. doi:10.1111/cts.12686 [PubMed: 31444839]
59. Stamp LK, Chapman PT, Barclay ML, et al. How much allopurinol does it take to get to target urate? Comparison of actual dose with creatinine clearance-based dose. Arthritis research & therapy. Nov 16 2018;20(1):255. doi:10.1186/s13075-018-1755-0 [PubMed: 30446002]
60. McAdams DeMarco MA, Maynard JW, Baer AN, et al. Diuretic use, increased serum urate levels, and risk of incident gout in a population-based study of adults with hypertension: the Atherosclerosis Risk in Communities cohort study. Arthritis and rheumatism. Jan 2012;64(1):121–9. doi:10.1002/art.33315 [PubMed: 22031222]
61. Savage PJ, Pressel SL, Curb JD, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: The Systolic Hypertension in the Elderly Program. SHEP Cooperative Research Group. Arch Intern Med. Apr 13 1998;158(7):741–51. doi:10.1001/archinte.158.7.741 [PubMed: 9554680]
62. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med. Apr 11 2005;165(7):742–8. doi:10.1001/archinte.165.7.742 [PubMed: 15824292]
63. Bruderer S, Bodmer M, Jick SS, Meier CR. Use of diuretics and risk of incident gout: a population-based case-control study. Arthritis Rheumatol. Jan 2014;66(1):185–96. doi:10.1002/art.38203 [PubMed: 24449584]
64. Weinman EJ, Eknoyan G, Suki WN. The influence of the extracellular fluid volume on the tubular reabsorption of uric acid. J Clin Invest. Feb 1975;55(2):283–91. doi:10.1172/JCI107931 [PubMed: 1127100]
65. El-Sheikh AA, van den Heuvel JJ, Koenderink JB, Russel FG. Effect of hypouricaemic and hyperuricaemic drugs on the renal urate efflux transporter, multidrug resistance protein 4. Br J Pharmacol. Dec 2008;155(7):1066–75. doi:10.1038/bjp.2008.343 [PubMed: 18724382]
66. Jutabha P, Anzai N, Kitamura K, et al. Human sodium phosphate transporter 4 (hNPT4/SLC17A3) as a common renal secretory pathway for drugs and urate. The Journal of biological chemistry. Nov 5 2010;285(45):35123–32. doi:10.1074/jbc.M110.121301 [PubMed: 20810651]
67. Stamp LK, Barclay ML, O'Donnell JL, et al. Furosemide increases plasma oxypurinol without lowering serum urate--a complex drug interaction: implications for clinical practice. Rheumatology. Sep 2012;51(9):1670–6. doi:10.1093/rheumatology/kes091 [PubMed: 22539486]
68. Iwanaga T, Kobayashi D, Hirayama M, Maeda T, Tamai I. Involvement of Uric Acid Transporter in Increased Renal Clearance of the Xanthine Oxidase Inhibitor Oxypurinol Induced by a Uricosuric Agent, Benzbromarone. Drug metabolism and disposition: the biological fate of chemicals. 2005;33(12):1791–1795. [PubMed: 16135657]
69. Anzai N, Miyazaki H, Noshiro R, et al. The multivalent PDZ domain-containing protein PDZK1 regulates transport activity of renal urate-anion exchanger URAT1 via its C terminus. The Journal of biological chemistry. Oct 29 2004;279(44):45942–50. doi:10.1074/jbc.M406724200 [PubMed: 15304510]
70. Miyazaki H, Anzai N, Ekaratanawong S, et al. Modulation of renal apical organic anion transporter 4 function by two PDZ domain-containing proteins. Journal of the American Society of Nephrology : JASN. Dec 2005;16(12):3498–506. doi:10.1681/ASN.2005030306 [PubMed: 16236806]
71. Higashino T, Matsuo H, Sakiyama M, et al. Common variant of PDZ domain containing 1 (PDZK1) gene is associated with gout susceptibility: A replication study and meta-analysis

in Japanese population. Drug Metab Pharmacokinet. Dec 2016;31(6):464–466. doi:10.1016/j.dmpk.2016.07.004 [PubMed: 27720648]

72. Li M, Li Q, Li CG, et al. Genetic polymorphisms in the PDZK1 gene and susceptibility to gout in male Han Chinese: a case-control study. International journal of clinical and experimental medicine. 2015;8(8):13911–8. [PubMed: 26550347]
73. Ribbing J, Jonsson EN. Power, selection bias and predictive performance of the Population Pharmacokinetic Covariate Model. J Pharmacokinet Pharmacodyn. Apr 2004;31(2):109–34. doi:10.1023/b:jopa.0000034404.86036.72 [PubMed: 15379381]
74. Portis AJ, Laliberte M, Tatman P, et al. High prevalence of gouty arthritis among the Hmong population in Minnesota. Arthritis care & research. Oct 2010;62(10):1386–1391. doi:10.1002/acr.20232 [PubMed: 20506247]
75. Roman YM, Lor K, Xiong T, Culhane-Pera K, Straka RJ. Gout prevalence in the Hmong: a prime example of health disparity and the role of community-based genetic research. Per Med. May 2021;18(3):311–327. doi:10.2217/pme-2020-0107 [PubMed: 33787318]

What is already known

- Allopurinol exhibits large variability in pharmacokinetics and pharmacodynamics.
- Patient characteristics and concomitant medications have been identified as sources of the variability but have not accounted for all of it.
- The impact of genetic variants has been explored but no significant association has been established with population pharmacokinetics and pharmacodynamics analysis.

What does this study add

- Genetic variants in *SLC22A12* were associated with oxypurinol clearance and variants in *PDZK1* were associated with urate-lowering effect of oxypurinol.
- The allopurinol maintenance dose to achieve target serum urate level depends on patients' body mass, renal function, and genetic variants in *SLC22A12* and *PDZK1*.

What is the clinical significance

- An individualized dosing approach is proposed to optimize allopurinol for Hmong adults with gout and/or hyperuricemia

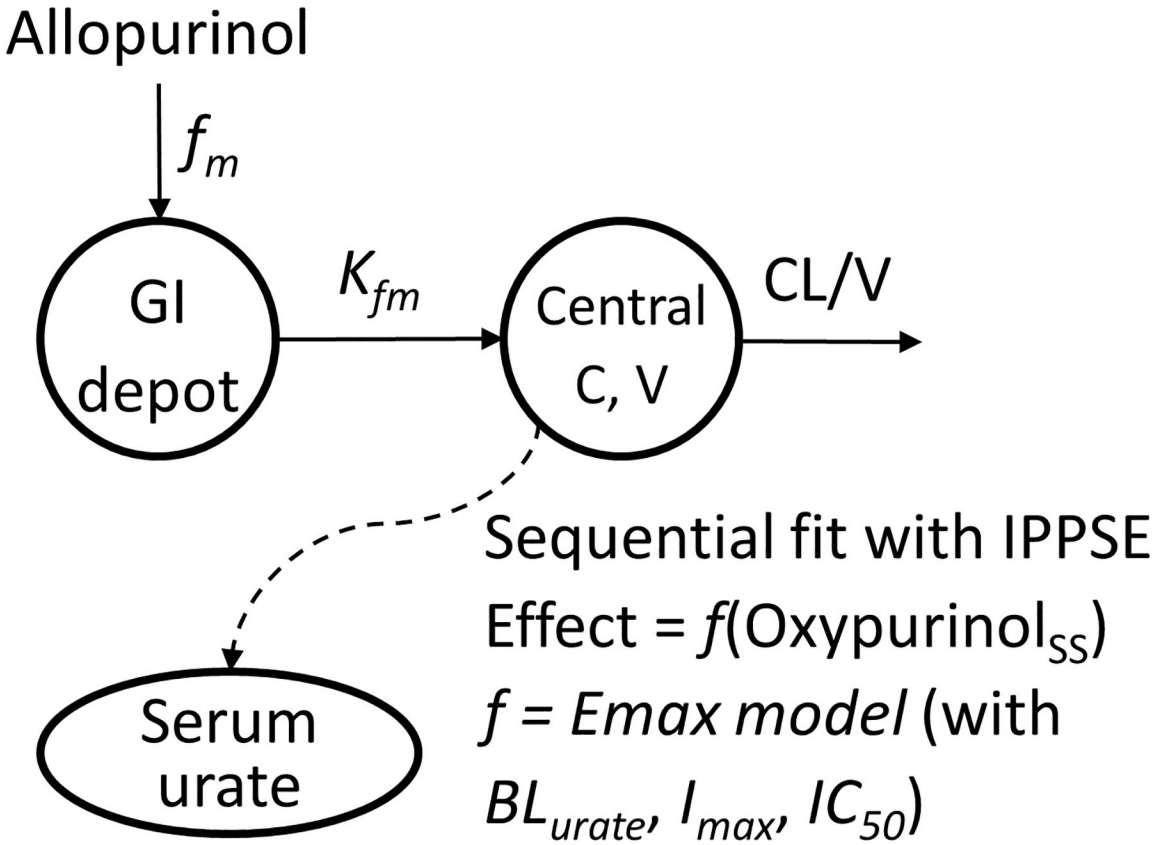

Figure 1.

The structural model of the pharmacokinetics and pharmacodynamics effect of allopurinol BL_{urate}, baseline serum urate; C, serum oxypurinol concentration; CL, apparent oxypurinol clearance; f_m, fraction of the allopurinol dose systemically converts to oxypurinol; K_{fm}, combined absorption and formation rate constant; I_{max}, maximum inhibitory effect of oxypurinol on xanthine dehydrogenase to inhibit urate production; IC_{50}, oxypurinol concentration required to inhibit 50% of the activity of xanthine dehydrogenase; IPPSE, individual pharmacokinetic parameters with standard error; V, apparent oxypurinol volume of distribution

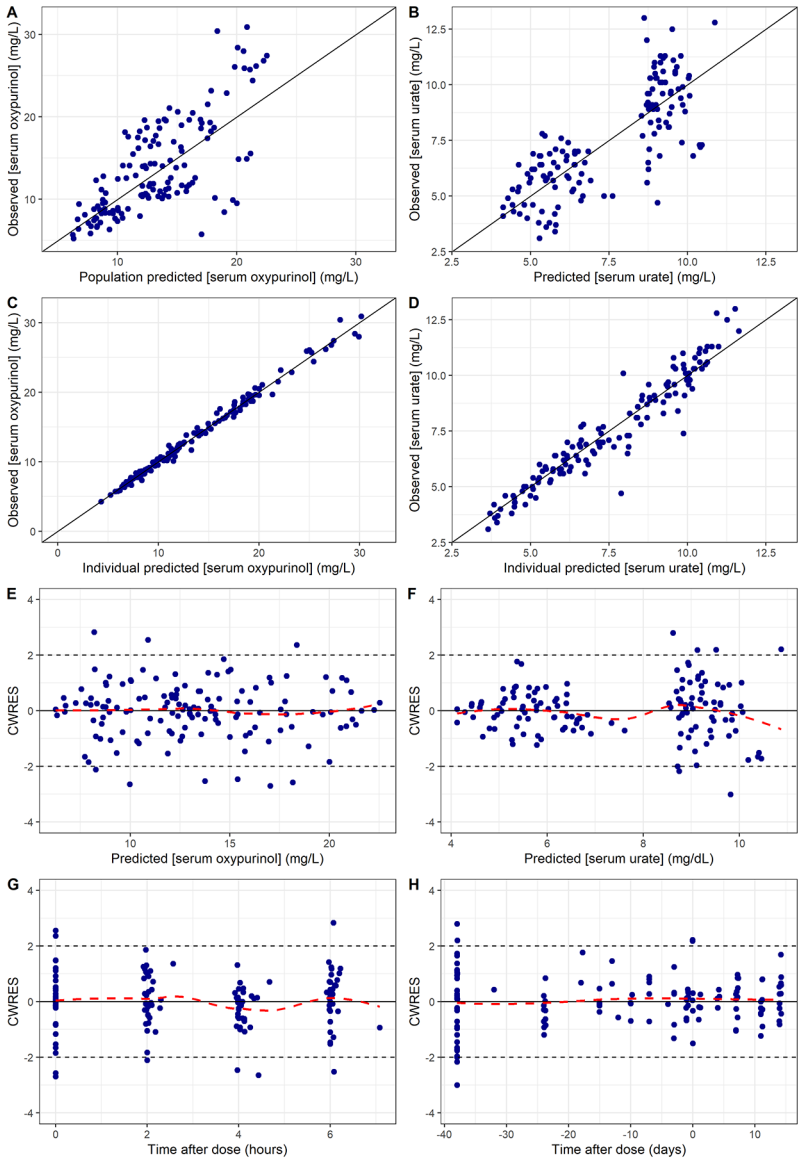

Figure 2.

Goodness-of-fit plots of the final PKPD models for oxypurinol.

A and B, observed versus population-predicted concentration for serum oxypurinol and serum urate.

C and D, observed versus individual-predicted concentration for serum oxypurinol and serum urate.

E and F, conditional weighted residuals versus population-predicted concentration for serum oxypurinol and serum urate.

G and H, conditional weighted residuals versus time after dose for serum oxypurinol and serum urate.

CWRES = conditional weighted residuals.

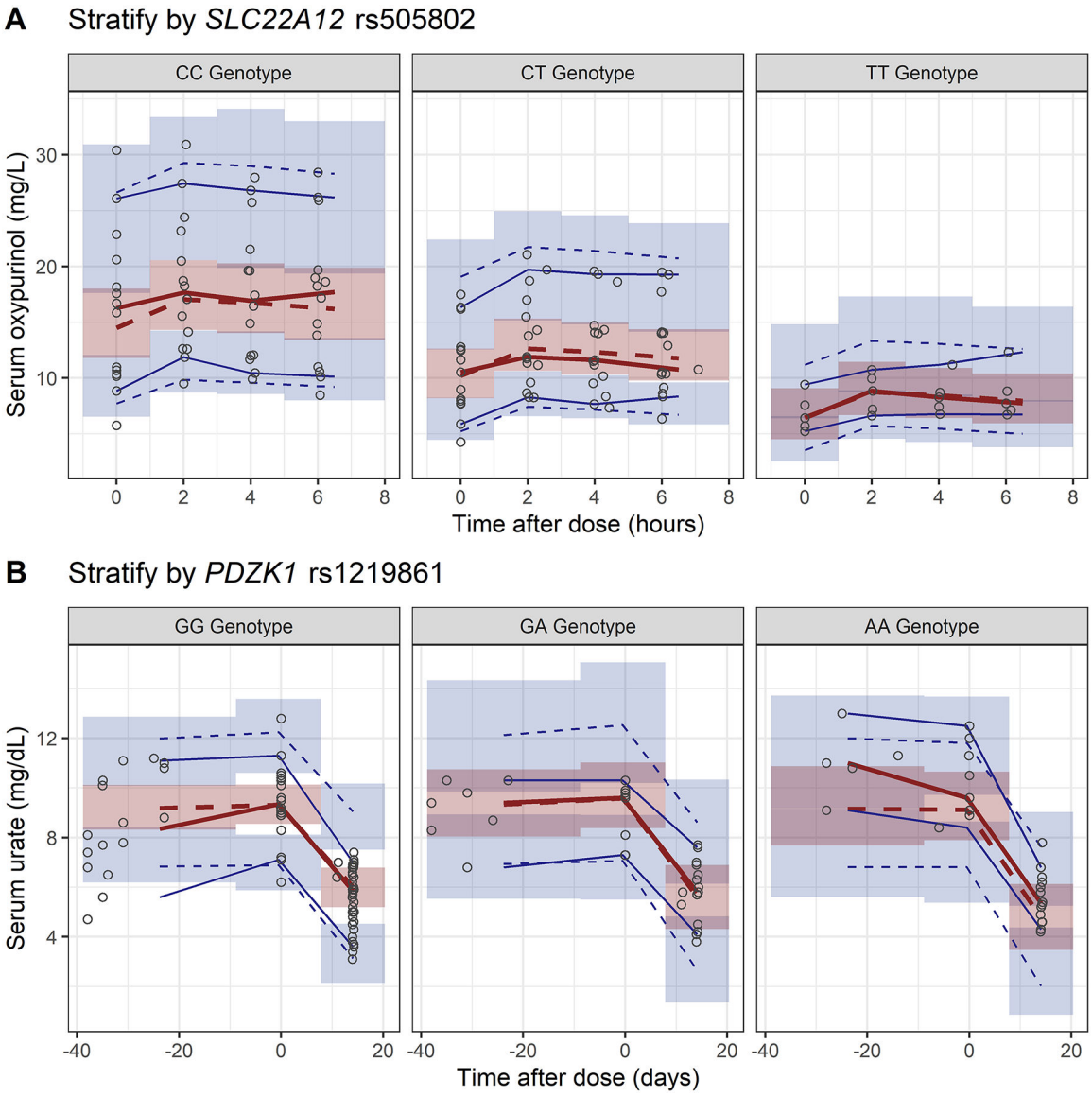

Figure 3.

Visual predictive checks of the final PKPD models for oxypurinol.

A, serum oxypurinol concentration stratified by *SLC22A12* rs505802 genotypes.

B, serum urate concentration stratified by *PDZK1* rs12129861 genotypes.

The open circles represent the observed data. The blue (5th and 95th) and red (50th) solid and dashed lines represent the percentiles of the observed and simulated data, respectively. The shaded areas are the 95% confidence intervals of the simulated concentrations for the corresponding percentile values.

Table 1.

GOUT-H participants characteristics

Characteristics[a]	**N = 34**[b]
Age (years)[b]	43 ± 13 (24–68)
Gender, male[c]	31 (91%)
Height (cm)[b]	160 ± 7 (146–179)
Weight (kg)[b]	84 ± 17 (54–134)
BMI (kg/m^2)[b,d]	32.5 ± 5.5 (21.6–47.0)
Normal[c]	1 (2.9%)
Overweight[c,d]	4 (12%)
Obesity[c],	29 (85%)
Estimated CrCL (mL/min)[b,e],	87 ± 31 (25–165)
15 ≤ Estimated CrCL < 30	1 (3%)
30 ≤ Estimated CrCL < 60	8 (24%)
Estimated CrCL ≥ 60	25 (74%)
Baseline serum urate (mg/dL)[b]	9.61 ± 1.67 (5.8–13.0)
Post-treatment serum urate (mg/dL)[b]	5.4 ± 1.1 (3.1 – 7)
Steady-state serum oxypurinol$_{0hr}$ (mg/L)[f]	10.6 [7.8, 16.3] (4.3–30.4)
Steady-state serum oxypurinol$_{6hr}$ (mg/L)[f]	12.6 [9.4, 18.1] (6.4–28.4)
Self-reported medications related to SU/gout[c,g]	
Drugs that lower serum urate	10 (29%)
Losartan	1 (2.9%)
HMG-CoA inhibitors	5 (15%)
Calcium channel blockers	5 (15%)
Drugs that increase serum urate	22 (65%)
Angiotensin converting enzyme inhibitors	5 (15%)
Angiotensin receptor blockers (not losartan)	1 (2.9%)
Beta-blockers	6 (18%)
Diuretics	4 (12%)
Non-steroidal anti-inflammatory drugs	16 (47%)

BMI, body mass index; CrCL, creatinine clearance; SU, serum urate

[a] Characteristics were assessed at the baseline study visit after 10 days washout period.

[b] Mean ± standard deviation (range)

[c] n (%)

[d] Overweight was defined as BMI 23.0–27.5 kg/m^2; obesity was defined as BMI > 27.5 kg/m^2 based on World Health Organization Asian criteria-based BMI[52].

[e] Estimated CrCL was calculated using Cockcroft-Gault Equation with adjusted body weight.

[f] Median [interquartile range] (range)

[g] Only medications that may impact serum urate are listed.

Table 2.

Parameter estimates for the base (without covariates) and final population pharmacokinetic/pharmacodynamic models using sequential fit

Parameter	Base model	Final model	SIR, median (95%CI)
Fixed parameters			
CL/f_m (L/h)	1	1.05	1.05 (0.92, 1.22)
V/f_m (L)	47.7	59.3	58.8 (50.8, 70.7)
K_{fm} (/h)	1.1 (fixed)	1.1 (fixed)	1.1 (fixed)
BL_{urate} (mg/dL)	9.3	9.0	9.0 (8.5, 9.5)
Imax (mg/dL)	6.1	7.6	7.7 (5.3, 11.3)
IC_{50} (mg/L)	8.0	17.6	18.2 (7.5, 32.8)
Effects of covariates on CL/f_m			
Standardized creatinine clearance (power)	-	0.45	0.45 (0.18, 0.73)
SLC22A12 rs505802 T allele[a]	-	0.32	0.32 (0.13, 0.55)
Effects of covariates on SU			
Standardized creatinine clearance (power) on baseline SU	-	−0.18	−0.18 (−0.33, −0.036)
PDZK1 rs12129861 A allele on IC_{50}[a]	-	−0.27	−0.27 (−0.38, −0.13)
Random effect parameters, CV% (RSE%) [shrinkage]			
BSV CL/f_m	42.8 [0%]	28.3 [0%]	28.3 (22.6, 34.5)
BSV V/f_m	40.7 [25%]	32.4 [30%]	31.6 (19.5, 43.0)
BSV K_{fm}	27.9 (fixed)	27.9 (fixed)	27.9 (fixed)
BSV BL_{urate}	11.1 [11%]	13.7 [6]	13.8 (10.1, 17.7)
BSV *Imax*	32.4 (fixed)	32.4 (fixed)	32.4 (fixed)
BSV IC_{50}	71.8 (fixed)	71.8 (fixed)	71.8 (fixed)
Residual error			
Serum oxypurinol, proportional (CV%) [shrinkage]	5.2 [23.2%]	5.2 [21.3%]	5.4 (4.5, 6.0)
Serum urate, additive (mg/dL) [shrinkage]	0.90 [16%]	0.69 [18%]	0.69 (0.49, 1.03)

BL_{urate}, baseline serum urate; f_m, fraction of the allopurinol systemically available as oxypurinol; CL/f_m, apparent clearance of oxypurinol; V/f_m, apparent volume of distribution of oxypurinol; K_{fm}, combined absorption and formation rate constant; I_{max}, maximum inhibitory effect of oxypurinol on xanthine dehydrogenase to inhibit urate production; IC_{50}, oxypurinol concentration at half maximum inhibitory effect; *CrCL*, creatinine clearance calculated using ideal body weight; FFM, fat free mass; Css_{oxy}, steady-state plasma oxypurinol concentration; SU, serum urate

[a]An additive genetic model was assumed for the effect of SNPs on the PKPD parameters. The fractional effect of genotype was calculated as 1 + estimated effect per allele.

Table 3.

Predicted allopurinol daily maintenance dose to achieve serum urate of <6 mg/dL with 75% of success rate, considering genetic variants of *SLC22A12* rs505802 and *PDZK1* rs12129861

		Fat Free Mass (FFM)					
	CrCL (mL/min)	**50 kg**	**60 kg**	**70 kg**	**80 kg**	**90 kg**	**100 kg**
				***SLC22A12* rs505802 CC**			
	≥15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	≥30 and <60	500	650	700	700	800	Alternative
	≥60	400	450	450	550	550	600
				***SLC22A12* rs505802 CT**			
***PDZK1* rs12129861 GG**	≥15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	≥30 and <60	700	750	Alternative	Alternative	Alternative	Alternative
	≥60	500	550	600	650	750	800
				***SLC22A12* rs505802 TT**			
	≥15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	≥30 and <60	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	≥60	600	650	750	Alternative	Alternative	Alternative
				***SLC22A12* rs505802 CC**			
	≥15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	≥30 and <60	400	450	500	600	600	650
	≥60	250	300	350	400	450	450
				***SLC22A12* rs505802 CT**			
***PDZK1* rs12129861 GA**	≥15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	≥30 and <60	550	600	650	750	800	Alternative
	≥60	350	400	450	500	550	550
				***SLC22A12* rs505802 TT**			
	≥15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	≥30 and <60	650	750	Alternative	Alternative	Alternative	Alternative
	≥60	450	500	550	650	700	750
				***SLC22A12* rs505802 CC**			
	≥15 and <30	550	600	700	800	800	Alternative
	≥30 and <60	250	300	350	400	400	450
	≥60	200	200	250	250	300	300
				***SLC22A12* rs505802 CT**			
***PDZK1* rs12129861 AA**	≥15 and <30	750	800	Alternative	Alternative	Alternative	Alternative
	≥30 and <60	350	400	400	450	500	550
	≥60	250	250	300	350	350	350
				***SLC22A12* rs505802 TT**			
	≥15 and <30	Alternative	Alternative	Alternative	Alternative	Alternative	Alternative
	≥30 and <60	400	500	500	600	650	700
	≥60	300	350	350	400	450	450

“Alternative” indicates an alternative medicine is preferred over allopurinol, given that the target serum urate was not achieved despite the maximum dose of allopurinol (800 mg/day). CrCL, creatinine clearance.