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THERAPEUTICS

Impact of non-adherence on the safety and efficacy of uric acid-lowering therapies in the treatment of gout

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AIMS

Dual-urate-lowering therapy (ULT) with xanthine oxidase inhibitor and uricosuric medications is a treatment option for severe gout. Uricosuric agents can cause hyperuricosuria, a risk factor for nephrolithiasis and acute uric acid nephropathy. The aims of the present study were to simulate the relationship between suboptimal drug adherence and efficacy, and to quantify the risk of hyperuricosuria in gout patients receiving mono- and dual-ULTs.

METHODS

The impact of poor medication adherence was studied using two-compartment pharmacokinetic (PK) models based on published evidence, and a semi-mechanistic four-compartment pharmacodynamic (PD) model. The PKPD model was used to simulate mono and dual-ULT in gout patients with either under-excretion (lowered clearance) or overproduction of uric acid, with sub-optimal adherence modelled as either a single drug holiday of increasing duration or doses taken at random.

RESULTS

Simulation results showed a surge in urinary uric acid occurring when dosing is restarted following missed doses. For under-excreters taking a 20-day drug holiday, the addition of 200 mg (or 400 mg) lesinurad to 80 mg febuxostat increased the percentage of patients experiencing hyperuricosuria from 0% to 1.4% (or 3.1%). In overproducers, restarting ULTs following drug holidays of more than 5 days leads to over 60% of patients experiencing hyperuricosuria.

CONCLUSIONS

Suboptimal medication adherence may compromise the safety and efficacy of mono- and dual-ULTs, especially in patients with gout resulting from an overproduction of uric acid. Clinicians and pharmacists should consider counselling patients with respect to the risks associated with partial adherence, and offer interventions to improve adherence or tailor treatments, where appropriate.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Uricosuric agents, used for the treatment of gout, increase the risk of hyperuricosuria and therefore also acute kidney injury.
- Adherence to urate-lowering therapies for treating gout is among the worst of any chronic disease.

WHAT THIS STUDY ADDS

- Restarting uricosuric treatment following a drug holiday increases the rate of episodic hyperuricosuria.
- Suboptimal medication adherence may compromise the safety and efficacy of mono- and dual-urate-lowering therapies, especially in patient groups such as those with gout resulting from an overproduction of uric acid.
- Clinicians and pharmacists should consider counselling patients with respect to the risks associated with partial adherence, and offer interventions to improve adherence or tailor treatments, where appropriate.

Introduction

Gout is a painful and disabling chronic disease which affects a large and increasing number of people and has proven difficult to treat [1]. Long-term treatment with urate-lowering therapies (ULTs) aims to reduce serum uric acid (sUA) concentrations to below the point of saturation (approximately 6 mg dl^{-1}). When treatment with a **xanthine oxidase** inhibitor (XOI) alone is unsuccessful, a uricosuric agent can be administered as a co-treatment [2]. Historically, the use of uricosuric agents for long-term therapy has been limited owing to possible hepatotoxicity (benzbromarone) and drug–drug interactions (**probenecid**). However, the **uric acid transporter-1** (URAT-1) inhibitor **lesinurad** has recently gained regulatory approved and is intended for long-term therapy in combination with an XOI (such as **allopurinol** or **febuxostat**) [3].

As they increase the renal excretion of UA, uricosuric agents such as lesinurad can cause hyperuricosuria (urinary excretion of UA ≥800 mg day^{-1} in men; ≥750 mg day^{-1} in women) [4]. High levels of urinary UA (uUA) can cause kidney damage, which may be acute – for example, through stone formation (nephrolithiasis) [5] or intrarenal obstruction (acute urate nephropathy) – or chronic, as in chronic (or gouty) nephropathy. Acute kidney injury can occur when UA concentrations in renal tubules reach supersaturation, which also depends on urine pH [6, 7]. Chronic nephropathy is thought to result from long-term hyperuricosuria, in which UA concentrations may be below supersaturation. The existence of chronic nephropathy remains controversial [8] but is supported by animal models and some epidemiological studies [9]. The harmful effects of UA on the kidney are a possible explanation of the association, in recent clinical trials, between lesinurad and an increase in the rate of raised serum creatinine and, for higher doses, with serious renal adverse events [10].

Adherence to ULT is known to be among the lowest of any chronic disease treatment [11, 12], with 70% of patients having a drug holiday of at least 60 days over 6 years. Poor adherence to allopurinol monotherapy is associated with lower treatment success rates [13]. While dual therapy increased response rates compared with monotherapy in clinical trials [14–16], an interruption in dosing (drug holiday) could result in high peaks in uUA concentration when treatment is restarted. Suboptimal implementation of the dosing regimen (e.g. late doses, skipping a dose or drug holidays) [17] may therefore increase the risk of renal adverse events caused by UA nephropathy.

The present study aimed to simulate the relationship between poor implementation of dosing and efficacy, and to quantify the risk of hyperuricosuria in gout patients receiving mono- and dual-ULT.

Methods

Strategy

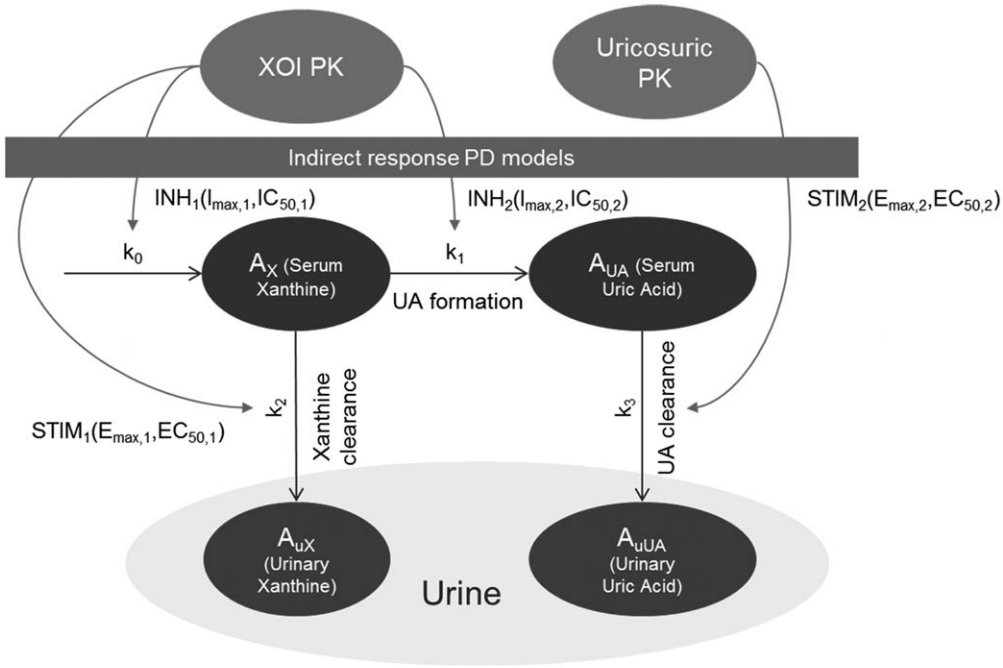
A semi-mechanistic pharmacokinetic–pharmacodynamic (PKPD) model, based on previous research on the systems pharmacology of the purine metabolic pathway [18], was developed to capture the pharmacology of ULTs (Figure 1). The system comprised four compartments utilizing a zero-order production rate (k_0) governing the formation of xanthine and first-order production rates characterizing its biotransformation to UA (k_1) and the elimination of xanthine (k_2) and UA (k_3) into the urine. These, in turn, were parameterized in terms of volumes and clearance terms.

The PD model characterizes the time course of sUA, uUA, xanthine and urinary xanthine. Two inhibitory indirect response (turnover) models were used to account for the effect of multiple doses of febuxostat on k_0 and k_1 [19]. A stimulatory indirect response [20] equation acting on the k_2 rate parameter was incorporated to model the increased xanthine renal clearance associated with febuxostat [21]. The clearance of UA upon multiple doses of lesinurad was modelled using a stimulatory indirect response equation acting on the k_3 rate parameter.

The system and drug PD model parameter estimates were obtained from the literature and other publicly available sources. As described below, some parameters values were taken directly from the literature, while others were estimated using nonlinear mixed-effects models and clinical trials data**.** The parameters required to characterize the pharmacodynamic model are given in Table 1.

PK

Two-compartment models with first-order absorption for febuxostat and lesinurad obtained from the literature [22, 23] were used to simulate typical and individual subject drug



System dynamics equations:

$$\frac{dA_X}{dt} = k_0 * INH_1 - k_1 * INH_2 * A_X - k_2 * STIM_1 * A_X \quad \text{(Eq. 1)}$$

$$\frac{dA_{UA}}{dt} = k_1 * INH_2 * A_X - k_3 * STIM_2 * A_{UA} \quad \text{(Eq. 2)}$$

$$\frac{dA_{uX}}{dt} = k_2 * STIM_1 * A_X \quad \text{(Eq. 3)}$$

$$\frac{dA_{uUA}}{dt} = k_3 * STIM_2 * A_{UA} \quad \text{(Eq. 4)}$$

No treatment steady-state:

$$k_2 = \frac{CLX}{VX} \quad \text{(Eq. 5)} \qquad k_3 = \frac{CLUA}{VUA} \quad \text{(Eq. 6)}$$

$$k_1 = \frac{k_3 * BUA}{BX * (M_{UA}/M_X)} \quad \text{(Eq. 7)} \qquad k_0 = \frac{k_1 * BX}{k_2 * BX} \quad \text{(Eq. 8)}$$

Pharmacodynamic models:

$$INH_1 = \frac{IC_{50,1}}{IC_{50,1} + C_F(t)} \quad \text{(Eq. 9)} \qquad INH_2 = \frac{IC_{50,2}}{IC_{50,2} + C_F(t)} \quad \text{(Eq. 10)}$$

$$STIM_1 = 1 + \frac{E_{max,1} * C_F(t)}{EC_{50,1} + C_F(t)} \quad \text{(Eq. 11)} \qquad STIM_2 = 1 + \frac{E_{max,2} * C_L(t)}{EC_{50,2} + C_L(t)} \quad \text{(Eq. 12)}$$

Figure 1

Diagrammatic and mathematical representations of the pharmacodynamics (PD) of dual-urate-lowering therapies. A_X and A_{UA} are the total time-varying amounts of xanthine and uric acid in serum respectively; A_{uX} and A_{uUA} are the total time-varying amounts of xanthine and uric acid in urine respectively; BUA, baseline amount of uric acid; BX, baseline amount of xanthine; $C_F(t)$ and $C_L(t)$ are the plasma concentrations of febuxostat of lesinurad, respectively; CLUA, renal clearance of uric acid; CLX, renal clearance of xanthine; $EC_{50,1}$ and $EC_{50,2}$ are drug concentrations corresponding to 50% of the maximum possible level of stimulation in the pharmacodynamic drug models $STIM_1$ and $STIM_2$ respectively; $E_{max,1}$ and $E_{max,2}$ are the maximum possible levels of stimulation in the pharmacodynamic drug models $STIM_1$ and $STIM_2$ respectively; $IC_{50,1}$ and $IC_{50,2}$ are the drug concentrations corresponding to 50% of the maximum possible level of inhibition in the pharmacodynamic drug models INH_1 and INH_2 respectively; INH1 and INH2 are inhibitory pharmacodynamic model drug functions; k_0, k_1, k_2 and k_3 are the rate parameters for the production of xanthine, xanthine to uric acid conversion, removal of xanthine to urine and removal of uric acid to urine, respectively; $STIM_1$ and $STIM_2$ are stimulatory pharmacodynamic model drug functions; VUA, volume of uric acid distribution; VX, volume of xanthine distribution

plasma concentration–time courses. The PK parameters, covariate effects and associated between-subject variability (BSV) are reproduced in Table 2.

PD

Parameters obtained from the literature. The mean rates of renal clearance of UA and xanthine (CLUA and CLX) in

Table 1

Pharmacodynamic (PD) parameters for febuxostat and lesinurad: literature and statistical estimates combined

Model	Name	Source	Parameter estimates		BSV (SD^2)	
System PD parameter	BX (mg)	Estimated	θ_1	8.94		NE
	VX (dl)	Estimated	θ_2	333		NE
	CLX (dl h^{-1})	Literature	θ_3	10.57		NE
	BUA (mg)	Estimated	θ_4	703		NE
	VUA (dl)	Estimated	θ_5	154		NE
	CLUA (dl h^{-1})	Literature	θ_6	4.11		NE
Febuxostat PD parameter	$E_{max,1}$	Assumed	θ_7	3		NE
	$EC_{50,1}$	Assumed	θ_8	0.001		NE
	$I_{max,1}$	Assumed	θ_9	1		NE
	$IC_{50,1}$	Estimated	θ_{10}	0.1320	η_3	0.2
	$I_{max,2}$	Assumed	θ_{11}	1		NE
	$IC_{50,2}$	Estimated	θ_{12}	0.00113	η_3	0.2
Lesinurad PD parameter[a]	E_0	Literature	θ_{13}	6.77		NE
	E^D_{max}	Literature	θ_{14}	−2.55	η_4	0.346
	b_{CrCl}	Literature	θ_{15}	0.564		NE
	EC^D_{50}	Literature	θ_{16}	0.0974		NE

BSV, between-subject variability; bCrCl, covariate effect parameter for creatinine clearance (ml min^{-1}); BUA, baseline amount of uric acid; BX, baseline amount of xanthine; CLUA, renal clearance of uric acid; CLX, renal clearance of xanthine; E_0, baseline sUA concentration; $EC_{50,1}$, drug concentration corresponding to 50% of the maximum possible level of stimulation $E_{max,1}$; $EC_{50}{}^D$, drug concentration corresponding to 50% of the maximum reduction in sUA; $E_{max,1}$, maximum possible level of stimulation for model $STIM_1$; $E_{max}{}^D$, maximum possible reduction in sUA; $I_{max,1}$, maximum possible level of inhibition in equation INH_1; $I_{max,2}$, maximum possible level of inhibition in equation INH_2; $IC_{50,1}$, drug concentration corresponding to 50% of maximum possible inhibition $I_{max,1}$; $IC_{50,2}$, drug concentration corresponding to 50% of maximum possible inhibition $I_{max,2}$; INH_1 (acting on k_0) and INH_2 (acting on k_1) are inhibitory pharmacodynamic model drug functions; k_0, k_1, k_2 and k_3, rate parameters for the production of xanthine, xanthine to uric acid conversion, removal of xanthine to urine and removal of uric acid to urine, respectively; NE, not estimated; SD, standard deviation; $STIM_1$ (acting on k_2), stimulatory pharmacodynamic model drug function; VUA, volume of uric acid distribution; VX, volume of xanthine distribution
Error model used: $\theta_i = \theta_u \exp(\eta_i)$
[a]Lesinurad: Parameters of the direct Emax model used to derive the corresponding parameters of the indirect response model in Figure 1

Table 2

Pharmacokinetic parameters for lesinurad and febuxostat

	Febuxostat		*Lesinurad*	
Parameter	**Estimate**	**BSV (CV%)**	**Estimate**	**BSV (CV%)**
CL/F_0 (dl h^{-1})[a]	49.3	18.3	69.9	63.4
b_CrCl	0.142	NA	0.322	NA
b_WT	0.155	NA		NA
Vc/F_0 (dl)[b]	322	NE	241	12.2
b_WT		NA	0.511	NA
Vp/F (dl)	222	NE	83	20.5
Q/F (dl h^{-1})	55.7	NE	4.48	NE
Ka (h^{-1})	13.7	176	0.69	121.7
Tlag (h)	0.23	NE	0.233	38.9

BSV, between-subject variability; CL/F, apparent clearance; CrCl, creatinine clearance rate; CV%, percentage coefficient of variation; Ka, first-order absorption; NA, not applicable; NE, not estimated; Q/F, intercompartmental clearance rate; Tlag, absorption time-lag; Vc/F, volume of the central compartment; Vp/F, volume of the peripheral compartment; WT, individual body weight (kg)
[a]Febuxostat: CL/F = CL/F_0 + b_CrCl*CrCl + b_WT*WT; Lesinurad: CL/F = CL/F_0 * (CrCl/87)^b_CrCl
[b]Lesinurad: VC/F = VC/F_0 * (WT/70)^b_WT

healthy volunteers, along with the BSV, were obtained using summary data from a phase I dose-escalation study of 154 healthy volunteers receiving febuxostat [24]. The reported average clearance in each group and standard deviations (see supplementary material) were used to obtain a weighted average estimate of population typical value and the BSV.

This trial also found that the CLX rate in subjects taking febuxostat, even at doses as low as 10 mg day^{-1}, increased three- to fivefold from baseline. This may result from the saturation of active transport processes responsible for the reabsorption of xanthine from the renal tubules [21]. A step function was assumed using a stimulatory E_{max} drug function (Equation 11 in Figure 1), with an $EC_{50,1}$ of 0.001 mg dl^{-1} (a low concentration associated with the 10 mg dose) and $E_{max,1}$ of 3.

A previous PD model of lesinurad used a direct-effect E_{max} model to relate the steady-state average plasma concentration of lesinurad to the individual's sUA concentration [23]. The parameters of the indirect model ($E_{max,2}$, $EC_{50,2}$) were derived from those given in the published direct model (E^D_{max} and EC^D_{50}) using the steady-state equations [19] (see supplementary material). The published model includes a covariate effect of creatinine clearance on the maximum reduction in UA, E^D_{max}. The stimulatory model drug function $STIM_2$ is given by Equation 12 in Figure 1, while the equations used to derive $E_{max,2}$ and $EC_{50,2}$ are given below.

$$E_{\max,2} = \frac{E_0}{E_0 - \left(E^D_{max}\left(\frac{CrCl}{87}\right)^{b_{crcl}}\right)} - 1$$

$$EC_{50,2} = \frac{E_{\max,2}\, EC^D_{50}}{E_0 / \left(E_0 - \left(\frac{E^D_{max}}{2}\right)\right) - 1} - EC^D_{50}$$

CrCl is the individual's creatinine clearance rate and E_0 is the baseline sUA concentration of trial participants used to derive the direct E_{max} model parameters.

Estimations using statistical modelling. All other parameters were estimated using nonlinear mixed-effects modelling and febuxostat phase I trial summary data on daily area under the plasma concentration–time curve (AUC) and 24-h urinary excretion of xanthine and UA [24] (see supplementary material). This was conditional on the clearance estimates and drug PD function parameters obtained directly from the literature in the previous section. A NONMEM dataset was created using the AUC and urinary data and the trial dosing schedule. Each value was an average across all individuals within a dose group and has, therefore, been replicated according to the number of subjects within the group, in order to weight by sample size.

The PKPD modelling was conducted using NONMEM 7.3 (ICON Development Solutions, Hanover, MD, USA) and the ADVAN6 routine for solving differential equations. The PD model was coded using the differential equations in Figure 1, where Equations 3 and 4 correspond directly to published data on 24-h urinary excretion [24]. However, additional sUA and serum xanthine accumulation compartments were added to compute the area under the concentration–time curve at 24-h intervals. Parameter estimation used the first-order algorithm, and different initial parameter estimates were tested. No random effects were included on system parameters estimated in NONMEM as the data points did not come from individual subjects. The inhibitory model drug functions INH_1 and INH_2 are given by Equations 9 and 10, respectively, in Figure 1.

In order to simplify the modelling procedure and make use of all available evidence, the statistical modelling was performed in two stages. The first stage used a published PKPD model of febuxostat that used an indirect inhibitory response model applied to a zero-order rate of UA production [22]. Rewriting UA production in the differential equations in our model as zero order, the literature parameter estimate of 0.0239 mg dl^{-1} was assumed for $IC_{50,2}$ and the remaining parameters were then estimated. In the second stage, the UA production was returned to being first order, such that it was a function of changing xanthine levels, and a new parameter estimate was made of $IC_{50,2}$ with all other parameters fixed.

Gout patient simulation model

We assumed that the febuxostat PD parameters estimated for healthy volunteers could be applied to gout patients with hyperuricaemia. However, systems parameters have been adjusted to be representative of a patient population. A typical patient sUA concentration was assumed to be 8.83 mg dl^{-1} (standard deviation 1.53) as this was the pretreatment sUA concentration for patients in the CRYSTAL (Combination Treatment Study in Subjects With Tophaceous Gout With Lesinurad and Febuxostat (NCT01510769)) trial, which compared febuxostat with lesinurad [25]. We considered two phenotypes – overproducers and under-excreters of UA [26, 27] – and modified the healthy subject system parameters accordingly. For overproducers, the amount of xanthine was scaled up, and for under-excreters the clearance of UA was scaled down in proportion to the sUA concentration (Table 3). This assumes the same volumes of distribution of xanthine and UA for patients as for healthy subjects.

Table 3

Individual system parameters for healthy subject and gout patients

Parameter	Healthy subject	Gout patient	
		Under-excreter	Overproducer
sUA (mg dl^{-1})		LN(8.83,1.53)	LN(8.83,1.53)
BX (mg)	θ_1	θ_1	θ_1*(BUA/θ_4)
VX (dl)	θ_2	θ_2	θ_2
CLX (dl h^{-1})	θ_3	θ_3	θ_3
BUA (mg)	θ_4	θ_5*sUA	θ_5*sUA
VUA (dl)	θ_5	θ_5	θ_5
CLUA (dl h^{-1})	θ_6	θ_6*(θ_4/BUA)	θ_6

BUA, baseline amount of uric acid; BX, baseline amount of xanthine; CLUA, renal clearance of uric acid; LN; Lognormal (mean, standard deviation); sUA, serum uric acid; VUA, volume of uric acid distribution; VX, volume of xanthine distribution

The model was used to simulate treatment with 120 days of ULT in a hypothetical cohort of 1000 patients with baseline characteristics corresponding to the CRYSTAL trial. The cohort was all male (95% were male in CRYSTAL) and baseline sUA, weight and age were assumed to be log-normally distributed, with mean and standard deviations taken from CRYSTAL (study 304) [28]. CrCl, calculated using the Cockcroft–Gault equation [29], overestimated the distribution of the trial participants. All estimates were reduced by 15 ml min^{-1}, and estimates below 30 ml min^{-1} were excluded to obtain a better representation of the trial population CrCl. The variability of drug effects in INH_1 and INH_2 could not be estimated and the IC_{50} parameters were assumed to vary according to η_3 with a coefficient of variation of 20%. Steady state was assumed following 30 days of simulated treatment and only the latter 60 days was used to derive results.

The outcomes of interest were the simulated time course of sUA and uUA concentrations, from which we estimated the proportion of patients responding (sUA below ≤5 mg dl^{-1} on day 120) and the proportion of patients experiencing hyperuricosuria (uUA ≥800 mg day^{-1} on any day). The normal range of the 24-h volume of urine is 0.5–1 ml kg^{-1} h^{-1} but is likely to be lower in the elderly [30, 31]. On this basis, a representative daily urine output for a 99 kg male of 15 dl was assumed for the purpose of estimating uUA concentrations. The soluble limit for UA is highly sensitive to urine pH, being much greater in alkaline than in acidic urine. For a given uUA concentration, the pH at which saturation would occur was estimated by fitting a linear model to literature data [32] to obtain: saturation pH = 6.36–40.96/[uUA].

Modelling adherence

The impact of poor adherence was studied for four different ULT options – namely, febuxostat 80 mg monotherapy and lesinurad 400 mg monotherapy, and febuxostat 80 mg combined with either lesinurad 200 mg or 400 mg. All are once-daily regimens, and it was assumed that doses are taken at the same time each day. Two types of poor adherence were considered. The first was a single drug holiday of increasing duration, from 1 day to 20 days, to assess the impact on uUA burden of restarting treatment following increasing lengths of drug holiday. The second assessed the impact of poor implementation on response rates and peaks in uUA by simulating doses taken completely at random, with a probability ranging from 1 to 0.1. For all dual-ULTs, missed doses included both drugs being missed simultaneously. A total of 30 simulations were conducted for each adherence scenario, which used random samples of the model parameter BSV, and the results were averaged over the range of simulation results.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [33], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [34, 35].

Results

The combined set of PD parameters and corresponding BSVs, which were derived or estimated from the literature, are presented in Table 1. Goodness-of-fit plots and visual predictive checks for the nonlinear mixed-effects modelling are provided as supplementary material.

With perfect adherence, uUA concentrations are maintained at low levels under the combined action of febuxostat 80 mg and lesinurad 200 mg (see plots for a typical patient in Figure 2). During a simulated drug holiday of 8 days, urinary concentrations increase as sUA concentrations return towards baseline. After dosing is restarted, peaks in uUA concentrations occur; for the typical under-excreter, the peak reached 39 mg dl^{-1}, which exceeds the typical average concentration for a healthy person (30 mg dl^{-1}). For the typical overproducer, the peak uUA concentration was 85 mg dl^{-1}, which exceeds the threshold for the typical average uUA concentration of an individual with hyperuricosuria (53 mg dl^{-1}). For the typical under-excreter, uUA concentrations after restarting treatment following an 8-day drug holiday could become supersaturated if the urinary pH was towards the acidic end of the normal range (pH <5.3; normal range 4.5–8.0). For the typical overproducer, peak uUA concentrations after restarting treatment are more likely to reach supersaturation at closer to the mid-point of the normal range, at approximately 5.9.

Across the population, increasing the length of a drug holiday increases the proportion of patients whose daily amount of UA excreted exceeds the threshold for hyperuricosuria upon restarting treatment (Figure 3). The proportion of patients with hyperuricosuria increases with increasing doses of lesinurad and is greatest for lesinurad 400 mg monotherapy. For under-excreters taking a 20-day drug holiday, the addition of 200 mg (or 400 mg) lesinurad to 80 mg febuxostat increased the percentage of patients experiencing hyperuricosuria from 0% to 1.4% (or 3.1%). In overproducers, restarting ULTs following drug holidays of more than 5 days led to over 60% of patients experiencing hyperuricosuria. In both patient groups, 1- or 2-day drug holidays were well tolerated compared with longer holidays, with only moderate increases in the rates of hyperuricosuria.

With perfect adherence, the proportion of patients treated to target (sUA ≤5 mg dl^{-1} on day 120) was greater than was observed in the CRYSTAL trial (Figure 4). However, success rates fell rapidly as an increasing proportion of doses were missed at random. For daily doses of febuxostat 80 mg, febuxostat 80 mg with lesinurad 200 mg, febuxostat 80 mg with lesinurad 400 mg and lesinurad 400 mg monotherapy, the success rates at 100% of doses taken in under-excreters were 87.2%, 94.5%, 96.0% and 15.4%, respectively. At 50% of doses taken at random, these success rates fell to 27.2%, 42.6%, 47.3% and 7.4%, respectively. The corresponding plots for overproducers are provided in the supplementary material.

Increasing the proportion of doses missed at random resulted in higher rates of hyperuricosuria due to randomly occurring drug holidays, especially in the presence of a uricosuric agent (Figure 4). The baseline daily uUA excreted in under-excreters was below healthy baseline levels and none of the simulated cohort showed hyperuricosuria in the absence of ULT. For dual-ULT with a uricosuric agent, however, randomly occurring drug holidays resulted in increasing

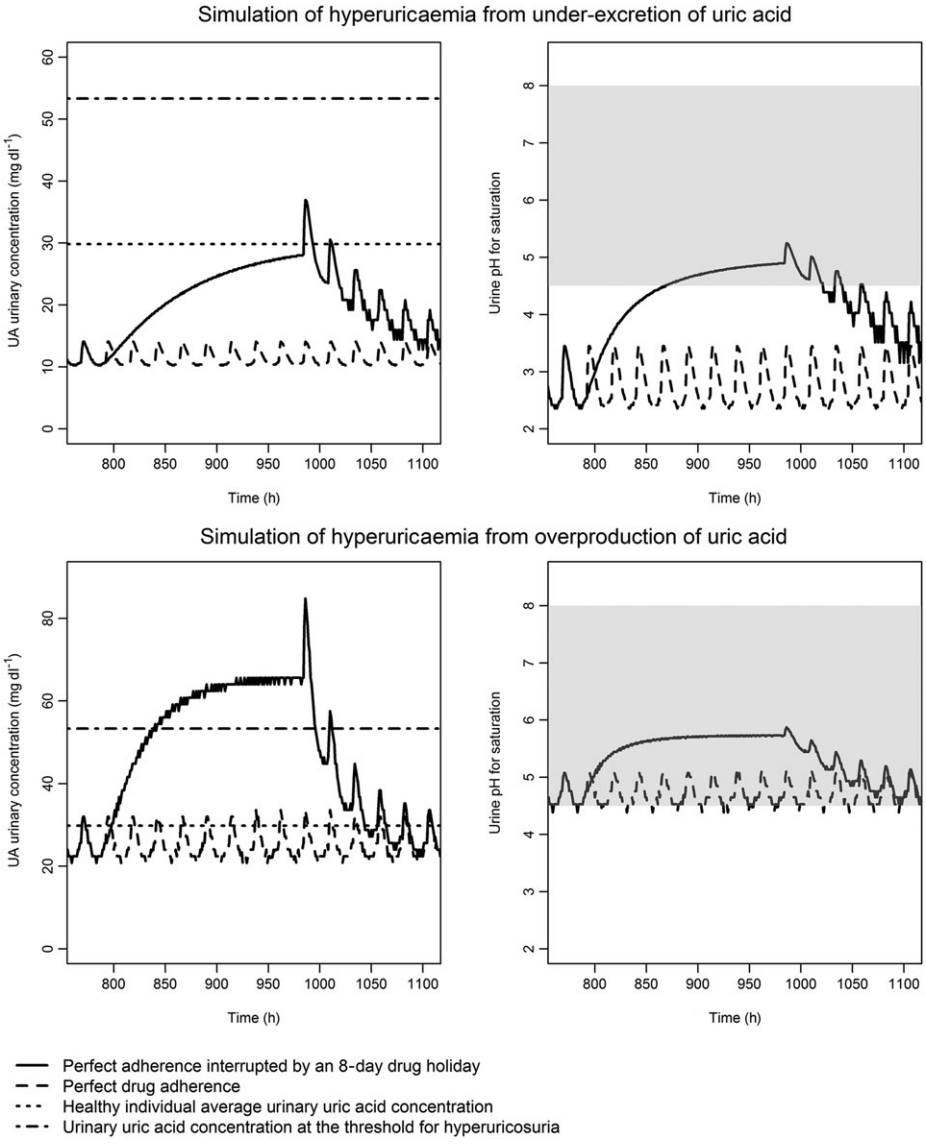


Figure 2

Simulated urinary uric acid (uUA) concentration and estimated pH for uric acid supersaturation, assuming a daily volume of urine of 15 dl. The simulated uUA concentration over time (left-hand panels) and the estimated pH at which this concentration would become supersaturated (right-hand panels). Imperfect adherence is modelled as an 8-day drug holiday (beginning on day 33). The shaded area represents the normal range for urine pH. The upper plots are the central estimates from the pharmacokinetic–pharmacodynamic model for a gout patient with hyperuricaemia from a reduced rate of uric acid clearance, and the lower plots for hyperuricaemia due to overproduction of xanthine. The urate lowering therapies used in these simulations were febuxostat 80 mg and lesinurad 200 mg, both once daily

rates of hyperuricosuria. For example, at 30% of doses taken, for febuxostat 80 mg with lesinurad 200 mg, febuxostat 80 mg with lesinurad 400 mg and lesinurad 400 mg monotherapy, the rates of hyperuricosuria were 1.3%, 3.2% and 4.9%, respectively.

Discussion

The use of uricosuric agents, either as monotherapy or in combination with an XOI, results in transient increases in uUA concentrations when dosing is restarted after a drug holiday. As a result, supersaturation of UA in urine can occur at pH values within the normal expected range, and therefore precipitation of UA in the renal tubules is more likely to occur during routine clinical practice. This effect is likely to be greater following a drug holiday from dual-ULTs than when starting treatment for the first time, where, as per the regulatory approval of lesinurad, patients must already have been taking an XOI. Specifically, our simulations indicated that peak uUA concentrations reach the threshold for supersaturation at a urinary pH of 5.3 for under-excreters and of 5.9 for overproducers, so that crystal formation may occur for a urinary pH at or below this level.

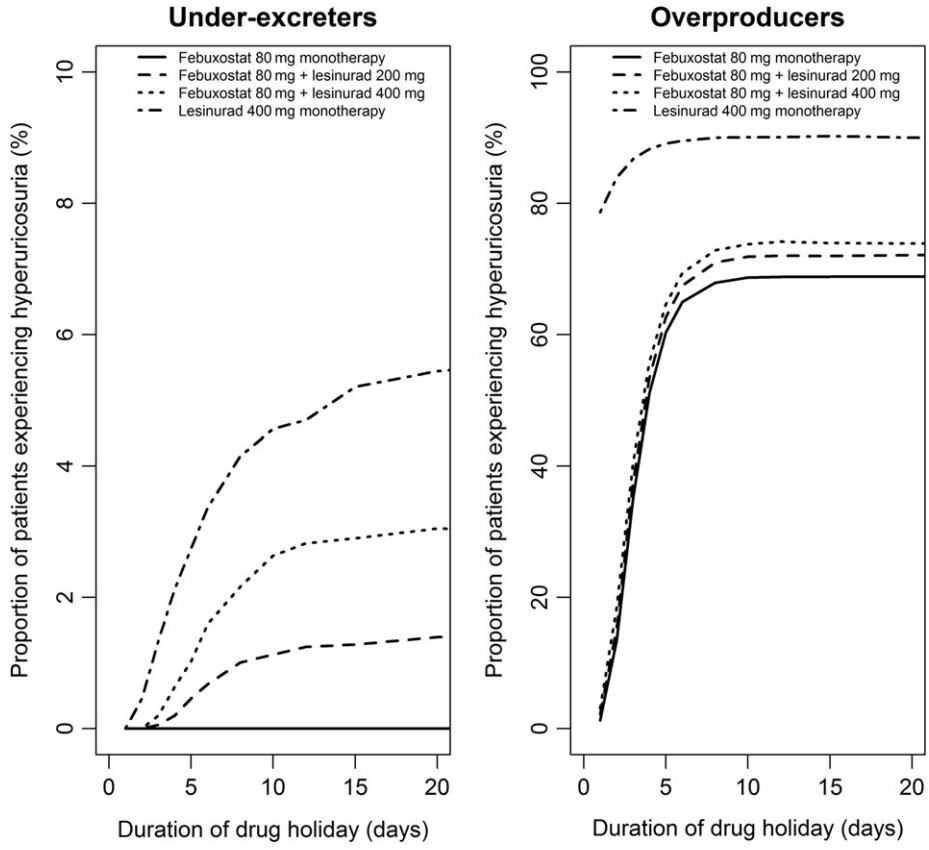


Figure 3

Proportion of simulated patients with 1-day hyperuricosuria following a single drug holiday taking place after 1 month of perfect adherence

Increasing the length of a drug holiday increased the proportion of patients whose daily amount of UA excreted exceeded the threshold for hyperuricosuria. The increase was more rapid for patients with overproduction, suggesting poorer drug forgiveness in this population. Treatment outcomes deteriorated rapidly as an increasing proportion of doses were missed at random. For under-excreters taking febuxostat 80 mg with lesinurad 200 mg, treatment-to-target rates fell by more than 50% when adherence reduced from 100% to 50%.

Approximately 90% of gout patients have hyperuricaemia caused by the renal under-excretion of UA [27]. In these cases, unless sUA concentrations are very high, or urinary volume is also lowered, uUA concentrations are likely to be lower than in healthy subjects. However, in simulations of drug holidays, after restarting dual-ULT, under-excreters had uUA concentrations raised to above the baseline levels for healthy subjects, and a small proportion exceeded the threshold for hyperuricosuria. For these patients to be at an increased risk of kidney damage, either a very low urinary output volume or a low urine pH (although still within the typical pH range) would probably be required. Urine pH is itself a primary predictor of nephrolithiasis as the solubility of UA is highly sensitive to small changes in pH [32].

Genetic disorders or a high-purine diet can be the cause of an overproduction of UA in the remaining 10% of gout patients [36]. Hyperuricosuria is a defining feature of UA overproduction [26], putting these patients at an increased risk of kidney injury without treatment. Our simulations suggest that in the case of very good medication adherence (≥80% of doses taken), dual-ULT would result in sustained reductions in sUA concentrations and also, therefore, uUA excreted. Regular drug holidays, however, would result in episodes in which uUA output was raised above its already high baseline. For this reason, uricosuric agents may not be appropriate for patients with hyperuricaemia due to UA overproduction [37], but no cautions are provided in the label for lesinurad [38].

To our knowledge, the present study was the first to investigate the relationship between medication adherence and the efficacy and safety of dual-ULT therapy for the treatment of gout. This was especially timely, given the recent approval of lesinurad for use in combination with an XOI in patients who have not responded on an XOI alone [39]. Our analysis benefited from having used a semi-mechanistic PD model which provides a level of complexity capable of capturing the nonsteady-state system dynamics. The effects of treatments were investigated in two distinct patient subgroups, the cause of hyperuricaemia being either an overproduction or under-excretion of UA. When comparing our simulation results with the findings from clinical trials, all of our perfect adherence simulations produced higher treatment success rates than had been reported in trials. Mathematical models such as this could be used to anticipate the problems resulting from suboptimal adherence, and potentially to help to identify the properties of more forgiving uricosuric agents.

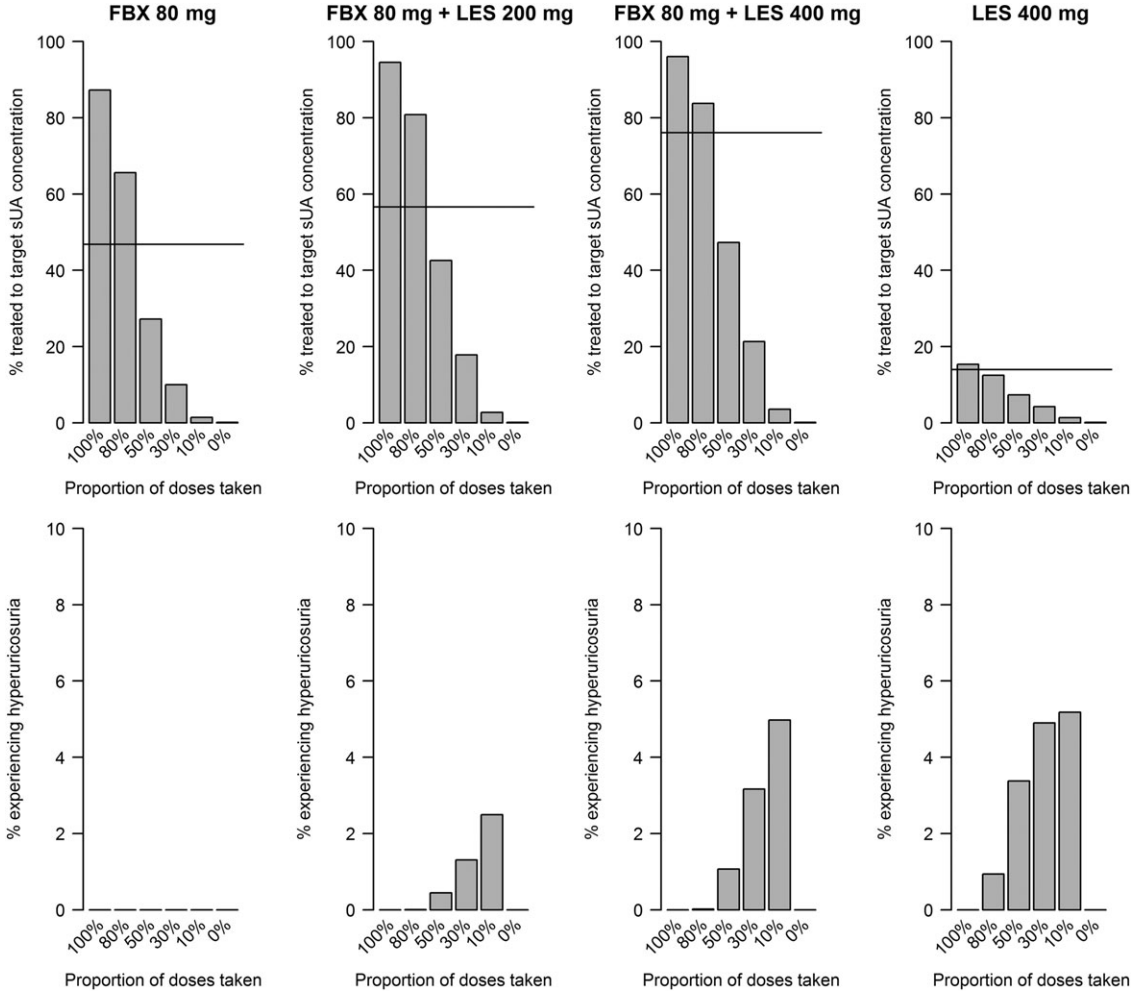


Figure 4

Treatment success rates (top row) and the proportion of patients experiencing 1-day hyperuricosuria during 2 months of urate-lowering therapy (bottom row). Horizontal lines provide the reference response rates for this treatment arm from the CRYSTAL trial comparing febuxostat and lesinurad, and Study 303 [25] for lesinurad 400 mg monotherapy. Results are for under-excreters of uric acid only; for overproducers, see the supplementary material. FBX: febuxostat; LES, lesinurad; sUA, serum uric acid

The main limitation of the study was our reliance on different sources of data from different populations. This limited our ability fully to quantify the variability and co-dependencies; nonetheless, we consider the model to be representative of existing dual-ULTs. We assumed that the nonrenal clearance of UA, which is responsible for around a third of total excretion [40], was negligible. Nevertheless, the contribution of nonrenal clearance relative to renal clearance will be lower in scenarios where a uricosuric agent is taken. Finally, the analysis focused on the XOI febuxostat but allopurinol is by far the most commonly prescribed ULT. However, we have no reason to believe that these findings do not extend to other XOIs (allopurinol) and uricosuric agents (probenecid and benzbromarone).

With the currently available ULTs, a large proportion of patients do not achieve sustained reductions in sUA to below saturation concentrations. The potential reasons for treatment failure include poor implementation of the treatment regimen (adherence), under-dosing, variation in treatment response and the underlying cause of hyperuricaemia [41]. Persistence with ULTs is known to be among the lowest of any chronic disease treatment [11, 12] and previous studies have provided evidence both for long [42] and short [43] drug holidays. The present study showed that renal safety may also be compromised by suboptimal medication adherence and highlights the need to improve adherence and adapt treatments to poorly adherent populations. This could include instructions on drug labelling [44], indicating a number of doses which can be missed based on the forgiveness of the drug to missed doses [45]. Such measures may improve the safety profile of future uricosuric agents, which for lesinurad may have influenced reimbursement decisions [46].

If gout patients adhere well to dual-ULT, then it appears to offer a means of further reducing sUA concentrations with a negligible increase in uUA output. However, regular drug holidays, which are commonplace among gout patients using ULTs, result in much lower rates of long-term treatment success and increased rates of hyperuricosuria when treatment is restarted. This has the potential to increase the risk of kidney damage in all patients, but especially those with

hyperuricaemia due to overproduction of UA. Further research is needed into the impact of adherence patterns on treatment success rates and kidney safety in order better to understand how dual-ULT could be used optimally in the treatment of hyperuricaemia in patients with gout. However, at present, counselling patients with respect to the risks associated with poor adherence should be advised.

Competing Interests

S.M. and E.S. are, or were, employees of Pfizer. The other authors have no competing interests to declare.

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Contributors

D.H.-M., E.S., S.M., S.L. and D.A.H. contributed substantially to the study conception or design, or the acquisition, analysis or interpretation of the data. D.H.-M. drafted the manuscript and E.S., S.M., S.L. and D.A.H. revised it critically for important intellectual content. D.H.-M., E.S., S.M., S.L. and D.A.H. gave final approval of the version to be published. D.A.H. agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13427/suppinfo

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