**Title**

Impact of non-adherence on the safety and efficacy of uric acid lowering therapies in the treatment of gout: A PKPD simulation study

**Authors**

Authors: Daniel Hill-McManus1, Elena Soto2, Scott Marshall2, Steven Lane3, Dyfrig Hughes1

Affiliations: 1) Centre for Health Economic and Medicines Evaluation, Bangor University; 2) Pharmacometrics, Pfizer Ltd, Sandwich, UK; 3) [Department](https://www.liverpool.ac.uk/translational-medicine/) of Biostatistics, University of Liverpool

Correspondence: Daniel Hill-McManus, Centre for Health Economic and Medicines Evaluation, Ardudwy Building, Normal Site, Bangor University, Bangor. LL57 2PZ. d.mcmanus@bangor.ac.uk. +44(0)1248 388479.

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**Abstract**

Dual-urate lowering therapy (ULT) with xanthine oxidase inhibitor (XOI) and uricosuric medications are a treatment option for severe gout. Uricosurics can cause hyperuricosuria, a risk factor for nephrolithiasis and acute uric acid nephropathy. The impact of poor medication adherence on the risk of hyperuricosuria was studied using 2-compartment PK models based on published evidence and a semi-mechanistic 4-compartment pharmacokinetic-pharmacodynamic (PKPD). The model was used to simulate mono and dual-therapy regimens with varying adherence patterns. Simulation results showed a surge in urinary uric acid occurs when dosing is restarted following missed doses. Very poor adherence results in negligible improvements in treatment success and increases the rate of episodic hyperuricosuria. Further research is needed into impact of adherence patterns on treatment success rate rates and kidney safety in order to better understand how dual-ULT could be optimally used in the treatment of hyperuricemia in patients with gout.

**Introduction**

Gout is a painful and disabling chronic disease which has proven difficult to treat and affects a large and increasing number of people.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). When treatment with a xanthine oxidase inhibitor (XOI) alone is unsuccessful, a uricosuric can be used in combination.2 The use of uricosurics for long-term therapy has been limited due 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.3

Because they increase the renal excretion of uric acid, uricosurics such as lesinurad, can cause hyperuricosuria (urinary excretion of uric acid ≥800 mg/day in men; ≥750 mg/day in women).4 High levels of urinary uric acid (uUA) can cause kidney damage which may be acute, such as stone formation (nephrolithiasis)5 and intrarenal obstruction (acute urate nephropathy), or chronic as in chronic (or gouty) nephropathy. Acute kidney injury can occur when uric acid concentrations in renal tubules reach supersaturation, which also depends on urine pH.6,7 Chronic nephropathy is thought to result from long-term hyperuricosuria which may be below supersaturation concentrations. The existence of chronic nephropathy remains controversial8, but is supported by animal models and some epidemiological studies.9 The harmful effects of uric acid 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 amongst the lowest of any chronic disease treatment11,12, 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 trials14–16, interruption in dosing (drug holiday) could result in high peaks in uUA concentration when treatment is restarted. Regular drug holidays, or poor implementation of the prescribed regimen17, may therefore increase the risk of renal adverse events caused by uric acid nephropathy.

This study aims to simulate the relation between poor implementation of dosing and efficacy, and to quantify the risk of hyperuricosuria in gout patients receiving dual- and mono-ULT.

**Results**

The combined set of PD parameters and corresponding between subject variabilities (BSV) 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 and lesinurad (Figure 1). 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, in the under-excreter the peak was at 39 mg/dl which exceeds the typical average concentration for a healthy person (30 mg/dl). For the overproducer the peak uUA concentration is 85 mg/dl which exceeds the threshold for typical average uUA concentration of an individual with hyperuricosuria (53 mg/dl). For under-excreters uUA concentrations after restarting treatment following an 8 day drug holiday could become supersaturated if the pH was acidic (pH<5.3; normal range 4.5-8). For overproducers, peak uUA concentrations after restarting treatment are expected to reach supersaturation at a higher pH of approximately 5.9.

Increasing the length of a drug holiday increases the proportion of patients whose daily amount of uric acid excreted exceeds the threshold for hyperuricosuria upon restarting treatment (Figure 2). The proportion of patients with hyperuricosuria increases with increasing doses of lesinurad and is greatest for lesinurad 400mg monotherapy. For under-excreters taking a 20 day drug holiday, the addition of 200mg lesinurad to 80mg febuxostat increased the percentage of patients experiencing hyperuricosuria form 0% to 1.4% and then to 3.1% with 400mg lesinurad. Drug holidays in overproducers taking ULTs very quickly lead to levels of hyperuricosuria in over 70% of patients. In both patient groups one- or two-day drug holidays are well tolerated compared to longer holidays with only moderate increases in the rates of hyperuricosuria.

After 120 days of treatment with perfect adherence, the proportion of patients treated to target (sUA ≤5mg/dL on day 120) is greater than was observed in the CRYSTAL trial (Figure 3). However, success rates fall rapidly as an increasing proportion of doses are missed at random. For febuxostat 80mg, febuxostat 80mg with lesinurad 200mg, febuxostat 80mg with lesinurad 400mg and lesinurad 400mg monotherapy, the success rates at 100% of doses taken are 87.2%, 94.5%, 96.0% and 15.4%, respectively. At 50% of doses taken at random, these success rates fall 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 results in higher rates of hyperuricosuria due to randomly occurring drug holidays, especially in the presence of a uricosuric (Figure 3). The baseline daily uUA excreted in under-excreters is below healthy baseline levels and none of the simulated cohort showed hyperuricosuria in the absence of ULT. For dual-ULT with a uricosuric, however, randomly occurring drug holidays resulted in increasing rates of hyperuricosuria. For example at 30% of doses taken, for febuxostat 80mg with lesinurad 200mg, febuxostat 80mg with lesinurad 400mg and febuxostat 400mg monotherapy the rates of hyperuricosuria are 1.3%, 3.2% and 4.9%, respectively

**Discussion**

The use of uricosurics, either as monotherapy or in combination with an XOI, results in transient increases in uUA concentrations when dosing is restarted after a drug holiday. This is predicted to raise the pH at which supersaturation of uric acid in urine could occur for a fixed volume of urine output, making supersaturation more likely. For a drug holiday from dual-ULTs this effect is likely to be greater than when starting treatment for the first time where, as per the regulatory approval of lesinurad, patients must already have been taking an XOI. Our simulations suggest that when uUA concentrations are at their peak the threshold for supersaturation is raised to 5.3 for under-excreters and 5.9 for overproducers, so that for a urinary pH at or below this level crystal formation may occur.

Increasing the length of a drug holiday increased the proportion of patients whose daily amount of uric acid excreted exceeded the threshold for hyperuricosuria. The addition of 200mg lesinurad to 80mg febuxostat increased the proportion of patients experiencing hyperuricosuria form 0% to 1.4% in under-excreters and from 68.8% to 72.1% in overproducers following a 20 day drug holiday. Treatment outcomes deteriorated rapidly as an increasing proportion of doses were missed at random. For under-excreters taking febuxostat 80mg with lesinurad 200mg efficacy fell from 94.5% to 42.6% and hyperuricosuria rose from 0% to 0.4%, when adherence reduced from 100% to 50%.

Approximately 90% of gout patients have hyperuricemia caused by the renal under-excretion of uric acid.18 In this case unless sUA concentrations are very high, or urinary volume is also lowered, these patients are likely to have uUA concentrations lower than healthy subjects. However, in simulations of drug holidays, after restarting dual-ULT these patients 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 would likely require either a very low urinary output volume or a low urine pH. Urine pH is the primary predictor of nephrolithiasis, since the solubility of uric acid is very sensitive to small changes in pH.19

Genetic disorders or a high-purine diet can be the cause of an overproduction of uric acid in the remaining 10% of gout patients.20 Hyperuricosuria is a defining feature of uric acid overproduction21 putting these patients at an increased risk of kidney injury without treatment. Our simulations suggest that in the case of very good medication adherence, 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 urinary uric output was raised above its already high baseline. For this reason uricosurics may not be appropriate for this patient group22, but no cautions are made in the label for lesinurad.23

To our knowledge this is the first study of the relationship between medication adherence and the efficacy and safety of dual-ULT therapy for the treatment of gout. This is 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.24 Our analysis benefits from having used a semi-mechanistic PD model which provides a level of complexity capable of capturing the non-steady state system dynamics. The effects of treatments have been investigated in two distinct patient subgroups; the cause of hyperuricemia being either an overproduction or under-excretion of uric acid. When comparing our simulation results with the findings from clinical trials, all of our perfect adherence simulations produced higher treatment success rates than was reported in trials. Treatment discontinuation was measured in the trial but the number of doses missed while patients continued on each treatment arm was not as far as we are aware.

The main limitation of this study was our reliance on different sources of data from different populations. This limited our ability to fully quantify the variability and co-dependencies, nonetheless, we consider the model to be representative of existing dual-ULTs. We assumed that non-renal clearance of uric acid, which is responsible for around a third of total excretion25, was negligible. The contribution of non-renal clearance relative to renal clearance will be less in scenarios where a uricosuric is taken. Finally, this paper has focussed 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 uricosurics (probenecid and benzbromarone).

With 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 adherence to treatment, under-dosing, variation in treatment response and the underlying cause of hyperuricemia.26 Adherence to ULTs is known to be amongst the lowest of any chronic disease treatment11,12 and studies provide evidence for both long27 and short28 drug holidays. This study shows that renal safety may also be compromised by poor medication adherence and highlights the need to improve adherence and adapt treatments to poorly adherent populations. This could include compliance instruction on drug labelling29, indicating a number of doses which can be missed based on the forgiveness of the drug to missed doses.30 Such measures may improve the safety profile of future uricosurics, which for lesinurad may have influenced reimbursement decisions.31

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 urinary uric acid output. However, regular drug holidays which are commonplace amongst 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 hyperuricemia due to overproduction of uric acid. Further research is needed into the impact of adherence patterns on treatment success rates and kidney safety in order to better understand how dual-ULT could be optimally used in the treatment of hyperuricemia in patients with gout.

**Methods**

*Strategy*

A semi-mechanistic pharmacokinetic-pharmacodynamic (PKPD) model, based on previous research on the systems pharmacology of the purine metabolic pathway32, was developed to capture the pharmacology of ULTs (Figure 4). The system was comprised of four compartments utilising a zero order production rate (k0) governing the formation of xanthine and first order production rates characterising its biotransformation to uric acid (k1) and the elimination of xanthine (k2) and uric acid (k3) into the urine. These in turn were parameterised in terms of volumes and clearance terms.

The PD model characterises the time course of sUA, uUA, xanthine and urinary xanthine. Two inhibitory indirect response models were used to account for the effect of multiple doses of febuxostat on k0 and k1. A stimulatory indirect response33 equation acting on the k2 rate parameter was incorporated to model the increased xanthine renal clearance associated with febuxostat.34 The clearance of uric acid upon multiple doses of lesinurad was modelled using a stimulatory indirect response equation acting on the k3 rate parameter.

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

*Pharmacokinetics*

Two-compartment models with first order absorption for febuxostat and lesinurad obtained from the literature35,36 were used to simulate typical and individual subject level drug plasma concentration time courses. The PK parameters, covariate effects and associated between subject variability are reproduced in Table 2.

*Pharmacodynamics*

1. Parameters obtained from literature

The mean rate of renal clearance of uric acid and xanthine (CLUA andCLX) in healthy volunteers, along with the between-subject variability, was obtained using summary data from a phase I dose-escalation study of 154 healthy volunteers receiving febuxostat.37 The reported average clearance in each group and standard deviations (supplementary material) were combined to estimate an overall population typical value and the between subject variability.

This trial also found that the rate of xanthine renal clearance in subjects taking febuxostat, even at doses as low as 10mg per day, increased 3- to 5-fold from baseline. This may result from saturation of active transport processes responsible for the reabsorption of xanthine from renal tubules.34 A step function was assumed using a stimulatory Emax drug function, presented below, where EC50,1 = 0.001 mg/dL (a low concentration associated with the 10mg dose), Emax,1 = 3 and CF(t) is the plasma concentration of febuxostat.

A previous PD model of lesinurad used a direct effect Emax model to relate steady-state average plasma concentration of lesinurad to the individuals’ sUA concentration.36 The parameters of the indirect model (Emax,2, EC50,2) were derived from those given in the published direct model ( and ) using the steady state equations38 (supplementary material). The published model includes a covariate effect of creatinine clearance on the maximum reduction in uric acid, . The stimulatory model drug function STIM2 is presented below, with parameters EC50,2 and Emax,2 and CL(t) is the plasma concentration of lesinurad.

CrCl is the individual’s creatinine clearance rate and E0 is the baseline sUA concentration of trial participants used to derive the direct Emax model parameters.

1. Estimated using statistical modelling

All other parameters were estimated using non-linear mixed effects modelling and febuxostat phase I trial summary data on daily area under the plasma concentration curve (AUC) and 24-hour urinary excretion of xanthine and uric acid.37 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 and the ADVAN6 routine for solving differential equations. The PD model was coded using the differential equations in Figure 4 where equations 3 and 4 correspond directly to published data on 24-hour urinary excretion.37 However, additional sUA and serum xanthine accumulation compartments were added to compute the area under the concentration curve at 24 hour 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 since the data points do not come from individual subjects. The inhibitory model drug functions INH1 and INH2 are of the form given below where CF(t) is the plasma concentration of febuxostat.

In order to simply 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 uric acid production.35 Rewriting uric acid production in the differential equations in our model as zero order the literature parameter estimate of 0.0239 mg/dl was assumed for IC50,2 and the remaining parameters were then estimated. In the second stage, the uric acid production was returned to being first order, such that it is a function of changing xanthine levels, and a new parameter estimate was made of IC50,2 with all other parameters fixed.

*Gout patient simulation model*

We assumed that the febuxostat pharmacodynamic parameters estimated for healthy volunteers could be applied to gout patients with hyperuricemia. 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 (standard deviation of 1.53) as this was the pre-treatment sUA concentration for patients in the CRYSTAL trial which compared febuxostat with lesinurad.39 We considered two phenotypes, overproducers and under-excreters of uric acid1, and modified the healthy subject system parameters accordingly. For overproducers, the amount of xanthine was scaled up and for under-excreters the clearance of uric acid was scaled down in proportion to the sUA concentration (Table 3). This assumes the same volumes of distribution of xanthine and uric acid for patients as for healthy subjects.

The model was used to simulate treatment with 120 days ULT in a hypothetical cohort of 1,000 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 lognormally distributed with mean and standard deviations taken from CRYSTAL.40 Creatinine clearance, calculated using the [Cockcroft-Gault](http://nephron.com/cgi-bin/CGSI.cgi) equation41, was reduced by 15 ml/min to better reflect the trial population CrCl. Variability of drug effects in INH1 and INH2 could not be estimated and the IC50 parameters were assumed to vary according to η3 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 on day 120) and the proportion of patients experiencing hyperuricosuria (uUA ≥800 mg/day on any day). The normal range of 24-hour volume of urine is 0.5-1 ml/kg/hr, but is likely to be lower in the elderly.42,43 On this basis a representative daily urine output for a 99kg male of 15dl has been assumed for the purpose of estimating uUA concentrations. The soluble limit for uric acid 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 data44 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 80mg monotherapy and lesinurad 400mg monotherapy, and febuxostat 80mg combined with either lesinurad 200mg or 400mg. 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 being a single drug holiday of increasing duration, from 1 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 between subject variability, and the results were averaged over the range of simulation results.

**Study Highlights**

WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

Uricosurics, used for the treatment of gout, increase the risk of hyperuricosuria and therefore also acute kidney injury. Medication adherence to urate lowering therapies for treating gout is amongst the worst of any chronic disease.

WHAT QUESTION DID THIS STUDY ADDRESS?

This is a study of how poor medication adherence to dual- and mono-urate lowering therapies could affect the renal excretion of uric acid and therefore the safety of these treatments.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?

Poor adherence, where patients return to treatment after a drug holiday, increases the rate of episodic hyperuricosuria when treatment includes a uricosuric.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS?

As poor medication adherence may compromise safety and efficacy of mono- and dual-urate lowering therapies, intervention to improve adherence or tailoring treatments to poorly adherence patients could be beneficial. Treatment with uricosurics may not be appropriate for certain patient groups, such as those with gout resulting from an overproduction of uric acid.

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**Author Contributions:** D.H.M., E.S. and S.M. developed the simulation models. D.H.M. performed the simulation modelling and wrote the manuscript. D.H., S.M. and S.L. provided technical support and edited the manuscript.

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**Figure legends**

Figure 1. Simulated urinary uric acid (uUA) concentration and estimated pH for uric acid supersaturation assuming a daily volume of urine of 15dl. The simulated uUA concentration over time (left-hand panel) and the estimated pH at which this concentration would become supersaturated (right-hand panel). Imperfect adherence modelled as an 8 day drug holiday. The shaded area represents the normal range for urine pH. The upper plots are the central estimates from the PKPD model for a gout patient with hyperuricemia from a reduced rate of uric acid clearance, and the lower plots for hyperuricemia due to overproduction xanthine.

Figure 2. Proportion of simulated patients with one-day hyperuricosuria following a single drug holiday taking place after one month of perfect adherence.

Figure 3. Treatment success rates (top row) and the proportion of patients experiencing one-day hyperuricosuria in two months of urate lowering therapy (ULT) (bottom row). Horizontal lines provide the reference response rates for this treatment arm from the CRYSTAL trial comparing febuxostat and lesinurad and study 303 for lesinurad 400mg monotherapy. Results are for under-excreters of uric acid only, for overproducers see the supplementary material. FBX: Febuxostat; LES: Lesinurad.

Figure 4. Diagrammatic and mathematical representations of the pharmacodynamics of dual-urate lowering therapy