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Response to Allopurinol and Febuxostat According to the Fractional Excretion of Urate in Men With Gout

Pascal Richette,[1,2] Anouk Walter-Petrich,[3,4] Quang Dinh Nguyen,[5] Matthieu Resche-Rigon,[3,4] Quang Huy Dinh Nguyen,[5] Minh Duc Do,[6] Thao Phuong Mai,[6] Tuan Duc Nguyen,[6] Fernando Perez-Ruiz,[7] Emmanuel Letavernier,[8,9] Tristan Pascart,[10] Augustin Latourte,[1,2] Hang Korng Ea,[1,2] and Thomas Bardin[1,2]

Objective. Body mass index (BMI), glomerular filtration rate (GFR), and pretreatment urate levels have been reported to influence the urate-lowering response to allopurinol. We investigated whether the fractional excretion of uric acid (FEUA) also modulates this response and relates to oxypurinol concentrations. We further evaluated its potential influence on febuxostat, not as a direct comparison, but to determine whether the effect of FEUA was specific to allopurinol.

Methods. The data are from n = 1,547 and n = 296 patients starting allopurinol and febuxostat, respectively. The relationship between FEUA (≤5.5% or >5.5%) and the dose response to allopurinol or febuxostat was assessed by linear mixed-effects regression models on serum urate levels and adjusted for BMI, estimated GFR (eGFR), and treatment doses. Concentrations of oxypurinol were measured in a subgroup of patients (n = 181). A multiple linear regression model was used to assess the association between FEUA and oxypurinol concentrations, adjusted for BMI, eGFR, allopurinol dosage, and serum urate levels.

Results. The median FEUA in the whole population was 4.0% (quartile 1–3: 3%–5.1%). The changes in serum urate levels for each 150-mg increase in allopurinol in patients with FEUA ≤5.5% or >5.5% were −72.37 (confidence interval [CI] −74.81 to −69.94) µM and −65.96 (CI −71.29 to −60.62) µM, respectively (P = 0.032). We found higher oxypurinol concentrations in patients with the lowest FEUA (P = 0.032). However, we did not observe any interaction between the febuxostat response and FEUA (P = 0.13).

Conclusion. Allopurinol is more effective in patients with low FEUA, probably because of the reduced renal excretion of oxypurinol. These data highlight the similarity between the renal handling of oxypurinol and urate.

INTRODUCTION

Allopurinol, an analog of hypoxanthine, is the recommended first-line medication for most people with gout.[1] After ingestion, approximately 80% to 90% of allopurinol is rapidly metabolized to oxypurinol, which is almost completely eliminated by the kidneys. Both allopurinol and oxypurinol inhibit xanthine oxidoreductase, the enzyme responsible for converting hypoxanthine to xanthine and xanthine to urate, primarily in the liver.[2]

There is considerable interindividual variability in response to allopurinol. Several clinical factors have been reported to be associated with a better response to allopurinol, including low body mass index (BMI), poor renal function as measured by the estimated glomerular filtration rate (eGFR), and high pretreatment urate levels.[3] Heritability might also influence the response to

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[1]Pascal Richette, MD, PhD, Augustin Latourte, MD, PhD, Hang Korng Ea, MD, PhD, Thomas Bardin, MD: Hôpital Lariboisière, Université Paris Cité, Assistance Publique Hôpitaux de Paris, Paris, France; [2]Pascal Richette, MD, PhD, Augustin Latourte, MD, PhD, Hang Korng Ea, MD, PhD, Thomas Bardin, MD: Hôpital Lariboisière, Université Paris Cité, INSERM U1132, Paris, France; [3]Anouk Walter-Petrich, PhD, Matthieu Resche-Rigon, MD, PhD: Hôpital Saint-Louis, Université Paris Cité, Assistance Publique Hôpitaux de Paris, Paris, France; [4]Anouk Walter-Petrich, PhD, Matthieu Resche-Rigon, MD, PhD: ECSTRRA team, UMR U1342, INSERM, Université Paris Cité, Paris, France; [5]Quang Dinh Nguyen, BSc, Quang Huy Dinh Nguyen, BSc: Vien Gut Medical Clinic, Ho Chi Minh City, Vietnam; [6]Minh Duc Do, MD, PhD, Thao Phuong Mai, MD, Tuan Duc Nguyen, MD: University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam; [7]Fernando Perez-Ruiz, MD, PhD: Medicine and Nursery School, University of the Basque Country, Basque Country, Spain; [8]Emmanuel Letavernier, MD, PhD: Hôpital Tenon, Sorbonne Université, Assistance Publique Hôpitaux de Paris, Paris, France; [9]Emmanuel Letavernier, MD, PhD: INSERM, UMR S 1155, Paris, France; [10]Tristan Pascart, MD, PhD: Hôpital Saint-Philibert, Université Lille Catholique, Lomme, France.

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Address correspondence via email to Pascal Richette, MD, PhD, at pascal.richette@aphp.fr.

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SIGNIFICANCE & INNOVATIONS

- Body mass index and renal function are two factors known to influence the response to allopurinol.
- We show that the fractional excretion of urate acid is also a variable that modulates the response to allopurinol.

allopurinol: the presence of the lysine (K) allele of ABCG2, a urate transporter expressed in the kidney but also in the intestine and the liver, has been reported to be associated with a reduced effect of allopurinol in some studies,[4,5] but not all.[6,7]

At the kidney level, two main factors influence the urate levels. The eGFR determines the filtered urate load, whereas the fractional excretion of uric acid (FEUA) reflects tubular secretion and reabsorption. Although largely independent when renal function is preserved, FEUA may increase as eGFR declines in advanced chronic kidney disease as a compensatory mechanism for urate excretion by residual nephrons or the involvement of intestinal urate excretion.[8–11]

Because renal underexcretion of urate, as defined by an FEUA ≤5.5%,[8,12] is the dominant cause of hyperuricemia in 80% to 90% of patients with gout,[1] studies have investigated the influence of FEUA on the response to uricosuric agents, particularly benzbromarone. Overall, these studies showed that patients with a low FEUA, that is, less than 5.5%, respond better to benzbromarone than patients with a higher FEUA do.[13]

Very few studies have investigated the effect of FEUA on the response to allopurinol.[14] Studies have shown that uricosurics increase the clearance of oxypurinol[15–17] because it is likely a substrate for URAT1, as is urate.[18]

We hypothesized that a low FEUA would enhance the urate-lowering response to allopurinol, independently of glomerular filtration, by reducing the renal clearance of oxypurinol. In contrast, because febuxostat is primarily metabolized in the liver, we hypothesized that its efficacy would not be influenced by FEUA.

Accordingly, the objective of this study was to assess whether FEUA modulates the hypouricemic effect of allopurinol or febuxostat. We also examined the relationship between FEUA and oxypurinol concentrations.

PATIENTS AND METHODS

Study population. Patients were recruited from the Vien Gut Medical Center, an outpatient clinic for people with gout for whom clinical, biologic, and imaging data are collected at each visit, according to a predefined protocol. For this study, we analyzed data from newly diagnosed patients between June 2017 and January 2023 for whom we had at least one month of follow-up of urate-lowering therapy (ULT). Gout was diagnosed according to the American College of Rheumatology/EULAR criteria.[19] We excluded women from the study population because the number of women among newly diagnosed patients was very low (n = 30) and because sex is associated with FEUA in different ethnic groups.[20]

This study was approved by the ethics committee of the University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam. Written informed consent was obtained from all participants. The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Treatment with xanthine oxidase inhibitors. All patients were started on a xanthine oxidase inhibitor with a treat-to-target strategy as follows: for those with an eGFR ≥60 mL/min/1.73 m^2, allopurinol was started at 150 mg/d (half a 300-mg tablet) for one month, and the dose was increased by 150 mg increment per month until the serum urate (SUA) target was <360 μM (60 mg/L) for two consecutive months. For patients with tophi, urate arthropathies, or more than six flares per year, the SUA target was <300 μM (50 mg/L). In patients with an eGFR <60 mL/min/1.73 m^2, febuxostat was started at 40 mg/d, with monthly increments of 40 mg until the urate target was achieved, up to 120 mg/d. Prophylactic colchicine (0.5–1 mg/d) was prescribed during the first months of the study. The median length of follow-up was 4.1 months (95% confidence interval [CI] 3.9–4.4).

Demographics and laboratory tests. Data on gout features and comorbidities, SUA levels, serum creatinine levels, and eGFR were collected before the initiation of ULT. SUA levels were monitored monthly until the urate target was obtained. The eGFR was estimated by the Modification of Diet in Renal Disease equation. The FEUA was calculated as (UUA × Pcr)/(PUA × Ucr) × 100, expressed as a percentage, where U and P represent the urinary and plasma concentrations, respectively; PUA represents the SUA levels; and cr represents the creatinine level. It is the ratio of urate clearance to creatinine clearance. The FEUA was determined by using spot-urine samples, as it has been demonstrated to be a valid method,[21] not different from the FEUA estimated by using 24-hour urine collection, which is very difficult to obtain for many patients.

Measurement of plasma oxypurinol and allopurinol concentrations. Among the study population, oxypurinol and allopurinol assays were available for 187 patients. A 50-μL solution of 40-μg/mL acyclovir was added to 500 μL of plasma from the patient sample and vortexed for 10 seconds. Then, 250 μL of a solution of 10% perchloric acid was added, and the mixture was vortexed for one minute. The sample was centrifuged at 17,000 revolutions per minute at 20°C for 10 minutes. Finally, the sample was filtered through a 0.22-μm filter and injected into the chromatographic system. The concentrations of allopurinol and oxypurinol in the plasma samples were identified via LC software from Shimadzu (Kyoto, Japan). Concentrations of oxypurinol and allopurinol were determined one month and two months after the initiation of allopurinol. Blood samples were taken on

average four hours after the morning dose of allopurinol. Among the 187 patients, n = 6 were excluded from the analysis because the plasma oxypurinol concentration was <3 mg/L (20 μM), a low concentration suggesting that these patients were not adherent to treatment, as previously reported.[3]

Statistical analysis. Categorical variables are described as frequencies (percentages); continuous variables are described as medians and interquartile ranges. Comparisons of continuous data were performed using the nonparametric Wilcoxon rank sum test. For comparisons of binary data, Fisher exact test was used.

Associations between FEUA and clinical or biochemical variables were first assessed using univariate logistic regression models. Variables significantly associated with FEUA ($P < 0.05$) in the univariate analysis were then entered into a multivariate logistic regression model to identify independent predictors of FEUA ≤5.5%. The interaction between FEUA and the dose response to either allopurinol or febuxostat (ie, lowering SUA levels) was assessed using linear mixed-effects regression models for urate levels, including a random intercept for patients to account for repeated measurements. The models were adjusted for BMI, eGFR, and treatment doses as fixed effects.

Subgroup analyses were performed with treatment-by-subset interactions tested using the Gail and Simon statistics, a method that analyzes qualitative interactions between treatment effects and patient subgroups.[22] An FEUA cutoff of 5.5% was used, as was done in several studies conducted in Asia.[8,12,23] To further assess whether FEUA provided information independent of eGFR, we also tested for collinearity between FEUA and eGFR using correlation analyses and variance inflation factors.[24]

A linear mixed-effects model for oxypurinol concentrations was used to assess the association between FEUA and oxypurinol concentrations, with a random intercept for patients to account for repeated measures, and adjusted for BMI, eGFR, allopurinol dosage, and SUA levels as fixed effects.

Because treatment allocation was based on renal function (allopurinol in patients with eGFR ≥60 mL/min/1.73 m^2 and febuxostat in those with eGFR <60 mL/min/1.73 m^2), the study was not designed to compare outcomes between the two drugs. All the tests were two sided, with $P \leq 0.05$ considered statistically significant. Statistical analyses were performed via R version 4.2.1 (The R Foundation, https://www.R-project.org/).

RESULTS

Demographic characteristics. The data are from 1,843 male patients who were newly diagnosed with gout and started ULT. Among these patients, 1,547 patients received allopurinol, and 296 received febuxostat. The demographic characteristics of the study population are shown in Table 1. The median (quartile 1–3 [Q1–Q3]) age of patients treated with allopurinol was 45 (38–53) years, with a median BMI of 24.7 (22.8–27) kg/m^2. In these patients, the median SUA level was 543 (464–613) μM, and the median eGFR was 95 (83–106) mL/min/1.73 m^2. Patients treated with febuxostat were older, had lower eGFR, were more likely to have diabetes or hypertension, and had higher SUA levels (all P values < 0.001).

FEUA in the study population. Before the initiation of ULT, the median (Q1–Q3) FEUA in the whole population was 4.0% (3%–5.1%; Figure 1A). It was slightly greater in patients receiving febuxostat who had lower renal function than in those receiving allopurinol: 4.4% (3.2%–6%) and 4.0% (3%–5%), respectively ($P < 0.0001$; Figure 1B).

According to the univariate analysis, an FEUA ≤5.5% was associated with higher eGFR, BMI, and triglyceride levels, and it was associated with younger age (all P values < 0.001). There was no association between FEUA and low-density lipoprotein cholesterol levels (Supplementary Table 1). Age (odds ratio [OR] 0.98 [95% CI 0.96–0.99], $P = 0.0002$) and eGFR (OR 1.01

Table 1. Baseline characteristics of patients treated with either allopurinol or febuxostat*

	Allopurinol (n = 1,547)	Febuxostat (n = 296)	*P* value
Age, y	45 [38–53]	57 [48–65]	<0.0001
BMI, kg/m^2	24.7 [22.8–27]	24.0 [21.8–26]	<0.0001
Comorbidities			
Chronic kidney disease	5 (0.3)	157 (53.2)	<0.0001
Type 2 diabetes	114 (7.4)	46 (15.5)	<0.0001
Hypertension	476 (30.8)	153 (51.7)	<0.0001
Cardiovascular diseases	1,022 (66.1)	234 (79.1)	<0.0001
Serum urate level, μM	543 [464–613]	561 [476.8–639.2]	0.007
eGFR, mL/min/1.73 m^2	95 [83–106]	59 [49–76.5]	<0.0001
LDL cholesterol, mmol/L	3.0 [2.4–3.7]	2.8 [2.2–3.6]	0.016
Triglycerides, g/L	2.5 [1.7–3.7]	2.3 [1.5–3.5]	0.017
FEUA, %	4.0 [3–5]	4.4 [3.2–6]	<0.0001

* Data are presented as medians [Q1–Q3] or numbers (percentages). CKD was defined as an eGFR less than 60 mL/min/1.73 m^2. Cardiovascular diseases include coronary artery diseases, heart failure, arrhythmia, and valvular heart disease. BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FEUA, fractional excretion of uric acid; LDL, low-density lipoprotein; Q, quartile.

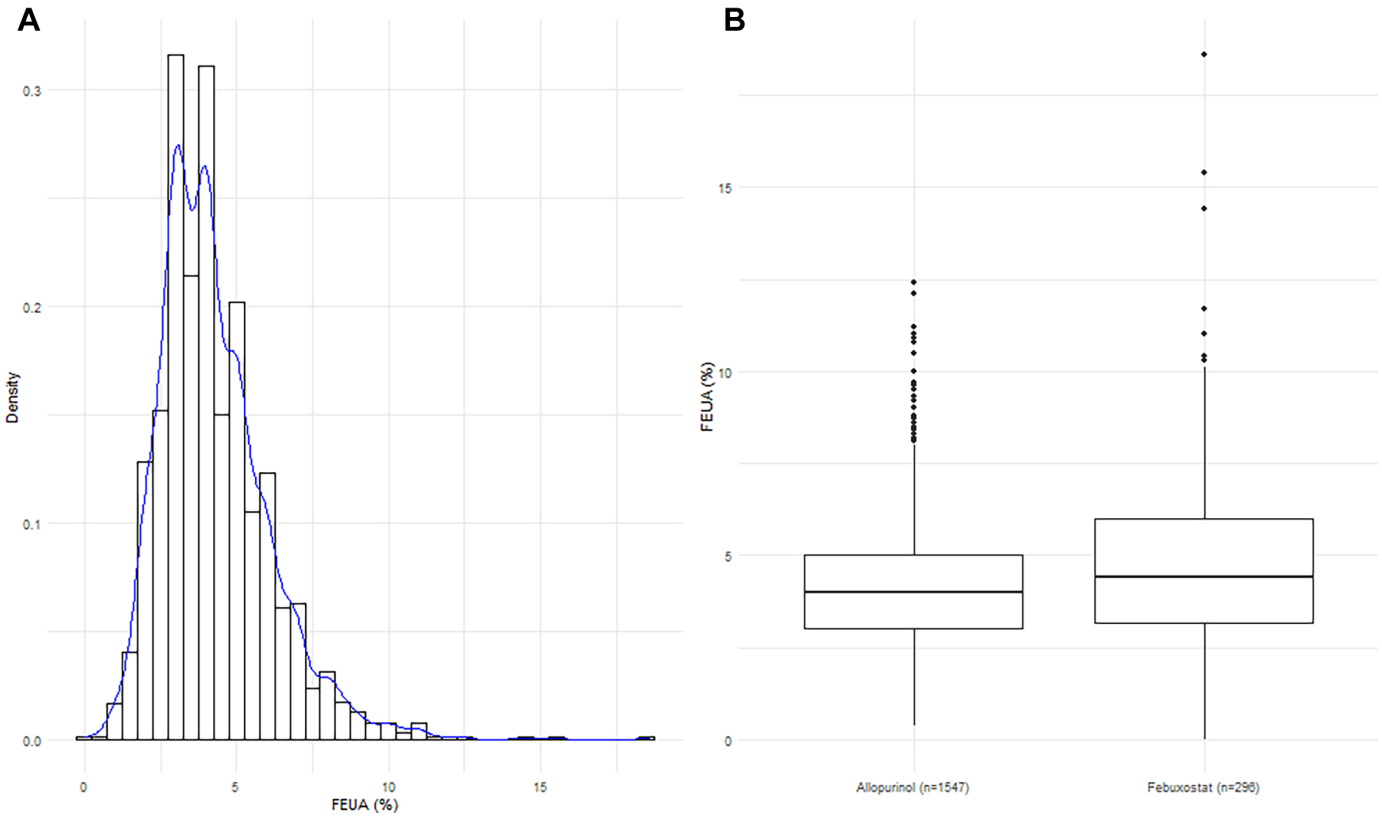

Figure 1. FEUA in the study population. (A) Distribution of the FEUA in 1,843 male patients with gout. (B) FEUA in patients who received allopurinol or febuxostat. FEUA, fractional excretion of uric acid.

[95% CI 1–1.02], P = 0.0008) were significantly associated with FEUA ≤5.5% in the multivariate model (Table 2), with a trend toward an association with triglyceride levels (OR 1.06 [95% CI 1.0–1.13], P = 0.064).

Response to allopurinol or febuxostat according to the FEUA. We then assessed the interaction between the FEUA and the hypouricemic effect of allopurinol. We found a significant interaction between FEUA and each 150-mg increment of allopurinol on reducing SUA levels (P = 0.032, adjusted for allopurinol, BMI, and eGFR; Table 3). The hypouricemic effect of allopurinol was more pronounced in patients with a low FEUA: the decreases in SUA levels for each 150-mg increment of allopurinol were −72.37 (CI −74.81 to −69.94) µM and −65.96 (CI −71.29 to −60.62) µM in patients with an FEUA ≤5.5% and an FEUA >5.5%, respectively (Figure 2A and Supplementary Table 2).

In contrast, we found no interaction between FEUA and febuxostat on reducing SUA levels (P = 0.13; Table 4). The association between the decrease in SUA levels for each 40-mg increment of febuxostat did not significantly differ across the two groups of patients defined by an FEUA ≤5.5% or >5.5% (Figure 2B and Supplementary Table 3). Variance inflation factors for all variables, including FEUA and eGFR, were below 2, indicating no collinearity in our models (Supplementary Figure 1).

Table 2. Multivariate analysis of factors associated with an FEUA ≤5.5%*

	OR (95% CI)	P value
Age, y	0.98 (0.96–0.99)	0.0002
BMI, kg/m^2	1.02 (0.99–1.06)	0.19
eGFR, mL/min/1.73 m^2	1.01 (1–1.02)	0.0008
Triglycerides, g/L	1.06 (1–1.13)	0.064

* BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FEUA, fractional excretion of uric acid; OR, odds ratio.

Table 3. Adjusted analysis of the effect of allopurinol on serum urate levels with a linear regression model (n = 1,537 patients)*

Variables	Beta	95% CI	P value
FEUA > 5.5%	−39.93	−53.27 to −26.59	<0.0001
Allopurinol (each 150 mg)	−72.37	−74.81 to −69.94	<0.0001
BMI, kg/m^2	3.75	2.56 to 4.95	<0.0001
eGFR, mL/mn/1.73 m^2	−0.26	−0.5 to −0.02	0.035
FEUA > 5.5% × allopurinol interaction	6.46	0.33 to 12.59	0.032[a]

* BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FEUA, fractional excretion of uric acid.
[a] Gail and Simon interaction test.

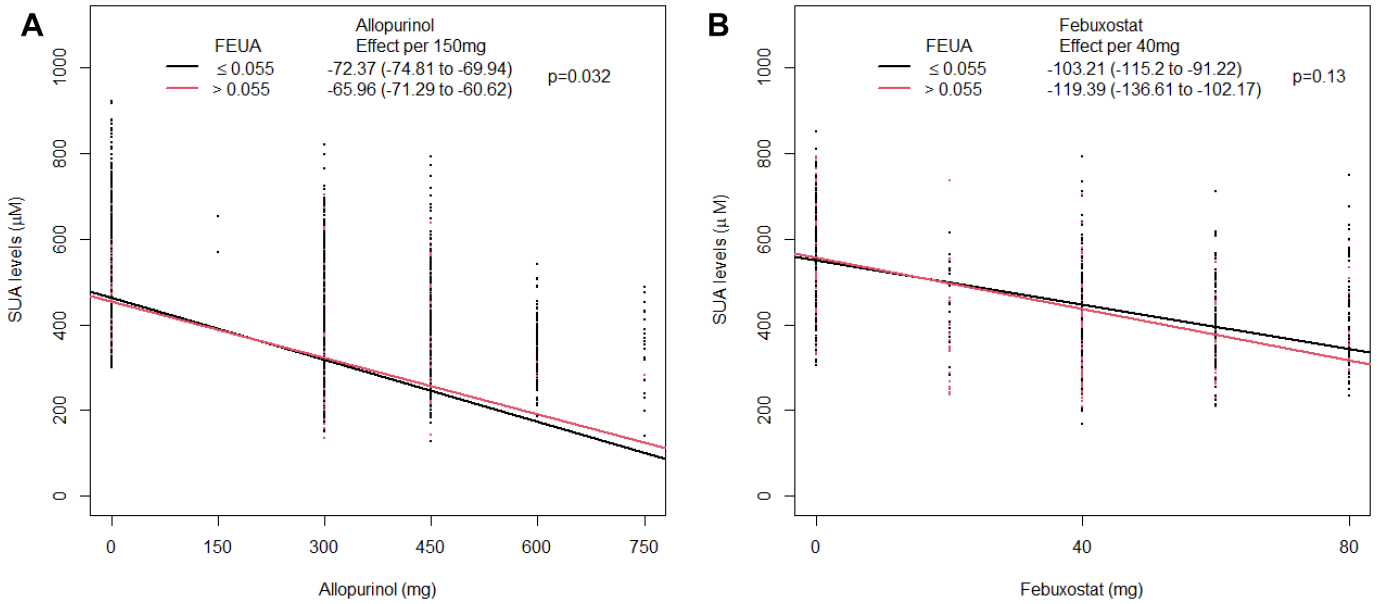

Figure 2. FEUA and response to xanthine oxidase inhibitors. (A) Response to allopurinol according to the FEUA. (B) Response to febuxostat according to the FEUA. FEUA, fractional excretion of uric acid; SUA, serum urate.

Relationship between oxypurinol concentrations and the FEUA. To explain the relationship we observed between an FEUA ≤5.5% and a better response to allopurinol, we evaluated the concentrations of oxypurinol, an active metabolite of allopurinol (Supplementary Table 4), according to the FEUA, in a subgroup of patients (n = 181). These patients had a median BMI of 24.7 (Q1–Q3: 22.5–27.2) kg/m^2 and a median eGFR of 93 (Q1–Q3: 79–106) mL/min/m^2. Only two patients took diuretics. We found a significant association between lower FEUA and higher oxypurinol concentrations (P = 0.032, adjustment for BMI, eGFR, allopurinol dosage, and SUA levels). There was a strong association between the concentrations of allopurinol and oxypurinol (P < 0.0001; Supplementary Table 5).

DISCUSSION

This study identified FEUA as a new covariate that modulated the hypouricemic effect of allopurinol. Although statistically significant, the difference in the hypouricemic effect of allopurinol according to FEUA was modest and of uncertain clinical relevance. Nevertheless, this finding reinforces the concept that the renal mechanisms regulating urate and oxypurinol handling are quite similar. A low FEUA was associated with a better response to allopurinol, independent of the GFR and BMI, which was likely due to a decrease in oxypurinol renal clearance. Although FEUA and eGFR were modestly associated, there was no collinearity supporting the independent contribution of FEUA beyond glomerular filtration to the response to allopurinol.

Table 4. Adjusted analysis of the febuxostat effect on serum urate levels via a linear regression model (n = 291 patients)*

Variables	Beta	95% CI	*P* value
FEUA > 5.5%	−39.76	−67.04 to −12.48	0.004
Febuxostat (each 40 mg)	−103.21	−115.2 to −91.22	<0.0001
BMI, kg/m^2	1.34	−1.48 to 4.16	0.35
eGFR, mL/mn/1.73 m^2	−0.74	−1.2 to −0.29	0.001
FEUA > 5.5% × febuxostat interaction	−15.26	−36.56 to 6.04	0.13[a]

* BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; FEUA, fractional excretion of uric acid.
[a] Gail and Simon interaction test.

The kidney is responsible for the majority of urate excretion in humans.[1] Renal excretion of urate is dependent on both the filtered urate load and the fraction of the filtered load that is eliminated in the urine, that is, the FEUA,[9,25] which is under the control of multiple urate transporters in the proximal tubule.[26]

We observed that the influence of FEUA on the allopurinol response is independent of the glomerular function. Although eGFR determines the filtered load of oxypurinol, FEUA captures the balance between secretion and reabsorption in the tubule, which critically shapes oxypurinol clearance. Thus, the improved hypouricemic response in patients with low FEUA, albeit modest, likely reflects increased tubular reabsorption of oxypurinol rather than decreased glomerular filtration.

Several factors have been reported to lower the FEUA and are therefore risk factors for hyperuricemia and gout. Heredity, which plays a key role in the genesis of the disease,[27] is undoubtedly one of the most important. Indeed, several SUA-associated single nucleotide polymorphisms have been reported to be associated with a lower FEUA,[28] notably at the *SLC2A9* locus, with differences depending on ethnicity groups.[20] In contrast, the Q141K variant of *ABCG2* has not been found to be associated with FEUA

variations[9] but might modify the response to allopurinol, although the data are conflicting. Other clinical variables reported to influence FEUA are male sex and BMI.[20] We did find an association between BMI and FEUA ≤5.5% in the univariate analysis, which was no longer significant in the multivariate analysis, suggesting an indirect effect of BMI on FEUA. Notably, a study conducted in people with overweight and obesity revealed that this association was observed only when urate levels increased following a fructose load.[29]

The doses of allopurinol needed to lower the SUA levels below 360 μM vary from one individual to another and depend on clinical and biologic factors. According to a recent study, these factors include ethnicity, BMI, pretreatment SUA levels, and renal function.[6] In contrast to what has been reported in previous studies,[3,30] neither the *ABCG2* genotype (rs2231142) nor the presence of diuretics were predictors of allopurinol efficacy in more recent papers.[6,7]

Multivariate analysis revealed that the hypouricemic effect of allopurinol was greater in patients with a low FEUA, that is, less than ≤5.5%, independent of BMI and kidney function. These data suggest that the mechanisms involved in the tubular secretion and excretion of urate could also modify the pharmacokinetics of allopurinol, independent of the GFR.

In contrast, we found no interaction between febuxostat and FEUA, a result that was expected because febuxostat is metabolized mainly in the liver and is virtually not eliminated by the kidneys. In line with our findings, Qi et al reported that the response to febuxostat, as assessed by the percentage of patients achieving SUA levels of less than 360 μM, was identical in patients with an FEUA ≥5.5% or <5.5%.[31]

Because the renal elimination of oxypurinol is the most important aspect of the pharmacokinetics of allopurinol,[15] we explored the association between FEUA and oxypurinol concentrations. We found that oxypurinol concentrations were higher in patients with a low FEUA, independent of BMI, eGFR, allopurinol dosage, and SUA levels. This is probably because the oxypurinol filtered at the glomerulus is then largely reabsorbed by the proximal tubules.

The mechanisms underlying the renal elimination of oxypurinol in patients with gout have not been extensively studied. Unlike allopurinol, which has a very short half-life of one hour, the half-life of oxypurinol is approximately 23 hours.[15] The finding that the renal clearance rate of oxypurinol was lower than the GFR but two to three times greater than that of urate led to the hypothesis that oxypurinol could be reabsorbed by renal tubules, such as urate.[32] This hypothesis was further supported by the observation of an increase in renal clearance of oxypurinol by uricosurics in patients with gout[15,16,33] but also in Dalmatian dogs.[32] In this breed of dog, urate excretion equals or exceeds the GFR because of a mutation in the *SLC2A9* gene, which codes for the urate transporter GLUT9,[34] explaining why renal urate reabsorption is lost almost entirely.[34]

It was subsequently shown that oxypurinol is a substrate of URAT1, highlighting the similarity in the renal handling of urate and oxypurinol. Thus, URAT1 might play a key role in the renal reabsorption of oxypurinol to the difference of OAT4, which seems to not be involved in this process.[18] Other studies have suggested that GLUT9 may also transport oxypurinol.[33,35]

Our study has limitations that must be considered. We recognize that the difference in the magnitude of the hypouricemic effect of allopurinol according to the FEUA is not large, so the clinical relevance at the individual level of this result is unknown. Our study population did not include women, which is explained by the very low prevalence of women treated at the Vien Gut Medical Center. Therefore, it is not possible to generalize our results to all patients with gout. Furthermore, the phenotype of the patients in our study are different from those included in similar studies conducted notably in Oceania and the US[3,6,7,20]: overweight and obesity are rare in our study population. In addition, individuals treated with allopurinol in our study had a preserved renal function (eGFR ≥ 60 mL/min/1.73 m^2), which may restrict the generalizability of our findings to gout populations with a higher prevalence of chronic kidney disease, in which the relationships between FEUA, oxypurinol clearance, and allopurinol response may differ. It is therefore difficult to compare our results with those already published in this area. Lastly, the oxypurinol threshold of 3 mg/L that we used to define nonadherent patients is questionable, as this threshold varies according to patient characteristics that we did not take into account.[36] In conclusion, our study revealed that, in addition to the GFR, the FEUA is a renal parameter that influences the response to allopurinol but not to febuxostat.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Richette confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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