International Urology and Nephrology (2019) 51:467–473
https://doi.org/10.1007/s11255-018-2051-2

NEPHROLOGY - ORIGINAL PAPER

Comparison of renoprotective effects of febuxostat and allopurinol in hyperuricemic patients with chronic kidney disease

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Received: 26 September 2018 / Accepted: 7 December 2018 / Published online: 2 January 2019

Abstract

Purpose This study aimed to compare the renoprotective effect between febuxostat and allopurinol in hyperuricemic patients with chronic kidney disease (CKD), about which limited data are available.

Methods 141 patients with stage 3 CKD and hyperuricemia were followed from June 2005 to April 2018. Thirty patients received febuxostat, 40 allopurinol and 71 conventional CKD management only (control group). We compared the mean serum uric acid levels, estimated glomerular filtration rate (eGFR) changes over time and renal survival time free from predefined renal disease progression among these 3 groups.

Results Overall, mean age was 62.6 ± 13.3 years, baseline eGFR 42.1 ± 8.8 mL/min/1.73 m^2, and serum uric acid 8.6 ± 1.5 mg/dL without intergroup difference. During the observation period (55.9 ± 31.8 months), febuxostat group, compared to both allopurinol and control group, had significantly lower mean serum uric acid levels (5.7 ± 1.0 vs. 7.1 ± 1.2 vs. 8.0 ± 0.8 mg/dL, $p < 0.001$) and maintained significantly higher mean eGFR values consistently for 4 years. Febuxostat group had significantly longer renal survival time free from renal disease progression than allopurinol and control group (87.7 (95% CI 71.2–104.2) vs. 77.6 (95% CI 60.2–94.9) vs. 48.7 (95% CI 39.3–58.1) months, respectively, $p < 0.001$). Cox proportional hazard model analysis adjusting for potent confounders revealed that febuxostat, with control group as reference, significantly reduced the risk of renal disease progression by 74.3% (hazard ratio 0.257 (95% CI 0.072–0.912), $p = 0.036$), while allopurinol showed insignificant result.

Conclusions Febuxostat seems to reduce serum uric acid level and to retard renal disease progression more effectively than allopurinol in hyperuricemic patients with CKD.

Keywords Febuxostat · Allopurinol · Hyperuricemia · Renal insufficiency

Introduction

Hyperuricemia has gained much attention recently as an independent risk factor for renal disease progression. Uric acid increases blood pressure and promotes renal vasoconstriction by activating renin–angiotensin system and inhibiting the release of endothelial nitric oxide [1, 2]. Notably, hyperuricemia leads to rapid decline in kidney function [3]. In this regard, lowering serum uric acid levels in patients with chronic kidney disease (CKD) appears to play a beneficial role in delaying progression of renal disease.

Although many studies [4–10] have evaluated the renoprotective effect of urate-lowering therapy (ULT) in hyperuricemic patients with CKD and supported its use in these patients, many clinical questions remain to be answered. One of the unanswered questions is which agent should be chosen when treating hyperuricemia in patients with CKD.

Allopurinol, a xanthine oxidase inhibitor, is a traditional urate-lowering agent that has long been used in patients with gout. It is generally tolerable and effectively lowers serum uric acid when used in proper doses. However, it has rare, but potentially lethal side effects such as hypersensitivity reactions including Stevens-Johnson syndrome [11]. This serious side effect is more common in patients with CKD, which makes physicians to hesitate to start or to escalate the dose of allopurinol in patients with CKD leading to insufficient control of hyperuricemia [12].

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Febuxostat was introduced in 2008 as an alternative agent to allopurinol. It inhibits xanthine oxidase more selectively and has more potent urate-lowering ability compared to allopurinol [13]. It is metabolized in the liver and excreted in feces and urine, making dose adjustment not required in patients with mild to moderate renal impairment [14]. Moreover, it was safe in most patients with gout who experienced severe cutaneous adverse event attributed to allopurinol [15].

Currently, a few studies [16–19] compared febuxostat with allopurinol with results favoring febuxostat. However, the observation period was relatively short (1–6 months) to observe the progression of renal disease, and additional long-term data are needed to clarify this issue. This study evaluated and compared the renoprotective effects of allopurinol and febuxostat in hyperuricemic patients with CKD in the long-term reaching 5 years in a real world setting.

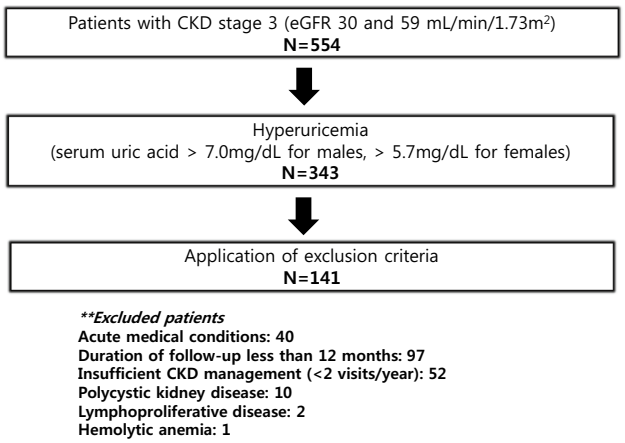

Fig. 1 Flow diagram of patient selection

Methods

Study subjects

We retrospectively reviewed the medical records of adult patients (> 18 years old) with CKD stage 3 defined as glomerular filtration rate between 30 and 59 mL/min/1.73 m^2 [20] and with hyperuricemia (serum uric acid level > 7.0 mg/dL for males, > 5.7 mg/dL for females) [21], who were managed and followed up longer than 12 months at Dongguk University Ilsan Hospital from June 2005 to April 2018. Patients with the following conditions were excluded: (1) acute medical conditions that affect kidney function; (2) acute kidney injury; (3) non-renal conditions associated with hyperuricemia (psoriasis, hemolytic anemia, lymphoproliferative disease, and rhabdomyolysis); (4) polycystic kidney disease, a disease in which no effective treatment exists to prevent disease progression; and (5) insufficient CKD management defined as less than 2 hospital visits per year. After searching for eligible patients based on inclusion and exclusion criteria in the electronic medical record system, we finally identified 141 eligible cases. A flow diagram of patient selection is shown in Fig. 1.

ULT

Of the 141 patients, 70 received ULT during the observation period. Thirty patients received febuxostat with 26 switching from allopurinol (febuxostat group). Sixteen (53.3%) patients received 40 mg/day, 12 (40%) patients 80 mg/day, and 2 (6.7%) patients 20 mg/day. The mean maintenance dose of febuxostat was 54.6 ± 21.6 mg/day. Forty patients received allopurinol throughout the observation period (allopurinol group). Twenty-two (55%) patients received 100 mg/day, 14 (35%) patients 200 mg/day, and 4 (10%) patients 300 mg/day; the mean maintenance dose of allopurinol being 164.0 ± 76.3 mg/day. The remaining 71 patients received conventional CKD management only (non-ULT group).

Study outcomes

We investigated baseline patient characteristics including age, sex, duration of follow-up, serum uric acid level and factors associated with renal disease progression such as proteinuria, blood pressure and etiologies of CKD. We assessed and compared the mean serum uric acid level, mean change of serum uric acid from baseline and mean estimated glomerular filtration rate (eGFR) calculated by CKD Epidemiology Collaboration (CKD-EPI) creatinine equation [22] at 1, 2, 3, 4 years after baseline and at the last follow-up between the 3 groups. We also compared the mean renal survival time free from renal disease progression defined as eGFR decline greater than 30% of baseline value, eGFR < 15 mL/min/1.73 m^2 or initiation of dialysis between the three groups and estimated the hazard ratio (HR) of febuxostat and allopurinol on the risk of renal disease progression with control group as reference after adjusting for potent confounders.

Statistical methods

Using SPSS version 19.0, we compared continuous variables with normal distribution by one way ANOVA test with Bonferroni as post-hoc analysis and categorical variables with chi square test between the three groups. Kaplan–Meier survival analysis was performed to compare renal survival free from renal disease progression between the three groups. Cox proportional hazard model was used to adjust potential confounders and to estimate the HR of ULTs on the risk of renal disease progression.

Compliance with ethical standards

This study was approved by the institutional review board (IRB) of Dongguk University Ilsan Hospital. Informed consent was waived by the IRB due to the retrospective nature of this study (IRB number 2015-64).

Results

Baseline patient characteristics

Overall, mean age was 62.6 ± 13.3 years, 80.9% were males, mean eGFR was 42.1 ± 8.8 mL/min/1.73 m^2, and the mean duration of follow-up was 55.9 ± 31.8 months. Diabetic and hypertensive nephropathy were the most common etiologies of CKD. There were no significant differences in baseline characteristics between the three groups except that gout patients were not included in the control group. Baseline values are presented in Table 1.

Renal outcomes

Overall outcome

During the observation period, renal disease progression occurred in 67/141 (47.5%) patients and 33/141 (23.4%) patients started dialysis; 8/141 (5.7%) patients died, and 1 patient experienced drug eruption probably triggered by the use of allopurinol and switched to febuxostat.

Uric acid and eGFR changes over time

Mean serum uric acid in febuxostat group was significantly lower than allopurinol and non-ULT group (5.7 ± 1.0 vs. 7.1 ± 1.2 vs. 8.0 ± 0.8 mg/dL, $p < 0.001$) and the mean serum uric acid change from baseline in febuxostat group was also significantly greater than the remaining two groups (−4.8 ± 1.9 vs. −2.5 ± 2.5 vs. −0.49 ± 1.88 mg/dL, $p < 0.001$). Mean eGFR values at 1, 2, 3, 4 years and at the last follow-up in febuxostat group was significantly higher than those of allopurinol and control group. Allopurinol group also had significantly lower mean serum uric acid level and greater serum uric acid change from baseline than non-ULT group, but the eGFR values were significantly higher than non-ULT group only at 2 years and at the last follow-up (Table 2).

Renal survival free from renal disease progression

Kaplan Meier survival analysis revealed that febuxostat group had significantly longer renal survival time free from renal disease progression than allopurinol and non-ULT group (87.7 (95% CI 71.2–104.2) vs. 77.6 (95% CI 60.2–94.9) vs. 48.7 (95% CI 39.3–58.1) months,

Table 1 Baseline patient characteristics

	Overall ($n = 141$)	Febuxostat ($n = 30$)	Allopurinol ($n = 40$)	Non-ULT ($n = 71$)	p-value
Age (mean ± SD, years)	62.6 ± 13.3	64.3 ± 13.1	62.3 ± 14.6	62.0 ± 12.8	0.731
Male sex [number (%)]	114 (80.9)	27 (90.7)	35 (87.5)	52 (73.2)	0.067
Duration of follow-up (mean ± SD, months)	55.9 ± 31.8	44.9 ± 31.3	59.3 ± 32.1	58.6 ± 31.1	0.101
eGFR (mean ± SD, mL/min/1.73 m^2)	42.1 ± 8.8	45.4 ± 8.3	41.9 ± 9.5	40.8 ± 8.5	0.059
Etiology of CKD [number (%)]					0.286
Diabetic	69 (48.9)	13 (43.3)	16 (40)	40 (56.3)	
Hypertensive	42 (29.8)	9 (30)	15 (37.5)	18 (25.4)	
Glomerulonephritis	11 (7.8)	1 (3.3)	6 (15)	4 (5.6)	
Miscellaneous	5 (3.5)	1 (3.3)	1 (2.5)	3 (4.2)	
Unknown	14 (9.9)	6 (20)	2 (5)	6 (8.5)	
*Proteinuria (*n*/*n* of available cases (%))	42/98 (42.8)	6/14 (42.9)	9/24 (37.5)	27/60 (45%)	0.821
Serum uric acid (mean ± SD, mg/dL)	8.6 ± 1.5	8.7 ± 1.6	9.0 ± 1.5	8.3 ± 1.3	0.055
Gout [number (%)]	36 (25.5)	18 (60)	18 (45)	0 (0)	< 0.001
BMI (mean ± SD, kg/m^2)	25.0 ± 3.8	25.3 ± 3.1	25.6 ± 3.8	24.5 ± 4.0	0.345
SBP (mean ± SD, mmHg)	136.1 ± 19.3	129.9 ± 15.4	134.3 ± 20.1	139 ± 19.8	0.128
DBP (mean ± SD, mmHg)	78.6 ± 12.3	77.8 ± 12.3	78.3 ± 11.4	79.1 ± 13.3	0.907
Use of antihypertensive agent [number (%)]	130 (92.1)	25 (83.3)	37 (94.9)	68 (95.8)	0.072

ULT urate-lowering therapy, *SD* standard deviation, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

*Proteinuria = urine dipstick test ≥ 1 +

Table 2 Changes of serum uric acid and eGFR values throughout observation period

Outcomes	Febuxostat ($n=30$)	Allopurinol ($n=40$)	Non-ULT ($n=71$)	p-value*	*Bonferroni***
Mean serum uric acid (mean ± SD, mg/dL)	5.7 ± 1.0 *a*	7.1 ± 1.2 *b*	8.0 ± 0.8 *c*	< 0.001	*a* < *b*, *a* < *c*, *b* < *c*
Serum uric acid change from baseline (mean ± SD, mg/dL)	− 4.8 ± 1.9 *d*	− 2.5 ± 2.5 *e*	− 0.49 ± 1.88 *f*	< 0.001	*d* > *e*, *d* > *f*, *e* > *f*
eGFR at 1 year after baseline (mean ± SD, mL/min/1.73 m^2, number of available cases)	47.4 ± 12.6, $n=21$ *g*	39.6 ± 15.0, $n=34$ *h*	34.3 ± 10.8, $n=53$ *i*	< 0.001	*g* > *i*
eGFR at 2 years after baseline (mean ± SD, mL/min/1.73 m^2, number of available cases)	44.3 ± 10.4, $n=14$ *j*	39.3 ± 15.6, $n=28$ *k*	28.6 ± 12.9, $n=50$ *l*	< 0.001	*j* > *k*, *j* > *l*, *k* > *l*
eGFR at 3 years after baseline (mean ± SD, mL/min/1.73 m^2, number of available cases)	49.2 ± 13.5, $n=13$ *m*	35.7 ± 19.3, $n=28$ *n*	28.1 ± 14.9, $n=45$ *o*	0.001	*m* > *n*, *m* > *o*
eGFR at 4 years after baseline (mean ± SD, mL/min/1.73 m^2, number of available cases)	42.2 ± 15.7, $n=9$ *p*	25.4 ± 18.5, $n=21$ *q*	26.6 ± 16.5, $n=38$ *r*	0.037	*p* > *q*, *p* > *r*
eGFR at the last follow-up	45.8 ± 17.4 *s*	35.5 ± 20.0 *t*	23.4 ± 16.5 u	< 0.001	*s* > *t*, *s* > *u*, *t* > *u*

ULT urate-lowering therapy, *SD* standard deviation, *eGFR* estimated glomerular filtration rate

*p-value obtained through one way ANOVA test

**Multiple comparison by Bonferroni test

respectively, log rank test $p < 0.001$). Survival curves are illustrated in Fig. 2.

Cox proportional hazards regression analysis for renal disease progression

We performed Cox proportional hazards regression analysis in order to adjust for potential confounders including diabetes mellitus (DM), baseline proteinuria, baseline eGFR ($p = 0.059$), and baseline uric acid level ($p = 0.055$) and to estimate the HR of ULT on renal disease progression. Febuxostat significantly reduced the risk of renal disease progression by 74.3% (HR 0.257 (95% CI 0.072–0.912), $p = 0.036$) with non-ULT as reference, while allopurinol did not show significant risk reduction ($p = 0.788$, Table 3).

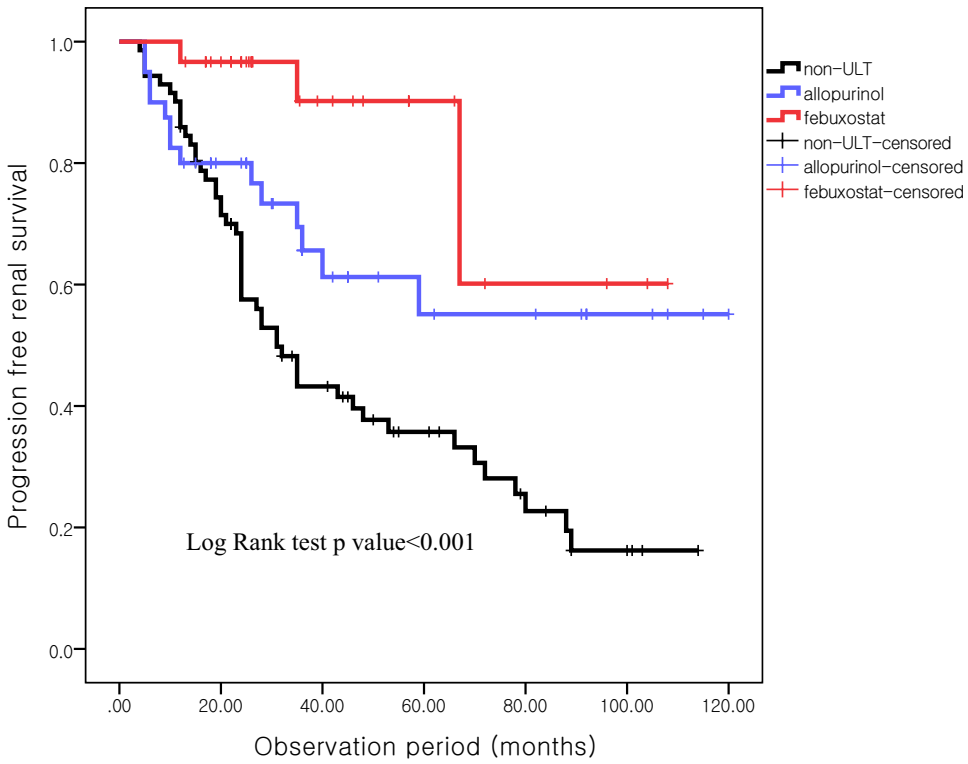

Fig. 2 Kaplan Meier survival curve about renal survival free from renal disease progression between febuxostat, allopurinol and non-ULT group

Table 3 Cox proportional hazards regression analysis of renal disease progression

Variables	B	Exp (B)*	95% CI for exp (B)		*p*-value
			Lower limit	Upper limit	
DM					
No (ref)					
Yes	0.332	2.301	1.201	4.406	0.012
Baseline proteinuria**					< 0.001
0 (ref)					
1 +	1.262	3.533	1.120	11.145	0.031
2 +	1.717	5.569	2.659	11.664	< 0.001
3 +	3.767	43.238	11.193	167.018	< 0.001
4 +	2.170	8.762	3.225	23.809	< 0.001
ULT					
Non-ULT (ref)					
Allopurinol	0.106	1.112	0.514	2.406	0.788
Febuxostat	− 1.358	0.257	0.072	0.912	0.036
Baseline eGFR					
< 45 mL/min/1.73 m^2 (ref)	− 0.524	0.592	0.273	1.283	0.184
≥ 46 mL/min/1.73 m^2					
Baseline uric acid					0.101
< 8 mg/dL (ref)					
8–9 mg/dL	− 0.756	0.470	0.227	0.973	0.042
> 9 mg/dL	− 0.527	0.590	0.291	1.199	0.145

CI confidence interval, *DM* diabetes mellitus, *ref* reference, *ULT* urate-lowering therapy

*Exp(B) = hazard ratio

**Proteinuria was measured by urine dipstick test

Discussion

This study retrospectively investigated the long-term (reaching 5 years) renoprotective effects of febuxostat and allopurinol in hyperuricemic patients with CKD. Febuxostat was more effective than allopurinol in lowering serum uric acid and in retarding renal disease progression. Febuxostat significantly reduced the risk of renal disease progression, while allopurinol did not.

In this study, the most common dose of febuxostat was 40 mg/day and that of allopurinol 100 mg/day. Considering that the most commonly prescribed dose of febuxostat and allopurinol in practice was 40 mg/day and 300 mg/day, respectively [23], allopurinol was under-dosed, while febuxostat was prescribed in similar doses as in patients with gout. This may explain the more potent urate-lowering effect in the febuxostat group and reflects that physicians are reluctant to prescribe higher doses of allopurinol in patients with CKD, though higher doses might exert better urate-lowering effect and probably be more renoprotective. As is well known, severe cutaneous adverse reaction due to allopurinol is more common in patients with CKD [11], which is a major hurdle in prescribing allopurinol in these patients. Skin reactions to febuxostat have also been reported [24], but they appear to occur much less frequently than in allopurinol users. In addition, the cross reactivity between febuxostat and allopurinol is currently unclear [25]. In this sense, febuxostat may be a better choice when treating hyperuricemia in patients with CKD.

Febuxostat group showed lower mean serum uric acid and maintained higher eGFR values than allopurinol and non-ULT group. This renoprotective effect of febuxostat is supported by other previous studies [26–28]. Switching from allopurinol to febuxostat effectively lowered the serum uric acid and appeared to prevent a decline in renal function [26, 27]. Febuxostat as well as benzbromarone were more potent than allopurinol in lowering serum uric acid levels and more likely prevented the progression to ESRD [28]. These results underscore the need for aggressive treatment of hyperuricemia in CKD for ULT to be renoprotective.

Goicoechea et al. [29] reported the long-term (median duration: 84 months) effect of fixed-dose allopurinol 100 mg/day in a post-hoc analysis of a randomized trial and estimated the risk reduction of renal event defined by the initiation of dialysis and/or doubling serum creatinine and/or ≥ 50% decrease in eGFR. They reported that therapy with allopurinol 100 mg/day reduced the risk of renal events by 68%. By contrast, allopurinol in this study did not show significant risk reduction in renal disease progression. This may be explained by several differences

in baseline patient characteristics such as age and baseline serum uric acid levels.

The beneficial effect of ULT might also be explained by xanthine oxidase inhibition, which is related to potent antioxidative effect [30]. However, this study was not adequately powered to clarify this issue, because no patient was treated with uricosuric agent. Xanthine oxidase inhibitors are more popular with a broader range of appropriate patients and recommended as first-line drugs for hyperuricemia in gout.

ULT was relatively safe in CKD patients in this study. Although the risk of severe cutaneous adverse reactions has attributed to the use of allopurinol in patients with CKD [12], only a single patient experienced a generalized drug eruption that resolved after treatment cessation. No patient experienced adverse events that may be attributed to febuxostat during the observation period. However, it should be noted that febuxostat also has potentially harmful side effects such as liver toxicity [31] and increased cardiovascular risk [32].

This study has several limitations. First, this study is retrospective in nature and might have a risk of selection bias. Although statistically insignificant, the three groups tended to be different in some baseline variables, which were included in the Cox proportional hazard model analysis as potent confounders. Second, the patients were relatively small in number from a single center. However, patients were followed for almost 5 years, which is long enough to observe renal disease progression.

In conclusion, febuxostat effectively lowered serum uric acid and significantly reduced the risk of renal disease progression in hyperuricemic patients with CKD, while allopurinol did not show significant risk reduction. Febuxostat seems to be a better option in treating hyperuricemia in patients with CKD.

Funding This study has not been financially supported by any specific fund.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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