Febuxostat Promoted Dissolution of Radiolucent Nephrolithiasis in Patients with Hyperuricemia

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Purpose: This study aimed to investigate the efficacy and safety of febuxostat in patients with radiolucent nephrolithiasis.

Materials and Methods: From March 2016 to June 2018, data of 96 patients with radiolucent nephrolithiasis and hyperuricemia who referred to the Third Affiliated Hospital of Sun Yat-sen University were retrospectively analyzed. These patients were divided into allopurinol 300mg/d (control), febuxostat 40mg/d (F40) and 80mg/d (F80) groups respectively. All patients took potassium citrate as a combination treatment and had been followed up for at least 6 months. Before treatment and on after 1st, 3rd and 6th month, complete blood count, serum uric acid (sUA), hepatic and renal function as well as ultrasound were carried out. Arthritic and gastrointestinal symptoms were also monitored. Computed tomography was performed before treatment and 6 months after medication.

Results: Compared with allopurinol group, F40 group showed no difference in urate-lowering effect, while F80 had the best effect across all the visits (P<0.01). At 6th month, 25(83.3%) cases of F80 group achieved sUA<6mg/dL, which was better than allopurinol group (18 cases, 58.1%) and F40 group (17 cases, 58.6%). In the dissolution effect of radiolucent calculi, F80 had the best effect, followed by F40 and then allopurinol (P<0.05). No statistical difference was observed in adverse events among three groups.

Conclusion: Febuxostat significantly decreased sUA, promoted radiolucent stone dissolution and reduced the total stone number, whereas it did not increase the adverse events.

Keywords: Nephrolithiasis; hyperuricemia; febuxostat; allopurinol

INTRODUCTION

Uric acid (UA) is the end chemical product of purine degradation in human. Since approximately 2/3 of uric acid passes out in urine, hyperuricemia usually cause high concentration of UA in the urine, which is called hyperuricosuria. When urine is supersaturated with undissolved UA, UA stones which are radiolucent form subsequently. Studies also demonstrated that hyperuricosuria promotes not only the UA stones but also the calcium oxalate stones[1-3]. It was reported that up to 10-15% of urinary stones and most of the radiolucent stones are UA stones[4-6]. Thus, lowering the serum UA (sUA) is an important intervention for nephrolithiasis treatment.

The two main approaches to lowering sUA are promoting the excretion and inhibiting the production[6,7]. Drugs promoting UA excretion, such as benzbromarone, usually exacerbate UA stones, for which reason they are contraindicated for patients with hyperuricemia and nephrolithiasis. Xanthine oxidase inhibitors, such as allopurinol and febuxostat, remarkably decrease hyperuricemia and hyperuricosuria and are beneficial in the treatment of UA stones[8]. Although the efficacy of febuxostat has been examined in primary gout, there are still no reports concerning the efficacy and safety of febuxostat as well as its advantages over allopurinol in radiolucent nephrolithiasis[9]. Herein, this study presents results about the efficacy and safety of febuxostat in radiolucent nephrolithiasis based on single-center retrospective study.

PATIENTS AND METHODS

Study population

This single-center retrospective study was approved by the institutional ethics committee of 3rd Affiliated Hospital of Sun Yat-sen University. All patients had signed informed consents for using related information. From March 2016 to June 2018, patients with nephrolithiasis who were referred to the 3rd Affiliated Hospital of Sun Yat-sen University were screened. Patients with radio-lucent nephrolithiasis and hyperuricemia which was defined as serum uric acid (sUA) greater than 8mg/dL were further selected based on inclusion and exclusion criteria for final analysis.

The inclusion criteria are:1)18-70 years old, sUA>8m/dL, BMI<30kg/m^2;2) ultrasound and CTU confirmed renal stones<2.5cm, stones were radiolucent in KUB, absence of ureteral or bladder stones or hydronephrosis or other congenital abnormalities; 3) serum creatine<130umol/L; 4) receiving single urate-lowering drug (allopurinol or febuxostat) and administration with potassium citrate as a combination treatment. Based on their medication, the selected patients were divided into three groups of allopurinol 300mg/d (100mg tid, con-

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Received September 2019 & Accepted February 2020

Table 1. Baseline data of selected patients

		Allopurinol 300mg/d	Febuxostat 40mg/d	Febuxostat 80mg/d	*P*
Patients number, n		34	30	32	-
Age,median (range),years		45(23-69)	47(26-74)	48(25-76)	0.365[a]
Gender,n(%)	Male	18(52.9)	14(46.7)	17(53.1)	0.903[b]
	Female	16(47.1)	16(53.3)	15(46.9)	
BMI, kg/m^2		23.3 ± 3.12	22.5±2.89	23.50±3.07	0.542[c]
Gouty tophi,n(%)		5(16.1)	3(10.0)	4(12.5)	0.718[d]
Baseline UA, median(range), mg/dL		9.72(8.1-13.6)	9.83(8.1-13.8)	9.92(8.1-14.2)	0.487
AST, mean±SD, U/L		25.56 ± 5.17	26.91 ± 4.88	24.77 ± 5.02	0.762
ALT, mean±SD, U/L		22.34 ± 5.34	24.98 ± 4.67	23.68 ± 4.89	0.469
Cr, mean±SD, umol/L		65.12 ± 9.24	68.34 ± 8.55	69.38 ± 10.12	0.387

[a], Cruskal-Wallis test. [b], χ^2 test. [c], ANOVA test. [d], Fisher exact test.
Abbreviations: BMI: body max index. UA: uric acid. AST: aspartate transaminase. ALT: Alanine aminotransferase. CR: Creatine.

trol group), febuxostat 40mg/d (40mg qd, F40 group) and 80mg/d (40mg bid, F80 group).

Patients were excluded when their baseline data met exclusion criteria. Exclusion criteria were:1) secondary hyperuricemia; 2) under gout attack or frequent gout attacks;3) liver dysfunction, AST/ALT>2 upper normal limit;4) white blood cells<4.0×109/L, hemoglobin<100 mg/dL, platelets< 100×109/L;5) receiving other urate-lowering agents or receiving ;2 kinds of urate-lowering agents; 6) using glucocorticoids, immunoimpressive agents, thiazine diuretics or other drugs that interfere with sUA; 7) a history of alcohol or drug abuse; 8) other severe or progressive diseases including cancer, heart diseases and chronic or severe infection, gastrointestinal, endocrine, pulmonary, cardiac, neurological, or cerebral diseases. 9) pregnant or breastfeeding woman.

Data Extraction and Evaluations

Regularly, patients with hyperuricemia who referred to our clinics were advised to drink enough water and maintain urine volume excessing 2000ml per day. Low purine intake was also recommended. The day before treatment and the day at 1,3,6 months after treatment, blood routine test, sUA, liver/kidney functions were determined. Ultrasound was performed on the day before treatment and the day at 1, 3, 6 months after treatment, while computed tomography (CTU) was performed on

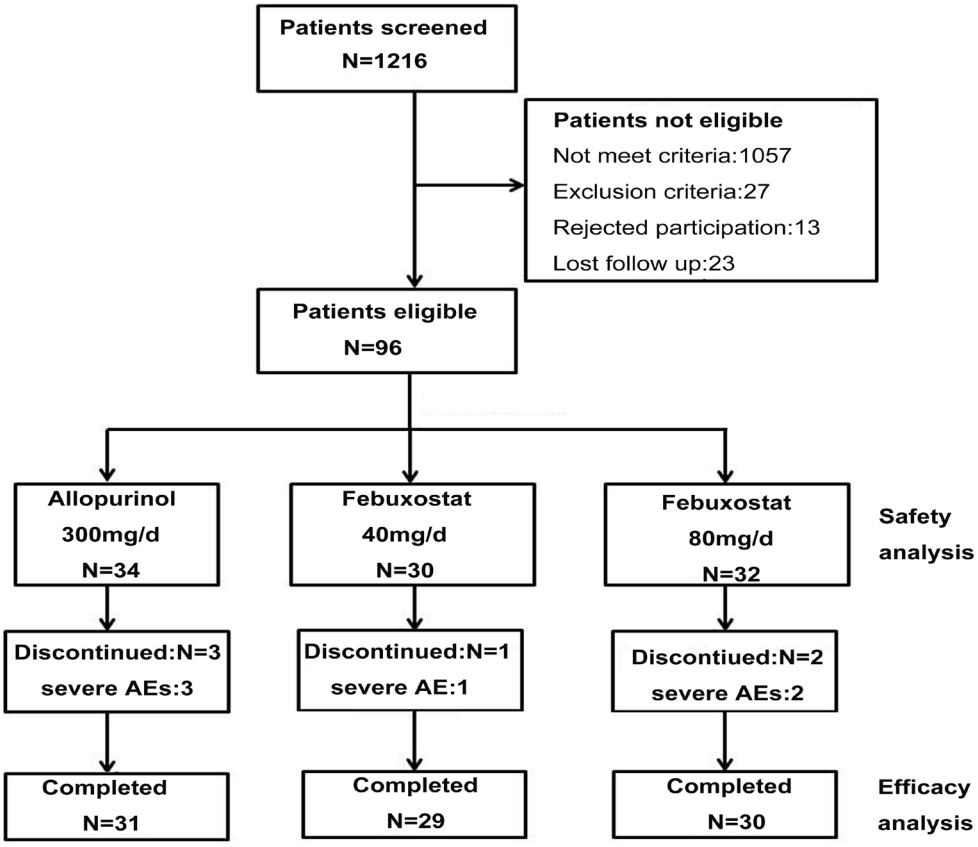

Figure 1. Flowchart of patients through the study. AEs, adverse events.

Table 2. Changes in urinary parameters for one-day urine collection measurements

Parameters	Allopurinol(n=23)	Febuxostat 40mg/d(n=25)	Febuxostat 80mg/d(n=23)	P^b
pH				
Baseline	5.93 (0.54)	5.83 (0.53)	5.78 (0.64)	0.659
Month 6	6.86 (0.48)	6.98-0.2 (0.49)	6.92 (0.65)	0.987
P^a	< 0.001	< 0.001	< 0.001	
Potasium(mEq/d)				
Baseline	85.0 (18.1)	82.3 (17.1)	84.2 (25.4)	0.708
Month 6	97.6 (18.8)	96.4 (23.9)	93.3 (29.7)	0.823
P^a	0.005	0.023	0.003	
Sodium(mEq/d)				
Baseline	231.1(45.6)	244.7 (35.4)	261.1(45.1)	0.06
Month 6	190.1(53.6)	192.4 (43.7)	201.9 (45.5)	0.672
P^a	0.009	< 0.001	0.001	
Citrate(mg/d)				
Baseline	558.1(143.8)	578.6 (132.2)	595.9 (122.3)	0.631
Month 6	628.5(127.3)	621.6 (112.3)	628.4 (109.0)	0.972
P^a	0.115	0.019	0.039	
Calcium(mg/d)				
Baseline	231.0 (61.9)	281.4 (60.5)	259.0 (34.3)	0.008
Month 6	227.1(44.7)	250.3 (67.2)	272.4 (27.3)	0.012
P^a	0.684	0.101	0.068	
Uric acid(mg/d)				
Baseline	946.8 (208.2)	932.2 (203.3)	954.2 (180.0)	0.923
Month 6	535.5 (108.6)	526.2 (130.9)	440.3 (112.0)	0.012
P^a	< 0.001	< 0.001	< 0.001	

[a], the differences at baseline and at month 6 in each group were compared using pairwise t test.
[b], the differences among groups at the same timepoint were compared using one-way ANOVA test.

the day before treatment and the day at 6 months after treatment. Hypersensitivity, gastrointestinal and cardiac symptoms, arthralgia, and gout flares were recorded. Patients who did not have complete data were excluded, but those who discontinued medication due to severe adverse events still remained in adverse events analysis so as not to underestimate the incidence of adverse events.

End points: 1) the change in sUA; 2) stones changes, including the maximum diameter and stone numbers; 3) adverse events. Patients whose maximum stone diameter decreased by >50% or the numbers of stones with diameter>5mm decreased were regarded as significantly effective cases.

Statistical analysis

Category variables were presented as frequencies or percent, statistical differences between groups were analyzed with χ^2 test or Fisher exact test. Continuous variables were presented as mean ± standard deviation (SD) or s median (range), statistical differences among three groups were analyzed using Kruskal-Wallis test or ANOVA test, and statistical differences between two groups were performed using students't test or Mann–Whitney U test. Pairwise comparisons were performed to analyze the changes of sUA levels, stones diameters, and numbers in each group before and after treatment. Two tailed $P < 0.05$ indicated statistical significance.

RESULTS

Patients' characteristics

In this study, a total of 96 patients were selected for final analysis, including 34, 30 and 32 cases for allopurinol group, F40 group and F80 group respectively. However, there were 3,1 and 2 patients who didn't complete medication for at least 6 months due to severe adverse events (**Figure 1**). Therefore, these patients were not included in the final efficacy analysis of serum uric acid (sUA) changes and stones changes, but still remained in adverse events analysis so as not to underestimate the incidence of adverse events. For all the eligible patients, the median (range) of age was 46 (23-76) years old, the median (range) sUA level was 9.87 (8.1-14.2) mg/dL, and gouty tophi were found in 12 patients. Baseline data for each group were shown in **Table 1**.

Serum uric acid (sUA) change

There were 31, 29 and 30 cases for allopurinol group, F40 group and F80 group respectively in the efficacy analysis of sUA change. The baseline median (range) sUA were 9.72(8.1-13.6), 9.83(8.1-13.8), and 9.92(8.1-14.2) mg/dL for allopurinol, F40 and F80 group respectively, with no statistical differences among groups. After treatment, sUA decline velocities were similar in allopurinol group and F40 group, whereas sUA dropped the fastest across the time (**Figure 2**). At the 1st month after treatment, the average decline of sUA were 2.42 ± 0.34, 2.58 ± 0.46 and 3.18 ± 0.52 mg/dL. At the 3rd month, the average decline of sUA were 3.96 ± 0.94, 4.11± 0.89 and 4.89 ± 1.32 mg/dL. At the 6th month, patients with sUA<6mg/dL were 25 (83.3%) in F80 group, which was much better than Allopurinol group (18 cases, 58.1%, $P < 0.01$) and F40 group (17 cases, 58.6%, $P < 0.01$).

Since all the patients were medicated with potassium citrate as the combination therapy and the urine pH is effective for examining the effects of citrate, we compared the urinary parameters at baseline and 6 months after treatment. Results of 24-hour urine collections are reported in Table 2. Although urine was remarkably alkalized by potassium citrate in each group ($P < 0.001$), there were no significant differences among three groups in pH at baseline or at the 6th month ($P = 0.659$ and 0.987). This means that the differences of treatment effects were mainly caused by urate-lowering drugs.

Stone changes

There were 31, 29 and 30 cases for allopurinol group, F40 group and F80 group respectively in the efficacy analysis of stones changes. The maximum diameter and the total number of the stones were used to evaluate the

Table 3. Stone changes after treatment

	Allopurinol 300mg/d	Febuxostat 40mg/d	Febuxostat 80mg/d
Patients included in analysis, n	31	29	30
Stone size, mm			
Baseline			
Mean(SD)	12.8 (6.3)	13.2 (5.8)	13.4 (7.1)
Median(range)	12 (6-24)	13 (6-26)	13.1(6-29)
At 6 mon			
Mean(SD)	7.7 (5.5)	7.9 (5.9)	5.8 (4.3) a,b
Median(range)	7 (3-21)	8 (3-20)	5.8 (3-19) a,b
Stone numbers			
Baseline, n	61	58	64
Mean(SD)	2.0 (0.4)	2.0 (0.5)	2.1 (0.7)
Median	2 (1-4)	2 (1-5)	3 (1-5)
At 6 mon, n	45	44	33 a,b
Mean(SD)	1.5 (0.3)	1.5 (0.5)	1.1(0.3) [a,b]
Median	1(0-5)	1(0-5)	1(0.4)
Dissolved stones, n(%)	16 (26.2)	14 (24.1)	31(48.4)[a,b]

[a], $P < 0.05$ when compared with allopurinol group. [b], $P < 0.05$ when compared with group of febuxostat 40mg/d.

stone burden. At the 6th month, the reduced maximum diameters were 5.1 mm (39.8%), 5.3mm (40.1%) and 7.6mm (56.7%) for allopurinol group, F40 and F80 groups respectively. There were 16(51.6%), 17(58.6%) and 22(73.3%) patients whose stones became smaller by more than 50%. Changes of the maximum diameter of stones showed no difference between the allopurinol group and the F40 group ($P = 0.11$). Among the three groups, F80 reduced the stone size the most significantly ($P < 0.05$). Regarding the stone number, there were 61, 58 and 64 stones in the allopurinol group, F40 and F80 groups respectively. After 6 months of treatment, there were 16 (26.2%), 14 (24.1%), and 31 (48.4%) stones being reduced, indicating F80 had the best reduction rate, followed by F40 and then the allopurinol group (**Table 3**). When significantly effective cases were defined as patients whose maximum stone diameter decreased by >50% or the stone number with diameter>5mm decreased, there were 18 (58.1%), 19 (65.5%) and 24 (80.0%%) cases with significant efficacy for each group (**Table 2**). Therefore, patients medicated with febuxostat 40mg twice daily had the best treatment efficacy in stone dissolution.

Adverse events (AEs)

In order to avoid underestimating the incidence of adverse events (AEs), those patients discontinued medication due to severe AEs and progressive symptoms still remained in AEs analysis. Data on AEs were summarized in Table 4. Among 96 patients, 32 (33.3%) patients experienced a total of 63 AEs. There were 24, 17, 22 events in allopurinol, F40 and F80 groups, respectively. There were 12/34 (35.3%), 9/30(30.0%) and 11/32(34.4%) patients of each group who experienced at least one AE ($P = 0.927$), suggesting the incidence of AEs in patients were similar among the three groups. Only 3 subjects in the allopurinol group discontinued medication, including 2 cases of hypersensitivity and 1 case of repeated gout attack, which required hospitalization. In the F40 group, 1 case of hypersensitivity stopped medications. Two patients discontinued medications in the F80 group, with 1 case of hypersensitivity and 1 case of abnormal myoenzymes that was suspected of myocardiopathy. Among all the AEs, liver dysfunction was the most common, but all recovered to normal liver function within 2 – 4 weeks and were able to switch to other urate-lowering agents (Table 4). Patients medicated with febuxostat 80mg/d experienced similar AEs with patients who medicated with febuxostat 40mg/d, indicating increasing febuxostat to 80mg/d could achieve better urate-lowering effect but did not increase AEs incidence.

DISCUSSION

Approximately 2/3 of uric acid is excreted through urine. Hyperuricemia results in elevated uric acid in urine, which is called hyperuricosuria. When the uric acid becomes saturated, it forms crystals thus uric acid stones reside in renal pelvis[10]. Uric acid stones are radiolucent in the X-ray. Allopurinol and febuxostat, as two classic urate-lowering drugs, inhibit xanthine oxidase to reduce serum uric acid, which results in lower uric acid excretion in urine[11]. Since allopurinol has a purine-like backbone, it affects enzymatic activity related to purine and pyrimidine metabolism and could

Table 4. Adverse events in the three groups

	Allopurinol 300mg/d, n=34	Febuxostat 40mg/d, n=30	Febuxostat 80mg/d, n=32
Liver dysfunction	7	8	9
Nonobstrunctive renal dysfunction	1	1	1
Abnormal complete blood count	2	2	1
Hyperlipidemia	1	3	6
Abnormal myoenzymes	0	1	2
Hypersensitivity	7	1	1
Gastrointestinal symptoms	6	1	2
Total AEs, n	24	17	22
Patients with AEs, n (%)	12(35.3)	9(30)	11(34.4)

Abbreviation: AEs, adverse events

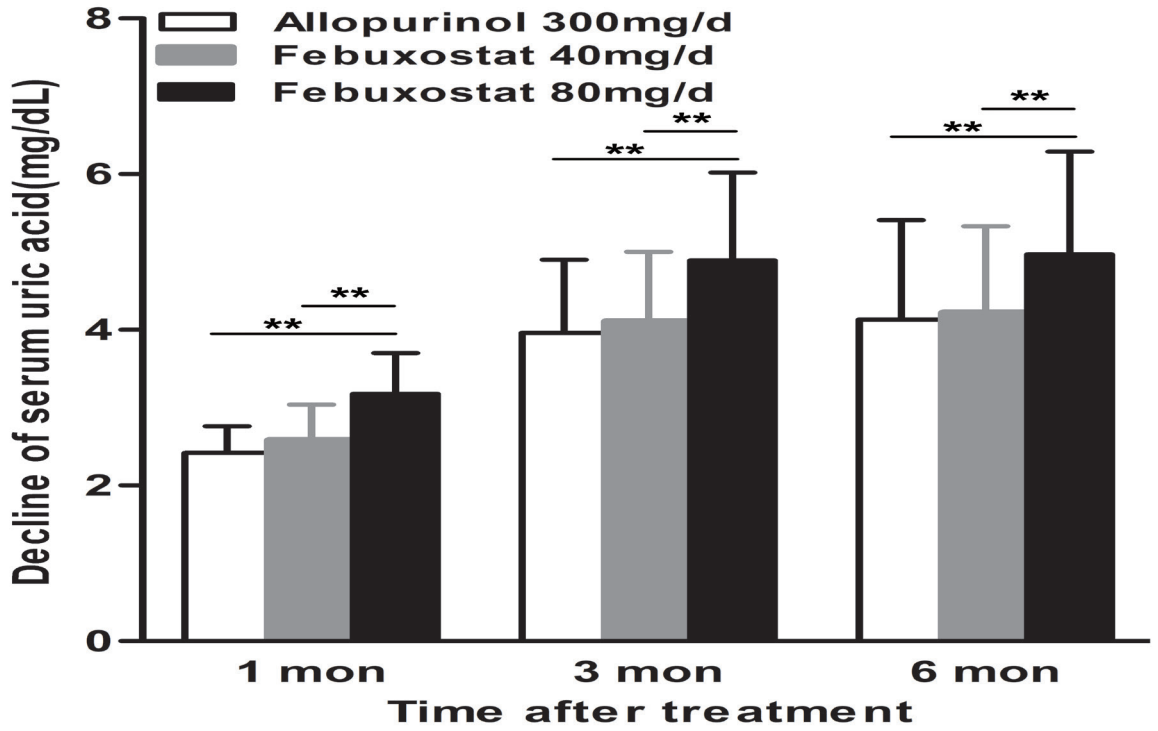

Figure 2. Changes of serum uric acid levels after treatment.

be reincorporated into nucleotides, thus reducing its urate-lowering effect and increasing adverse events. However, febuxostat has a different configuration from purine, which gives it a better inhibitory effect and specificity[12]. It selectively occupies the access channel to the molybdenum-pterin active site of the enzyme. Furthermore, febuxostat is primarily metabolized in the liver, and renal elimination plays a minor role in febuxostat pharmacokinetics. Although reports have clarified the efficacy of allopurinol in nephrolithiasis[13,14], the efficacy and safety of febuxostat especially in radiolucent stones remains unclear[9].

This study is a single-center retrospective study aiming to compare the efficacy and safety of allopurinol and febuxostat in radiolucent nephrolithiasis. The results demonstrated that febuxostat 40mg/d achieved a similar urate-lowering effect with allopurinol 300mg/d. Moreover, febuxostat 80mg/d had a better treatment effect than allopurinol and febuxostat 40mg/d while the incidences of adverse events were similar. Our study suggests that febuxostat is an effective and safe urate-lowering agent for radiolucent nephrolithiasis.

It has been reported that hyperuricosuria contributes not only uric acid nephrolithiasis but also calcium oxalate stones, both of which comprise about 90% of nephrolithiasis[15,16]. Therefore, urate-lowering agents may promote the dissolution of a large part of urinary stones. A randomized multicenter clinical trial by David S. Goldfarb et al. demonstrated that febuxostat 80mg/d or allopurinol 300mg/d promoted dissolution of calcium oxalate stones, and that both agents had similar treatment effects[4]. Our results revealed that febuxostat 80mg/d was better for radiolucent stones dissolution. Several reasons explain why febuxostat promoted stone dissolution in our study. On one hand, febuxostat inhibited uric acid production, thus lowering uric acid concentration in the urine and preventing uric acid crystal formation in the renal pelvis. On the other hand, a combination therapy of potassium citrate increased urine pH, which increased the solubility of uric acid. Based on these results, we proposed that lowering uric acid might be helpful for the dissolution of calcium oxalate stones or radiolucent stones.

Balancing the drug effect and adverse events is of top priority in practice. Our results showed that when increasing drug dose from 40mg/ to 80mg/d, febuxostat significantly reduced serum uric acid in a shorter time, but its adverse events were similar to allopurinol 300mg/d. Although studies suggested that increment of allopurinol dose correlated with improved urate-lowering effect, the adverse events would also increase proportionally[17]. To date, 300mg/d of allopurinol is most regarded as a safe dose, further dose increment was not recommended because the risks are over the merits[18]. As for febuxostat 80mg/d, it did not cause more adverse events while achieving a better treatment effect, suggesting febuxostat had a bigger dose window[19]. It should be noted that liver dysfunction was the most common adverse event in our study, which could be explained by that febuxostat is metabolized by oxidation and glucuronidation in the liver. Recently, studies reported that febuxostat could cause higher mortality in patients with gout and cardiovascular diseases[20,21]. In our study, 1 case of suspected cardiomyopathy was observed in patients medicated with febuxostat 80mg/d. Therefore, cardiovascular adverse events should be strictly monitored when using high dose of febuxostat.

There were several limitations of this study. Firstly, the sample size was relatively small for a common disease like nephrolithiasis. Since it was a single-centered retrospective study, bias was inevitably introduced to some extent, but results were statistically significant

and efficient to draw a conclusion. Secondly, the follow up period of 6 months was relatively short. Dissolution of large stones needs a long time, and therefore the clearance rate of large stones couldn't be evaluated. In this study, we defined effective cases as patients whose maximum stone diameter decreased by >50% or the numbers of stones with diameter>5mm reduced, which would help in treatment efficacy evaluation. Theoretically, the pure uric acid stones could be dissolved and passed to achieve total clearance at last. We will continue to follow up these patients and evaluate the long-term treatment of febuxostat. Finally, only one kind of urine-alkalized agent potassium citrate was used in this study. In practice, urine alkalization directly affects the treatment effect, thus urate-lowering agents are usually combined with urine-alkalized agents to improve the excretion. We didn't compare which urine-alkalized agent would be better in combination with febuxostat.

CONCLUSIONS

This single-center retrospective study compared the treatment efficacy and safety of allopurinol 300mg/d, febuxostat 40mg/d, and febuxostat 80mg/d in radiolucent nephrolithiasis. Our results demonstrated that compared with allopurinol, febuxostat achieved much better efficacy while keeping a similar incidence of adverse events. Febuxostat in combination with urine-alkalized agents is better recommended in the treatment of radiolucent stones.

ACKNOWLEDGEMENT

This work was financially supported by Science and Technology Planning & Social Development Project of Guangdong Province of China (2017A020215027).

CONFLICT OF INTEREST

The authors report no conflict of interest.

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