

Comparison of efficacy and safety between febuxostat and allopurinol in early post-renal transplant recipients with new onset of hyperuricemia

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Summary

What is known and objective: Febuxostat and allopurinol are xanthine oxidase inhibitors for urate-lowering therapy. The efficacy and safety of febuxostat and allopurinol have been mostly reported in hyperuricemia patients with normal renal function. Here, we aimed to compare the effects of these two drugs in early post-renal transplant recipients, focusing on evaluating the urate-lowering effect and recovery of allograft renal function.

Methods: A retrospective cohort study was performed in early post-renal transplant recipients with new onset of hyperuricemia receiving febuxostat or allopurinol therapy. Serum uric acid (UA) and estimated glomerular filtration rate (eGFR) were detected on days 3, 7 and 15 and months 1, 3 and 6 after therapy initiation. Liver and blood functions were monitored and other adverse events were recorded.

Results and discussion: A total of 48 and 33 patients were enrolled in the febuxostat and allopurinol groups, respectively. Significant UA-lowering effects were observed on day 3 in both groups. Febuxostat caused a more rapid UA decline, starting on day 3 and lasting for 1 month. The most apparent contrast was found in UA level (267.25 ± 93.66 vs 334.18 ± 96.56 $\mu\text{mol/L}$, $P = 0.003$) on day 7; 62.5% and 30.3% of patients achieved target UA level in febuxostat and allopurinol groups respectively on day 3 ($P = 0.004$), but there was no significant difference between two groups from days 15 to months 6. The median times to achieve target UA level were 3 and 5 days in febuxostat and allopurinol groups respectively ($P = 0.002$). The eGFR levels and recovering rates were gradually upregulated but no significant differences were found between two groups. No abnormalities related to febuxostat or allopurinol were observed.

What is new and conclusion: This is the first comprehensive evaluation of UA-lowering effects of febuxostat and allopurinol in early post-renal transplant recipients.

Shen and Li equally contributed to the study.

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Febuxostat caused a marginally quicker serum UA-lowering effect than allopurinol, but there was no advantage for long-term use of febuxostat. The drugs had no significant differences in impacting renal allograft function recovery, and both were well tolerated.

KEY WORDS

allopurinol, efficacy, febuxostat, hyperuricemia, renal allograft function, renal transplantation, safety

1 | WHAT IS NEW AND OBJECTIVE

Hyperuricemia is a metabolic disorder that causes the level of serum uric acid (UA) to exceed the upper limit of the normal reference level. Hyperuricemia is one of the common complications in renal transplant recipients, with an incidence rate from 25.1% at 3 months to 44.2% at 5 years after transplantation.¹ Risk factors for hyperuricemia include reduced renal allograft function and drugs (particularly calcineurin inhibitors and diuretics).²⁻⁴

Studies have suggested a positive association between hyperuricemia and progression of disease in individuals with renal insufficiency, including chronic kidney disease (CKD) and unrecovered allograft kidney.⁵⁻¹⁰ Elevated serum UA is associated with abnormal endothelial function, mitochondria dysfunction and glomerular arteriopathy and also could result in the formation of urate crystals in the nephron collecting ducts with tubular obstruction and then cause the damage of kidney structure progressively.¹¹

Available UA-lowering agents include the xanthine oxidase inhibitors such as febuxostat, allopurinol and benzbromarone. Benzbromarone increases the urinary excretion of uric acid, but the use of benzbromarone is limited due to reduced effects in patients with renal insufficiency and the risk of severe hepatotoxicity.¹² Febuxostat and allopurinol have both been shown to be efficacious in hyperuricemia and gout and are well tolerated, thus recommended for UA-lowering therapy, especially in patients with renal insufficiency.¹³ While a more potent UA-lowering effect has been shown with febuxostat, there was no evidence that febuxostat is superior to allopurinol for clinically relevant outcomes and, given its higher cost, febuxostat should not be routinely used for chronic gout.¹⁴

For patients with CKD, many studies have been reported the beneficial effects of febuxostat and allopurinol on renal function. A randomized controlled trial demonstrated that allopurinol reduced the rate of decline in GFR in patients with CKD with eGFR <60 mL/min/1.73 m².¹⁵ Febuxostat showed a renoprotective effect and retarded the progression of kidney disease in patients compared with allopurinol.¹⁶⁻¹⁹ However, the impact of these two drugs on allograft renal function is conflicting. A retrospective analysis²⁰ of 54 renal transplant recipients using allopurinol demonstrated that allopurinol use was associated with preservation of eGFR in renal transplant recipients. Other studies found no apparent effect on eGFR for febuxostat²¹ and did not find a difference in change of eGFR from baseline between febuxostat and allopurinol in stable renal

transplant recipients.²² Moreover, renal function can change over time in post-operative renal transplant recipients,²³ and it is plausible to hypothesize an effect of promoting renal function recovery of febuxostat or allopurinol based on the protective effect in renal insufficiency patients with CKD. It is therefore useful to study the time-varying effects of febuxostat and allopurinol on serum UA levels in post-renal transplant recipients with new onset of hyperuricemia. Data about the safety of febuxostat and allopurinol in post-renal transplant recipients also need to be replenished.

Thus, we performed a retrospective cohort study to compare the effects on reducing serum UA level, the influence on renal allograft function recovery and the safety between febuxostat and allopurinol in post-renal transplant recipients with hyperuricemia.

2 | METHODS

2.1 | Study patients

We reviewed medical records of all post-renal transplant recipients hospitalized between January 2015 and September 2017 at the First Affiliated Hospital of Sun Yat-sen University in Guangzhou, China. The inclusion criteria were as follows: (a) serum UA level ≥ 420 $\mu\text{mol/L}$ for male and post-menopausal women, serum UA level ≥ 360 $\mu\text{mol/L}$ for non-menopausal women; (b) receiving febuxostat or allopurinol for lowering serum UA level. The exclusion criteria were as follows: (a) age <18 years or >70 years; (b) concomitant gout or hyperuricemia before receiving renal transplantation; (c) discontinued treatment of immunosuppressive agents because of medical reasons; (d) death; (e) use allopurinol or febuxostat before receiving renal transplantation to prevent the occurrence of hyperuricemia; (f) discontinued serum UA-lowering agents, or the treatment of hyperuricemia for patients was changed from febuxostat to allopurinol or benzbromarone, or changed from allopurinol to febuxostat or benzbromarone during the follow-up period.

2.2 | Study design

This was a single-center, retrospective observational cohort study designed to compare the effects of febuxostat and allopurinol on lowering serum UA level, renal allograft function recovery and safety in early post-operative renal transplantation patients with hyperuricemia. The study was performed in accordance with

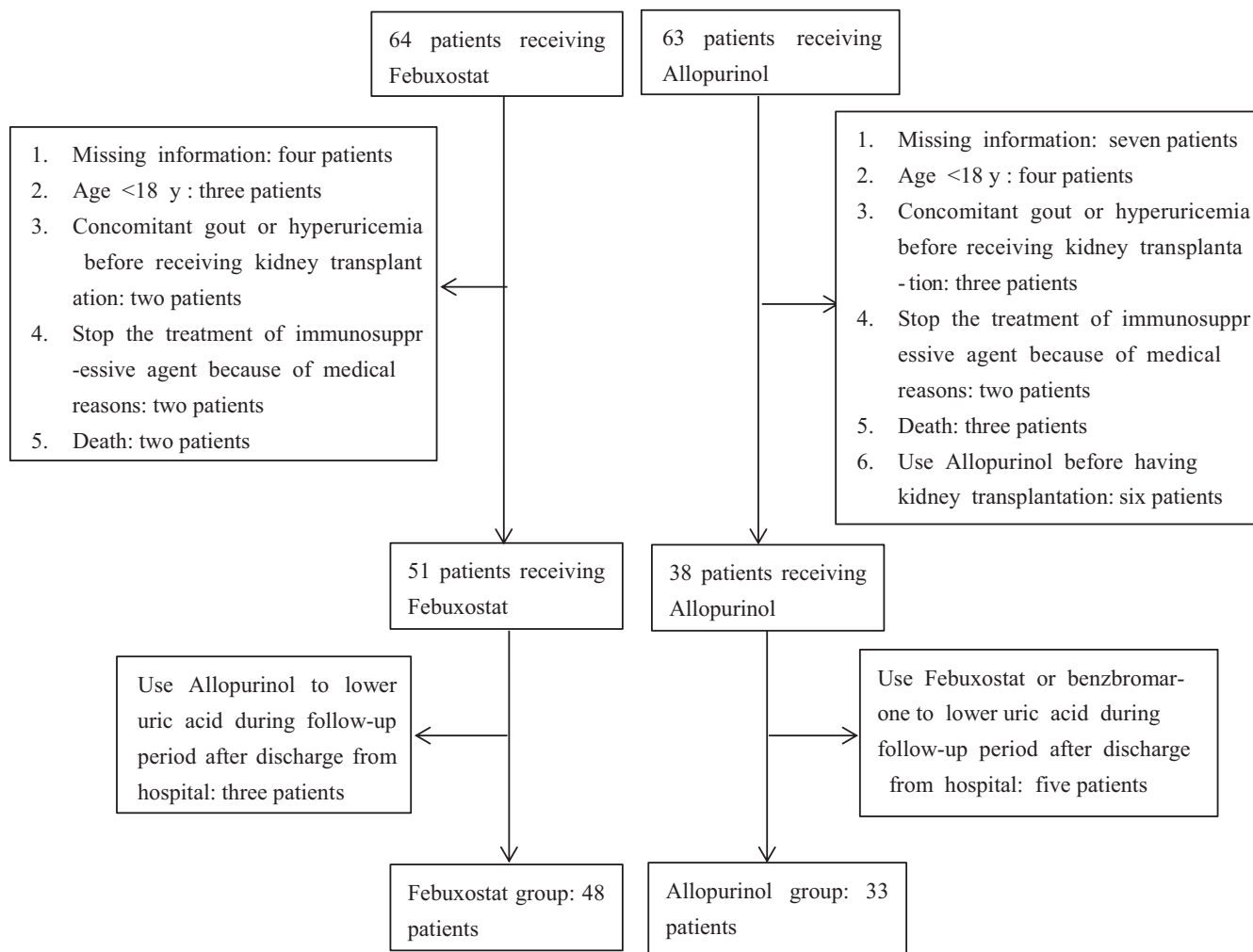


FIGURE 1 Flow of participants included in the study

the Declaration of Helsinki and the Principles of Good Clinical Practice. The Institutional Research Ethics Committee approved the study.

The patient enrolment flow chart is shown in Figure 1. There were 6 months follow-up after beginning the treatment of hyperuricemia. Patients in the febuxostat group were given 40 mg once daily of febuxostat tablets (Jiangsu Wanbang Pharmacy Ltd., Xuzhou, China), and the frequency was adjusted according to the serum UA level. Patients in allopurinol group were given allopurinol tablet (Shanghai Xinyi Wanxiang Pharmacy Ltd., Shanghai, China) 50-100 mg per dosage or sustained release capsules (Heilongjiang Aolida Ned Pharmaceutical Co. Ltd., Harbin, China) 250 mg per dosage, and frequency was adjusted according the serum UA level.

All of the recipients were given a triple immunosuppressive regimen of tacrolimus (Prograf, Astellas, Killorglin, Ireland) or cyclosporin A (Huadong medicine Co. Ltd., Zhejiang, China), mycophenolate mofetil (Cellcept, Roche, Basel, Switzerland) and prednisone (Guangdong Huanan Pharmacy Ltd, Dongguan, China). Initial doses of tacrolimus or cyclosporin A were administered according to body weight and preoperatively started on the day of transplantation and continued with these doses, until the first

measurement of tacrolimus C_0 was performed in the morning of day 3 and cyclosporin A C_0 was performed in the morning of day 7. Subsequent tacrolimus or cyclosporin A doses were adjusted basing on the results of C_0 monitoring, target C_0 range at 6-8 ng/mL was maintained for tacrolimus and 150-200 ng/mL for cyclosporin A.

2.3 | Data collection

Patient demographic features (age, sex, BMI, baseline blood pressure, baseline lipid levels, cause of end-stage renal disease, donor type, delayed graft function rate, the time post-transplantation when UA-lowering drugs initiated) and medication data (scheme of immunosuppressive treatment, trough level of tacrolimus and cyclosporine when beginning UA-lowering treatment, concomitant drugs, the dosage of febuxostat and allopurinol) were collected at the time of entry. The dosages of immunosuppressive agents and other concomitant drugs were continued and adjusted according to each individual patient's clinical condition. For evaluating the UA-lowering effect and impact on renal function recovery, serum UA and creatinine levels were detected on days 3, 7

TABLE 1 Baseline demographic and clinical characteristics

	Febuxostat N = 48	Allopurinol N = 33	P-value
Female, N (%)	32 (66.67)	21 (63.64)	0.778
Age, year	35.50 ± 22.00	35.00 ± 14.00	0.532
BMI, kg/m ²	21.05 ± 2.97	22.03 ± 3.17	0.161
Cause of ESRD, no. of patients (%)			
Hypertension	28 (58.33)	17 (51.52)	0.168
Diabetes mellitus	2 (4.17)	0 (0)	
Glomerulonephritis	8 (6.67)	4 (12.12)	
IgA nephropathy	2 (4.17)	4 (12.12)	
Polycystic kidney diseases	2 (4.17)	0 (0)	
Unknown	6 (12.50)	8 (24.24)	
Donor type, N (%)			
Deceased donor	39 (81.25)	22 (66.67)	0.135
Living donor	9 (18.75)	11 (33.33)	
2nd kidney transplants, N (%)	2 (4.17)	0 (0)	0.646
Time post-transplant that the uric acid lowering drugs were initiated, days	12 ± 9	12 ± 10	0.494
Delayed graft function, no. of patient (%)	7 (14.58)	4 (12.90)	0.749
Initial scheme of immunosuppressive treatment, N (%)			
Tacrolimus + mycophenolate + glucocorticoid	46 (95.83)	31 (93.94)	0.701
Cyclosporine + mycophenolate + glucocorticoid	2 (4.17)	2 (6.06)	
Trough level of tacrolimus when the uric acid lowering drugs were initiated, ng/mL	6.85 ± 4.7	6.2 ± 3.9	0.262
Trough level of cyclosporine when the uric acid lowering drugs were initiated, ng/mL	137.5 ± 17.68	137.5 ± 88.39	1.000
Systolic blood pressure, mm Hg	151.04 ± 15.80	147.45 ± 18.29	0.349
Diastolic blood pressure, mm Hg	93.42 ± 11.36	94.21 ± 10.65	0.752
TC, mmol/L	4.78 ± 1.38	4.68 ± 1.22	0.734
TG, mmol/L	1.38 ± 1.14	1.69 ± 1.66	0.408
LDL, mmol/L	2.91 ± 0.99	2.88 ± 2.70	0.891
HDL, mmol/L	1.17 ± 0.28	0.99 ± 0.39	0.007
Systolic blood pressure, mm Hg	151.04 ± 15.80	147.45 ± 18.29	0.349
Diuretic	38 (79.17)	26 (78.79)	0.967
PPIs	48 (100)	31 (93.94)	0.318
Aspirin	3 (6.25)	5 (15.15)	0.347

Values for categorical variables are given as number (percentage); for continuous variables, as mean ± standard deviation or median ± interquartile range.

ESRD, end-stage renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPIs, proton-pump inhibitor; TC, total cholesterol; TG, triglyceride.

and 15 and months 1, 3 and 6 after initiation of febuxostat and allopurinol treatment. Adverse events were evaluated by medical records and laboratory data including white blood cell count (WBC), haemoglobin (Hb), platelet (PLT), alanine aminotransferase (ALT) and aspartic transaminase (AST) were also collected for safety evaluation.

The IDMS-traceable MDRD equation²⁴ was used to calculate estimated glomerular filtration rate (eGFR) for all included patients, $eGFR[mL/min/1.73 m^2] = 175 \times Scr^{-1.154} \times age^{-0.203}$ (0.742 if female).

(Scr = serum creatinine (mg/dL), Scr: 1 mg/dL = 88.402 μmol/L, 1 μmol/L = 0.0113 mg/dL).

2.4 | Statistical analysis

Statistical analyses and calculations were performed using SPSS software (version 22; SPSS/IBM, Armonk, NY) and Prism 6 (GraphPad Software, La Jolla, CA). Quantitative variables were described with mean ± standard deviation (SD) if normally distributed

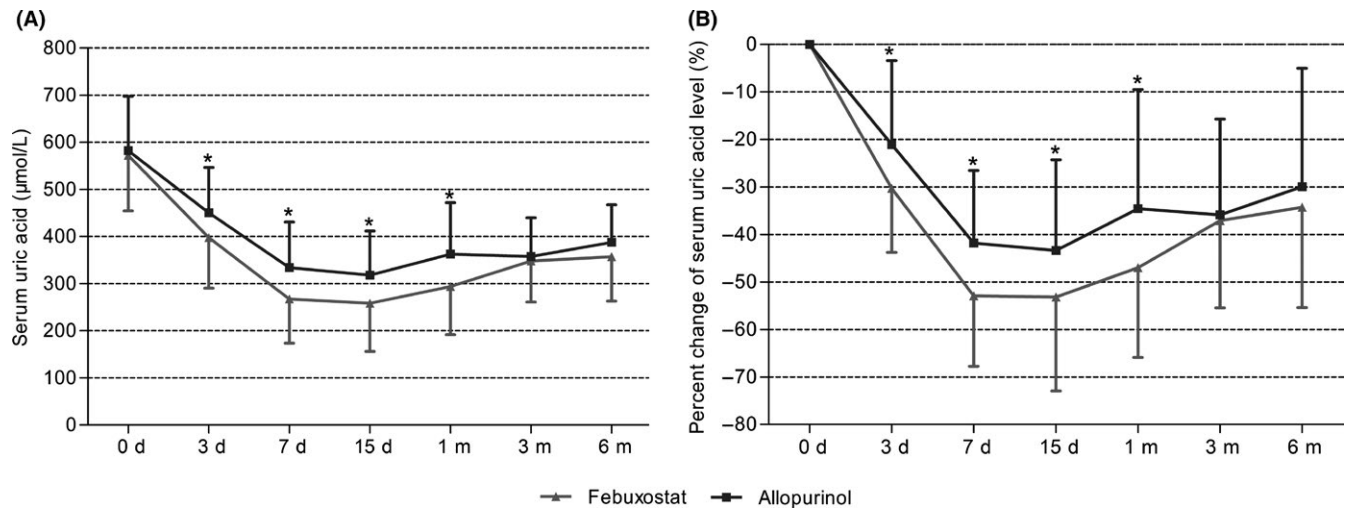


FIGURE 2 Effects of febuxostat and allopurinol on A, serum uric acid levels and B, percentage changes of serum uric acid levels for early post-renal transplant recipients after initial treatment. Values are given as mean ± standard deviation, * $P < 0.05$

or median ± interquartile range (IQR) if not normally distributed. Qualitative variables are given as counts and ratios (%). Baseline variables were compared between febuxostat group and allopurinol group to detect any variability at baseline. Between-group comparison of numeric parametric data was done by unpaired *t* test or Wilcoxon rank sum test. To determine differences between groups of categorical data (eg proportion of patients who achieve target serum uric acid), chi-square test or Fisher's exact test were used as applicable. $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient baseline characteristics

The flow chart in Figure 1 showed that 64 patients receiving febuxostat and 63 patients receiving allopurinol were screened for initial enrolment. With further exclusion, 48 patients in the febuxostat group and 33 patients in the allopurinol group were available for analysis. Baseline characteristics are presented in

TABLE 2 The serum uric acid levels, percentage changes of serum uric acid levels and percentage of patients who achieved target serum uric acid levels in febuxostat group and allopurinol group in different time

	Serum uric acid	Percentage changes of serum uric acid levels	Percentage of patients who achieved target serum uric acid levels
Febuxostat			
Pretreatment	572.23 ± 117.80	0.00	0.00 (48/48)
Day 3	397.58 ± 106.98*	-30.31 ± 13.45*	62.50 (30/48)*
Day 7	267.25 ± 93.66*	-52.92 ± 14.82*	93.75 (45/48)*
Day 15	258.61 ± 102.50*	-53.16 ± 19.77*	89.13 (41/46)
Month 1	294.22 ± 102.59*	-46.97 ± 18.93*	82.61 (38/46)
Month 3	347.89 ± 86.82	-37.10 ± 18.33	75.56 (34/45)
Month 6	357.32 ± 94.37	-34.25 ± 21.14	73.53 (25/34)
Allopurinol			
Pretreatment	587.06 ± 106.11	0.00	0.00 (33/33)
Day 3	450.39 ± 96.21	-21.06 ± 17.66	30.30 (10/33)
Day 7	334.18 ± 96.56	-41.79 ± 15.28	75.76 (25/33)
Day 15	317.91 ± 93.70	-43.38 ± 19.12	81.82 (27/33)
Month 1	362.73 ± 109.00	-34.56 ± 25.10	66.67 (22/33)
Month 3	357.77 ± 82.29	-35.89 ± 20.19	70.00 (21/30)
Month 6	387.52 ± 79.70	-29.93 ± 24.92	58.62 (17/29)

Serum uric acid is expressed in µmol/L, percentage change of serum uric acid level is expressed in %, and values are given as mean ± standard deviation. Percentage of patients who achieve target serum uric acid is expressed in %, and values are given as percentage (number of patients/total number). * $P < 0.05$ vs allopurinol in different time.

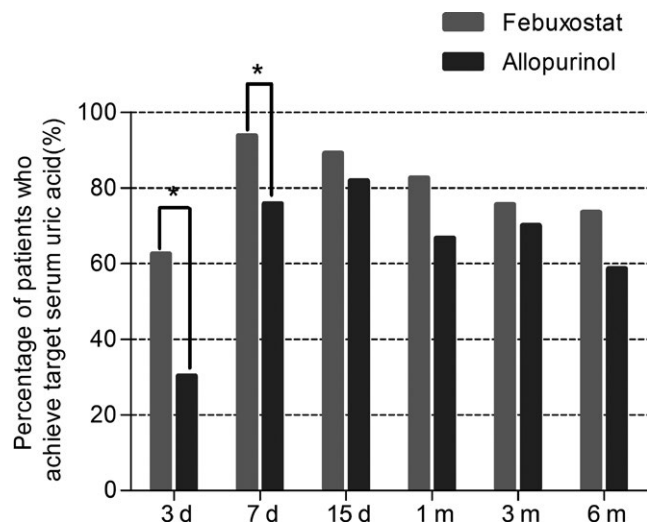


FIGURE 3 Percentage of patients who achieved target serum uric acid levels in febuxostat group and allopurinol group in different time. * $P < 0.05$

Table 1. There were no significant differences in the febuxostat and allopurinol groups with respect to baseline variables, apart from the level of high-density lipoprotein (HDL), which was higher in the febuxostat group at baseline. In the febuxostat group, three patients switched from 40 mg twice daily to 40 mg once daily according to the level of serum UA, and four patients increased the frequency to 40 mg once daily due to uncontrolled UA level at initial 40 mg once two days; the other 41 patients maintained 40 mg once daily throughout the study. In the allopurinol group, eight patients were given allopurinol sustained release capsules with 250 mg twice daily, five patients adjusted the sustained release capsules from 250 mg once 2 days to once daily based on the serum UA level, five patients using 50 mg allopurinol tablet changed the frequencies between once daily and twice daily, and the other 15 patients kept the tablet at 50 mg once daily throughout the study.

3.2 | Efficacy in lowering serum uric acid

The mean serum UA levels of febuxostat and allopurinol groups were $572.23 \pm 117.80 \mu\text{mol/L}$ and $587.06 \pm 106.11 \mu\text{mol/L}$ before the treatment ($P > 0.05$). As shown in Figure 2A and Table 2, there was a decrease in UA levels in febuxostat and allopurinol groups after initiation of treatment, whereas the UA levels were significantly lower in febuxostat group than in allopurinol group on day 3, 7 and 15 and month 1 ($P < 0.05$). The most apparent difference was found on day 7, with UA levels $267.25 \pm 93.66 \mu\text{mol/L}$ for febuxostat group and $334.18 \pm 96.56 \mu\text{mol/L}$ for allopurinol group ($P = 0.003$). The significant differences between the two groups disappeared on months 3 and 6. Similar results were found in the serum UA decline proportion (Figure 2B and Table 2). On day 7, the decline proportions were $52.92\% \pm 14.82\%$ in the febuxostat group and $41.79\% \pm 15.28\%$ in the allopurinol group ($P = 0.002$).

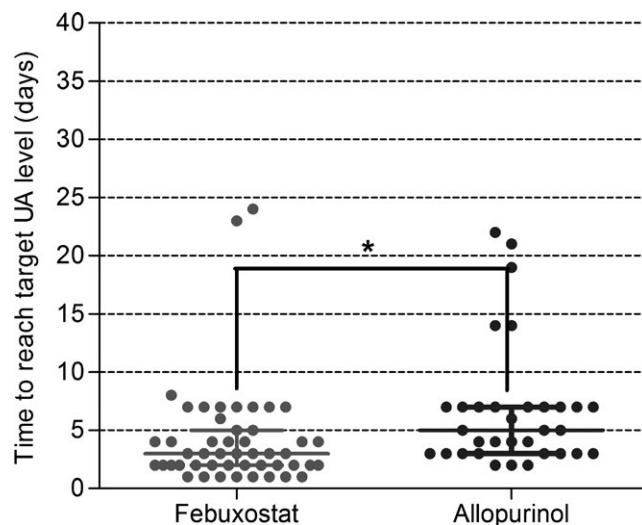


FIGURE 4 Time to reach target serum uric acid levels in febuxostat group and allopurinol group of early post-renal transplant recipients with new onset of hyperuricemia. * $P < 0.05$. Spots stand for the time to reach target serum uric acid level for every patient. Straight horizontal lines stand for median and interquartile range

We investigated the effects of the two drugs on the percentage of patients achieving target serum UA level (Figure 3 and Table 2) and observed that 62.50% and 30.30% of patients achieved target UA level in febuxostat and allopurinol group on day 3 respectively ($P = 0.004$), and the proportions were 93.75% and 75.76% on day 7 ($P = 0.046$). However, no significant differences were observed from day 15. Furthermore, Figure 4 showed that the median times to achieve target UA level was 3 days and 5 days in the febuxostat group and allopurinol group, respectively ($P = 0.002$).

Overall, the above data suggest that, compared to allopurinol, febuxostat may cause a slightly quicker serum UA-lowering effect at the beginning of treatment, but the advantage disappeared relatively quickly with the extension of treatment.

3.3 | Impacts on renal allograft function recovery

eGFR was adopted for evaluation of renal allograft function recovery. As shown in Figure 5A and Table 3, the eGFRs in baseline were 13.40 ± 30.66 and $18.52 \pm 21.69 \text{ mL/min/1.73 m}^2$ in the febuxostat and allopurinol groups, respectively ($P > 0.05$); they then increased gradually to 60.21 ± 19.85 and $51.00 \pm 18.50 \text{ mL/min/1.73 m}^2$. However, no significant differences were found between the two groups in all of the monitoring time. Likewise, similar results were also found in the increasing rate of eGFR (Figure 5B and Table 3).

3.4 | Safety

Common adverse drug reactions related to febuxostat and allopurinol include abnormalities of hematologic and hepatic functions. Thus, laboratory data including WBC, PLT, Hb, ALT and AST were analyzed throughout the study, and no abnormalities related to the

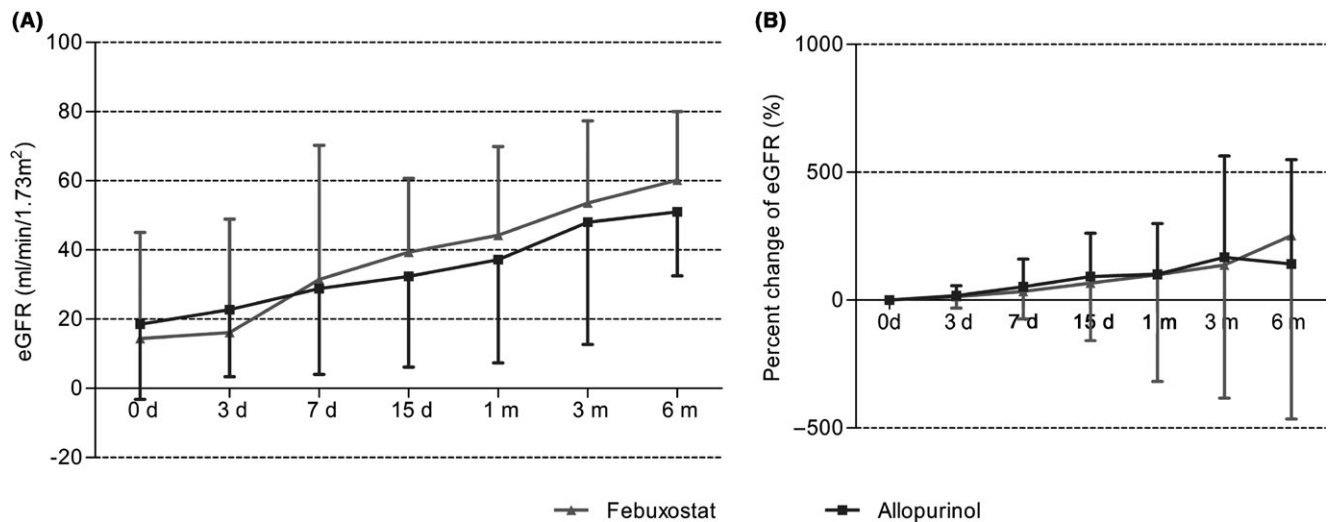


FIGURE 5 Effects of febuxostat and allopurinol on A, estimated glomerular filtration rates and B, percentage changes of eGFR for early post-renal transplant recipients after initial treatment. eGFR is expressed in mL/min/1.73 m², values are given as median ± interquartile range except values of febuxosta group and allopurinol group in month 6 are given as mean ± standard deviation. Values in figure (B) are given as mean ± standard deviation

two drugs were observed (Table 4). Meanwhile, none of the patients in both groups experienced other adverse reactions related to febuxostat or allopurinol. During the study period, there happened one patient in the febuxostat group with ALT and AST levels rising from 11 U/L to 12 U/L in the beginning to 172 U/L and

TABLE 3 Estimated glomerular filtration rate and percentage changes of eGFR in febuxostat group and allopurinol group of early post-renal transplant recipients after initial treatment

	eGFR	Percentage changes of eGFR
Febuxostat		
Pretreatment	13.40 ± 30.66	0.00
Day 3	16.13 ± 32.75	13.33 ± 43.95
Day 7	31.43 ± 38.83	33.83 ± 106.70
Day 15	39.33 ± 21.40	67.02 ± 225.72
Month 1	44.25 ± 25.67	99.69 ± 417.76
Month 3	53.58 ± 23.76	132.27 ± 520.89
Month 6	60.21 ± 19.85 ^a	252.33 ± 716.80
Allopurinol		
Pretreatment	18.52 ± 21.69	0.00
Day 3	22.72 ± 19.39	18.33 ± 38.36
Day 7	28.87 ± 24.85	52.54 ± 108.37
Day 15	32.38 ± 26.22	92.18 ± 169.72
Month 1	37.15 ± 29.84	101.03 ± 198.85
Month 3	48.03 ± 35.35	167.37 ± 396.55
Month 6	51.00 ± 18.50 ^a	141.27 ± 408.56

eGFR is expressed in mL/min/1.73 m², and values are given as median ± interquartile range except value ^a are given as mean ± standard deviation. Percentage changes of eGFR are expressed in %, and values are given as median ± interquartile range.

95 U/L at month 1, which might be explained by the use of tacrolimus, because ALT and AST recovered to normal levels after switching tacrolimus to cyclosporine A. Besides, in the febuxostat group, one patient had leucopenia and another one had hyperkalemia. In the allopurinol group, one patient had hyperkalemia and another one had mild diarrhea. However, all of the above adverse reactions were not considered to be related to febuxostat or allopurinol, since these reactions improved after discontinuation of other suspected drugs (such as mycophenolate mofetil induced diarrhoea and tacrolimus induced hyperkalemia) while continuing use of febuxostat or allopurinol.

4 | DISCUSSION

In our present study, febuxostat was demonstrated to cause a slightly quicker serum UA lowering effect than allopurinol at the beginning of treatment, while the advantage disappeared with the extension of treatment. No significant differences were found between the two drugs in promoting the renal allograft function recovery. The therapy for hyperuricemia with febuxostat and allopurinol in post-renal transplant recipients were both well tolerated, and no severe adverse effects were observed.

Serum UA levels and decline proportions between febuxostat and allopurinol groups showed significant variances on days 3, 7 and 15 and month 1, but disappeared on months 3 and 6 in our study. A similar result was observed in another retrospective study²⁵; stable renal transplant recipients with hyperuricemia prescribed febuxostat, allopurinol and benzbromarone had no significant difference in serum UA levels on the months 1, 3, 6 and 12 ($P > 0.05$). This phenomenon may owe to the reason that both drugs had to be adjusted with lower dosage or reduced

TABLE 4 Safety of febuxostat and allopurinol in patients who used febuxostat or allopurinol to lower serum uric acid after having renal transplantation

	WBC × 10 ⁹ /L		Hb, g/L		PLT × 10 ⁹ /L		ALT, U/L		AST, U/L	
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Median ± IQR	Range	Median ± IQR	Range
Febuxostat										
Pretreatment	10.57 ± 4.45	3.14-22.53	97.19 ± 15.86	69-139	149.23 ± 45.86	58-185	14.5 ± 12.75	5-151	17.50 ± 10.75	6-299
Month 1	7.02 ± 2.72	3.00-16.00	108.13 ± 18.59	77-150	204.76 ± 75.91	39-407	18.00 ± 16.00	5-172	17.00 ± 13.00	11-95
Month 3	5.93 ± 2.32	2.00-12.00	122.96 ± 16.95	85-152	213.36 ± 50.19	133-328	16.00 ± 15.00	2-62	21.00 ± 8.50	10-52
Month 6	6.91 ± 1.82	4.00-11.00	130.50 ± 17.71	90-157	224.00 ± 57.93	99-324	13.00 ± 8.50	5-92	18.50 ± 6.25	11-70
Allopurinol										
Pretreatment	10.03 ± 3.48	4.00-18.00	94.97 ± 17.12	64-134	136.70 ± 47.09	69-302	16.00 ± 20.00	4-63	15.00 ± 12.50	6-120
Month 1	7.79 ± 2.98	3.00-17.00	93.21 ± 16.51	68-134	212.85 ± 78.07	109-461	18.00 ± 15.50	6-47	17.00 ± 10.00	8-31
Month 3	5.73 ± 2.60	2.00-13.00	113.27 ± 16.96	78-150	207.27 ± 48.49	107-325	15.50 ± 10.25	4-29	19.00 ± 8.25	11-31
Month 6	6.41 ± 2.10	3.00-12.00	114.38 ± 23.20	70-154	208.86 ± 51.42	103-340	18.00 ± 16.00	5-85	21.00 ± 6.50	13-45

ALT, alanine aminotransferase; AST, aspartate transaminase; Hb, haemoglobin; PLT, platelet; WBC, white blood cell.

dosing frequency for better controlling the UA level at appropriate concentration.

Median time to achieve target serum UA level was marginally shorter in febuxostat group than in allopurinol group in renal transplant recipients (3 vs 5 days, $P = 0.02$). A recent retrospective study²⁶ also indicated that febuxostat led to faster achievement of target serum UA levels than allopurinol in patients diagnosed with gout (346 vs 397 days and 431 vs 478 days for reaching serum UA levels <6 mg/dL and <5 mg/dL, respectively, $P < 0.001$ for both comparisons). As compared to gout, shorter time to reach target serum UA level was observed in post-renal transplant recipients with new onset of hyperuricemia, probably because UA excretion disorder was caused by renal tubule injury of renal allograft,² and serum UA levels may be easily controlled for functional recovery of renal allograft.

Although hyperuricemia has been known to negatively be correlated with eGFR and associated with the worsening of renal allograft function,¹⁰ whether UA-lowering therapy using febuxostat or allopurinol plays a role in promoting renal allograft function recovery is still unclear. In our study, gradual recoveries of renal allograft function in both febuxostat and allopurinol group were demonstrated by increasing eGFR, and we found no significant variances between the two drugs in impacting eGFR increase. Febuxostat and allopurinol show a renoprotective effect and prevent the progression of renal disease in CKD patients.^{15,27} Febuxostat and allopurinol may have a promotion effect on renal allograft function recovery in early post-renal transplant recipients, but this needs further research.

No severe adverse effect was found in our study, which was confirmed by previous studies related to the safety of febuxostat or allopurinol in renal transplantation recipients. However, the safety of these two drugs in renal transplantation recipients still need to be verified by enlarging the number of patients and extending the follow-up period.

5 | WHAT IS NEW AND CONCLUSION

As we know, few studies have been reported on the effects of febuxostat and allopurinol in renal transplant recipients with hyperuricemia. A retrospective case-control study performed in renal transplant recipients suggested that allopurinol reduced serum UA levels and is associated with preservation of eGFR.²⁰ Besides, UA-lowering effects of febuxostat in renal transplant patients were also investigated.^{21,24} As compared to the reported studies, we compared the efficacy and safety of febuxostat and allopurinol.

In conclusion, febuxostat caused a slightly quicker serum UA-lowering effect than allopurinol at the beginning of the treatment in early post-renal transplant recipients. There was no significant difference between the two drugs in impacting the renal allograft function recovery. Both drugs were well tolerated, but long-term safety needs to be further assessed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTIONS

Pan Chen and Changxi Wang involved in the conception and design of the study. Changxi Wang, Longshan Liu and Qian Fu acquired the data. Xiaoju Shen, Jingjie Li, Xiang Gao and Xiao Chen analysed and interpreted the data. Xiaoju Shen and Jingjie Li drafted the article. Pan Chen, Jingjie Li and Xiang Gao critically revised the article for important intellectual content.

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