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Original article

Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients with chronic kidney disease (NU-FLASH trial for CKD)

Akira Sezai (MD, PhD)[a,*], Masayoshi Soma (MD, PhD)[b], Kin-ichi Nakata (MD, PhD)[a], Shunji Osaka (MD, PhD)[a], Yusuke Ishii (MD)[a], Hiroko Yaoita (MD)[a], Hiroaki Hata (MD, PhD)[a], Motomi Shiono (MD, PhD)[a]

[a] Department of Cardiovascular Surgery, Nihon University School of Medicine, Tokyo, Japan
[b] Department of General Medicine, Nihon University School of Medicine, Tokyo, Japan

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ABSTRACT

Background: The NU-FLASH trial demonstrated that febuxostat was more effective for hyperuricemia than allopurinol. This time, we compared these medications in patients with chronic kidney disease (CKD) from the NU-FLASH trial.

Methods and results: In the NU-FLASH trial, 141 cardiac surgery patients with hyperuricemia were randomized to a febuxostat group or an allopurinol group. This study analyzed 109 patients with an estimated glomerular filtration rate (eGFR) $\leq$60 mL/min/1.73 m^2, and also analyzed 87 patients with stage 3 CKD. The primary endpoint was the serum uric acid level. Secondary endpoints included serum creatinine, urinary albumin, cystatin-C, oxidized low-density lipoprotein, eicosapentaenoic acid/arachidonic acid ratio, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, and high-sensitivity C-reactive protein.

Among patients with an eGFR $\leq$ 60 mL/min/1.73 m^2, uric acid levels were significantly lower in the febuxostat group than the allopurinol group from 1 month of treatment onward. The serum creatinine, urinary albumin, cystatin-C, oxidized low-density lipoprotein, eicosapentaenoic acid/arachidonic acid ratio, and high-sensitivity C-reactive protein were also significantly lower in the febuxostat group. Similar results were obtained in the patients with stage 3 CKD.

Conclusion: In cardiac surgery patients with renal dysfunction, febuxostat reduced uric acid earlier than allopurinol, had a stronger renoprotective effect than allopurinol, and also had superior antioxidant and anti-inflammatory effects.

Introduction

While the short-term results of cardiac surgery are generally good [1], appropriate treatment for frequent complications such as diabetes, hypertension, hyperlipidemia, chronic kidney disease (CKD), and hyperuricemia is necessary to obtain a favorable remote outcome. Among these complications, hyperuricemia is reported to be associated with the onset and progression of CKD [2]. There has been an increasing number of reports about the association between hyperuricemia and other lifestyle-related diseases such as hypertension, hyperlipidemia, arteriosclerosis, obesity, and CKD [3,4]. Allopurinol has long been regarded as a first-line drug for the treatment of hyperuricemia. However, adverse reactions such as renal dysfunction, hepatic dysfunction, Stevens-Johnson syndrome, and hypersensitivity vasculitis have been reported with allopurinol, and its efficacy is insufficient in some cases [5,6]. In addition, the dose that can be administered is limited in CKD patients.

Febuxostat was developed in Japan for the treatment of hyperuricemia. It became available in the USA from 2009, Europe from 2010, and Japan from 2011. A potent uric acid-lowering effect of this drug has been reported [7]. We previously conducted a comparative study of febuxostat and allopurinol (the Nihon University working group study of Febuxostat and usuaL

* Corresponding author at: Department of Cardiovascular Surgery, Nihon University School of Medicine, 30-1 Oyaguchi-kamimachi, Itabashi-ku, Tokyo 173-8610, Japan. Tel.: +81 3 3972 8111; fax: +81 3 3955 9818.
E-mail address: asezai.med@gmail.com (A. Sezai).

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Allopurinol therapy for patientS with Hyperuricemia: NU-FLASH study), and reported that "In addition to reducing uric acid (UA) to a significantly lower level than allopurinol, febuxostat showed a renoprotective effect, inhibited oxidative stress, displayed anti-atherogenic activity, had an antihypertensive effect, and prevented vascular endothelial damage in cardiac surgery patients with hyperuricemia" [8]. However, that study did not compare the two drugs in patients with CKD, so we analyzed the CKD patients from the NU-FLASH trial in the present study.

Methods

Study protocol

The subjects were patients with an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 before treatment from among the patients enrolled in the previous NU-FLASH trial (University Hospital Medical Information Network study ID: UMIN000005964) that compared febuxostat (Teijin Pharma Ltd., Tokyo, Japan) with allopurinol (GlaxoSmithKline K.K., Tokyo, Japan) for hyperuricemia.

Endpoints: The primary endpoint was the serum UA level after treatment. The secondary endpoints were as follows: serum creatinine (s-Cr), eGFR, urinary albumin, cystatin-C, oxidized low-density lipoprotein (O-LDL), eicosapentaenoic acid/arachidonic acid (EPA/AA) ratio, total cholesterol (T-cho), triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), high-sensitivity C-reactive protein (hs-CRP), and adverse reactions.

UA, s-Cr, T-cho, TG, LDL, and HDL were measured before the start of treatment as well as after 1, 3, and 6 months of treatment, while urinary albumin, cystatin-C, O-LDL, and the EPA/AA ratio were measured before treatment and after 3 and 6 months of treatment. Adverse reactions were classified as acute attacks of gout, skin reactions, renal dysfunction (increase of s-Cr by ≥50%), hepatic dysfunction (increase of aspartate aminotransferase/alanine aminotransferase by ≥50%), gastrointestinal symptoms, and allergic reactions. The target serum uric acid level was ≤6.0 mg/dL, and the dose of each test drug was increased up to a maximum of 60 mg/day for febuxostat or 300 mg/day for allopurinol. In patients with an eGFR ≤ 30 mL/min/1.73 m^2, the maximum daily dose was 40 mg for febuxostat and 200 mg for allopurinol. eGFR was calculated according to the methods proposed for Japanese persons by the Japanese Society of Nephrology (men: $194 \times sCr^{-1.094} \times age^{-0.287}$, women: $194 \times sCr^{-1.094} \times age^{-0.287} \times 0.739$) [9].

Statistical analysis

For parametric data, results were expressed as the mean ± standard error of the mean (SEM). For time-course analysis, repeated measures ANOVA with Fisher's protected least squares difference test was used. Comparisons between the febuxostat group and the allopurinol group were done with the *t*-test. In all analyses, $p < 0.05$ was considered statistically significant.

Results

Out of the 141 patients enrolled in the NU-FLASH study, 109 patients had an eGFR ≤ 60 mL/min/1.73 m^2 and 87 patients had stage 3 CKD (Fig. 1). The baseline characteristics of the two groups are shown in Table 1. None of the subjects was taking losartan, which has been reported to reduce uric acid levels [10]. All patients were stable with no changes in oral medications and dietary therapy at 1 year or more after cardiac surgery, and none of them commenced a new diet and/or exercise regimen.

Patients with an eGFR ≤ 60 mL/min/1.73 m^2

Primary endpoint

UA (Fig. 2): There was no significant difference in UA between the 2 groups before the start of treatment (8.73 ± 0.90 mg/dL in the febuxostat group vs. 8.63 ± 1.00 mg/dL in the allopurinol group,

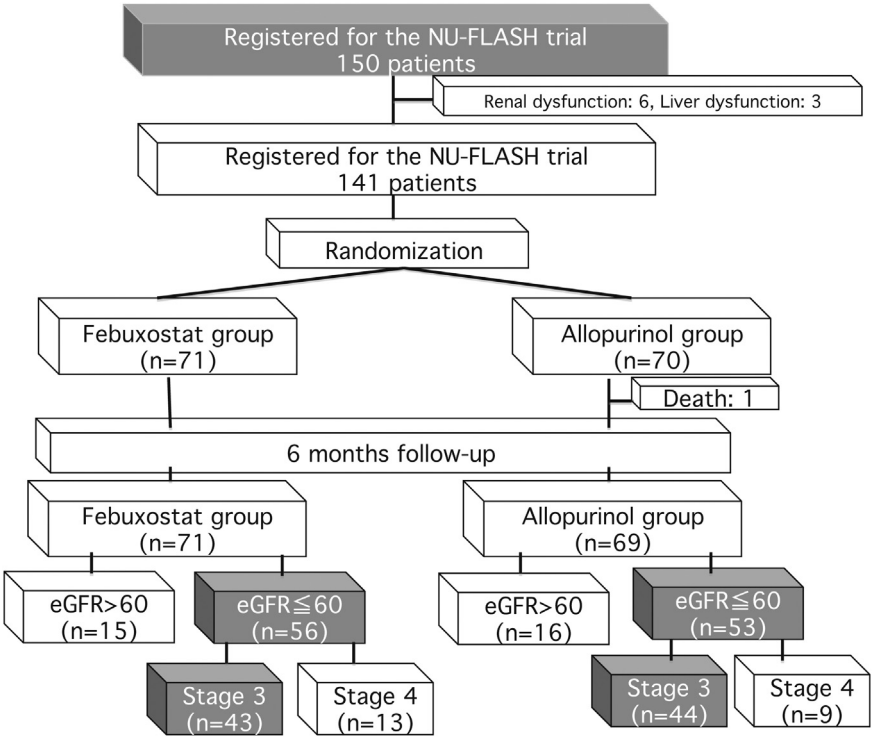

Fig. 1. Study population. NU-FLASH, Nihon University working group study of Febuxostat and usuaL Allopurinol therapy for patientS with Hyperuricemia; eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2).

Table 1
Baseline characteristics.

	eGFR < 60 mL/min/1.73 m²		CKD stage 3	
	Febuxostat	Allopurinol	Febuxostat	Allopurinol
Number	56	53	43	44
Age (years)	69.4 ± 10.0	69.1 ± 9.2	68.5 ± 10.2	68.3 ± 9.1
Gender (male: female)	43:13	42:11	40:3	39:5
Basic disease				
Ischemic heart disease	24	23	21	21
Valvular disease	22	21	14	14
Aortic disease	10	8	8	8
Congenital disease	0	1		1
Risk factors				
Diabetes mellitus	21	19	16	16
Hypertension	47	40	39	34
Dyslipidemia	32	29	26	25
Cerebrovascular disease	10	5	9	5
Obesity	14	13	9	10
Smoking	18	23	16	20
Medication				
ARB	35	29	27	21
ACE-I	4	5	2	4
Calcium antagonist	26	27	20	24
Beta blocker	29	30	20	25
Statin	38	32	31	29
Furosemide	22	20	13	13

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

Table 2
Changes in renal function and lipid parameters in eGFR < 60 mL/min/1.73 m².

	Pretreatment	1 month	3 months	6 months
Serum creatinine				
Febuxostat	1.37 ± 0.24	1.27 ± 0.40[#]	1.22 ± 0.22[*,#]	1.23 ± 0.24[*,#]
Allopurinol	1.35 ± 0.31	1.39 ± 0.40	1.36 ± 0.38	1.37 ± 0.37
eGFR				
Febuxostat	40.11 ± 10.4	43.6 ± 11.5[#]	45.3 ± 11.6[#]	45.2 ± 12.1[#]
Allopurinol	41.5 ± 10.6	41.4 ± 10.6	42.3 ± 12.7	42.3 ± 12.7
Total cholesterol				
Febuxostat	163.9 ± 26.0	160.9 ± 27.6	165.2 ± 27.4	167.2 ± 31.4
Allopurinol	160.3 ± 30.9	158.6 ± 26.7	164.1 ± 27.5	166.8 ± 27.0
Triglycerides				
Febuxostat	170.7 ± 112.3	156.4 ± 97.6	161.8 ± 104.3	160.4 ± 138.5
Allopurinol	165.3 ± 103.2	172.6 ± 131.2	174.0 ± 129.2	166.5 ± 113.7
LDL				
Febuxostat	89.1 ± 19.1	87.4 ± 25.9	88.5 ± 21.1	91.5 ± 22.2
Allopurinol	87.4 ± 25.4	84.7 ± 18.2	87.8 ± 20.7	92.1 ± 23.8
HDL				
Febuxostat	52.4 ± 14.9	50.3 ± 12.2	51.5 ± 12.1	52.9 ± 12.5
Allopurinol	55.8 ± 14.6	51.1 ± 12.1	51.6 ± 10.7	52.8 ± 15.7
hs-CRP				
Febuxostat	0.17 ± 0.40	0.13 ± 0.18[*]	0.12 ± 0.12[*]	0.13 ± 0.14[*]
Allopurinol	0.20 ± 0.22	0.44 ± 1.18	0.28 ± 0.45	0.36 ± 0.58

eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.
[*] $p < 0.05$ febuxostat vs. allopurinol.
[#] $p < 0.05$ pre vs. each level.

$p = 0.966$), but the UA level was significantly lower in the febuxostat group than the allopurinol group from 1 month after starting administration (1 month: $p < 0.0001$; 3 months: $p = 0.012$; 6 months: $p = 0.014$).

Secondary endpoints

(1) *s-Cr and eGFR* (Table 2): There were no differences in pretreatment s-Cr or eGFR between the 2 groups. s-Cr was significantly lower after 3 and 6 months of administration in the febuxostat group than the allopurinol group (1 month: $p = 0.075$; 3 months: $p = 0.049$; 6 months: $p = 0.038$), and it showed a significant decrease relative to baseline at all times in febuxostat group (all $p < 0.0001$). There were no significant differences in eGFR between the febuxostat group and the allopurinol group after the start of treatment (1 month: $p = 0.675$; 3 months: $p = 0.52$; 6 months: $p = 0.38$), but there was a significant increase relative to baseline at all times in the febuxostat group (all $p < 0.0001$).

(2) *Urinary albumin* (Table 3): There was no difference in the pretreatment level between the 2 groups ($p = 0.835$), but the albumin levels measured after 6 months were significantly lower in the febuxostat group than the allopurinol group (3 months: $p = 0.085$; 6 months: $p = 0.039$).

(3) *Cystatin-C* (Table 3): There was no difference in the pretreatment cystatin-C level between the 2 groups ($p = 1.00$), but significantly lower after 3 and 6 months of administration in the febuxostat group than the allopurinol group (3 months: $p = 0.018$; 6 months: $p = 0.013$).

(4) *O-LDL* (Table 3): There was no difference in the pretreatment level between the 2 groups ($p = 0.991$), but the 6-month level was significantly lower in the febuxostat group (6 months: $p = 0.042$).

(5) *EPA/AA ratio* (Table 3): There was no difference in the pretreatment ratio between the 2 groups ($p = 1.00$), but the

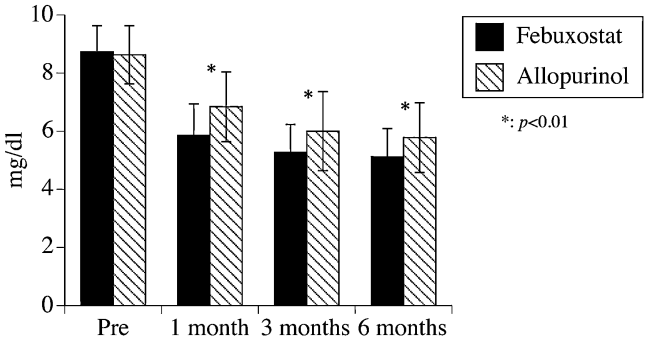

Fig. 2. Changes in the uric acid level in patients with estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m².

Table 3
Changes of other parameters in eGFR < 60 mL/min/1.73 m².

	Pretreatment	3 months	6 months
Urinary albumin			
Febuxostat	128.3 ± 342.8	73.4 ± 207.7	66.8 ± 138.3[*]
Allopurinol	120.3 ± 295.2	208.4 ± 438.1	196.4 ± 376.6
Cystatin-C			
Febuxostat	1.56 ± 0.46	1.47 ± 0.38[*]	1.53 ± 0.45[*]
Allopurinol	1.56 ± 0.51	1.71 ± 0.53	1.68 ± 0.47
Oxidized LDL			
Febuxostat	95.2 ± 28.4	93.9 ± 33.2	85.5 ± 28.7[*]
Allopurinol	93.2 ± 29.4	97.1 ± 26.9	100.5 ± 25.9
EPA/AA ratio			
Febuxostat	0.45 ± 0.24	0.54 ± 0.41[*]	0.50 ± 0.39
Allopurinol	0.45 ± 0.34	0.39 ± 0.23	0.39 ± 0.19

eGFR, estimated glomerular filtration rate; AA, arachidonic acid; EPA, eicosapentaenoic acid; LDL, low-density lipoprotein.
[*] $p < 0.05$ febuxostat vs. allopurinol.

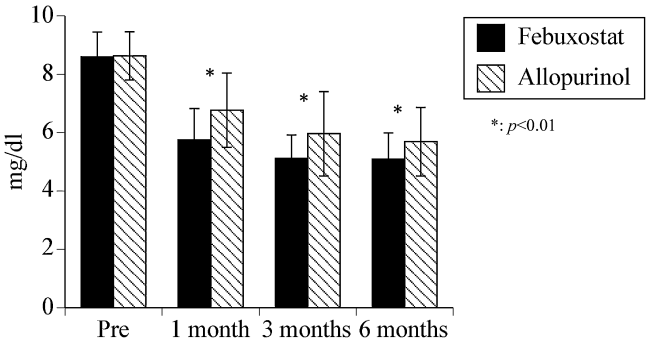

Fig. 3. Changes in the uric acid level in stage 3 chronic kidney disease (CKD) patients.

3-month values were significantly higher in the febuxostat group than the allopurinol group (3 months: $p = 0.025$).

(6) *T-cho, TG, LDL, and HDL* (Table 2): There were no differences in these parameters between the 2 groups either before or after treatment.

(7) *hs-CRP* (Table 2): There was no difference in pretreatment hs-CRP between the 2 groups ($p = 0.936$), but hs-CRP was significantly lower after 1 to 6 months of administration in the febuxostat group than the allopurinol group (1 month: $p = 0.087$; 3 months: $p = 0.017$; 6 months: $p = 0.011$).

Patients with stage 3 CKD

There were no significant differences in any parameters between the 2 groups before treatment. After the start of treatment, the following parameters were significantly lower in the febuxostat group than the allopurinol group (Fig. 3, Tables 4 and 5): the UA level (1 month: $p = 0.046$; 3 months: $p = 0.031$), urinary albumin (3 months: $p = 0.001$; 6 months: $p = 0.006$), and hs-CRP (1 month: $p = 0.002$; 3 and 6 months: $p < 0.001$). The EPA/AA ratio was significantly higher in the febuxostat group than the allopurinol group after 3 months of administration ($p = 0.001$). Although significant differences were not observed, cystatin-C and O-LDL were lower in the febuxostat group than the allopurinol group at 3 months (cystatin-C, $p = 0.078$; O-LDL, $p = 0.079$).

Discussion

The present sub-analysis of the NU-FLASH trial demonstrated that febuxostat rapidly reduced the serum UA level in CKD patients and also had a stronger renoprotective effect than allopurinol based on the changes of s-Cr, urinary albumin, and cystatin-C. In addition, the changes in O-LDL and the EPA/AA ratio suggested that febuxostat had stronger anti-oxidant and anti-atherogenic effects than allopurinol.

A randomized controlled trial of febuxostat versus allopurinol showed that the UA level was reduced more rapidly by febuxostat, but there has been no such trial in CKD patients. Sakai et al. performed a retrospective study in 60 patients with CKD, and reported a significant decrease in serum UA and an increase in eGFR after switching from allopurinol to febuxostat [11]. Tsuruta et al. compared 51 patients who switched from allopurinol to febuxostat with 22 patients who continued allopurinol, and reported that serum UA was significantly decreased while eGFR was increased after switching to febuxostat [12]. Shibagaki et al. administered febuxostat to 70 patients with CKD (stages 3b, 4, and 5) for 24 weeks, and reported that the reduction in serum UA was >40% in stage 3b and >50% in stages 4 + 5, along with an increase in eGFR [13]. In a prospective study, Akimoto et al. treated 17 hemodialysis patients with febuxostat alone and found a significant reduction in the serum level of 8-hydroxydeoxyguanosine, which has been reported to be an oxidative stress biomarker [14]. Thus, there have been various reports about the superior effect of febuxostat on renal function compared with allopurinol. In the present study, the data for s-Cr, urinary albumin, and cystatin-C also showed stronger renal protection by febuxostat than allopurinol. Dose reduction of allopurinol is needed for patients with renal dysfunction because it is less lipid-soluble, undergoes renal excretion, and its metabolite (oxipurinol) is active. In contrast, the metabolite of febuxostat is inactive and undergoes biliary excretion [6,7]. It was reported that lowering serum UA

Table 4
Changes in renal function and lipid parameters in CKD stage 3.

	Pretreatment	1 month	3 months	6 months
Serum creatinine				
Febuxostat	1.31 ± 0.23	1.23 ± 0.24	1.17 ± 0.20	1.18 ± 0.23
Allopurinol	1.26 ± 0.23	1.27 ± 0.26	1.25 ± 0.25	1.27 ± 0.27
eGFR				
Febuxostat	43.6 ± 8.5	47.0 ± 10.3	48.3 ± 9.3	49.2 ± 10.1
Allopurinol	45.0 ± 7.8	45.2 ± 9.8	45.9 ± 10.4	45.3 ± 10.6
Total cholesterol				
Febuxostat	168.7 ± 11.3	151.9 ± 98.1	153.9 ± 98.6	160.9 ± 144.5
Allopurinol	152.3 ± 86.6	157.5 ± 122.1	155.8 ± 112.2	147.9 ± 86.3
Triglycerides				
Febuxostat	170.7 ± 112.3	156.4 ± 97.6	161.8 ± 104.3	160.4 ± 138.5
Allopurinol	165.3 ± 103.2	172.6 ± 131.2	174.0 ± 129.2	166.5 ± 113.7
LDL				
Febuxostat	85.8 ± 25.2	85.9 ± 23.6	88.4 ± 23.0	90.3 ± 24.1
Allopurinol	91.2 ± 20.1	84.3 ± 18.9	88.6 ± 21.6	95.1 ± 25.1
HDL				
Febuxostat	53.0 ± 15.0	50.1 ± 12.3	51.3 ± 12.1	53.1 ± 13.1
Allopurinol	54.2 ± 15.8	50.9 ± 13.0	51.3 ± 11.5	52.5 ± 17.0
hs-CRP				
Febuxostat	0.17 ± 0.43	0.09 ± 0.10*	0.11 ± 0.12*	0.11 ± 0.10*
Allopurinol	0.20 ± 0.24	0.30 ± 0.62	0.29 ± 0.48	0.37 ± 0.63

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.
* $p < 0.05$ febuxostat vs. allopurinol.
# $p < 0.05$ pre vs. each level.

Table 5
Changes of other parameters in CKD stage 3.

	Pretreatment	3 months	6 months
Urinary albumin			
Febuxostat	194.0 ± 175.2	52.5 ± 69.1*	70.9 ± 145.0*
Allopurinol	203.2 ± 317.3	239.8 ± 475.9	218.8 ± 406.5
Cystatin-C			
Febuxostat	1.43 ± 0.40	1.35 ± 0.30	1.41 ± 0.39
Allopurinol	1.46 ± 0.40	1.60 ± 0.45	1.58 ± 0.41
Oxidized LDL			
Febuxostat	93.6 ± 26.0	94.3 ± 32.2	85.4 ± 28.2
Allopurinol	92.4 ± 27.3	98.3 ± 27.5	100.7 ± 24.7
EPA/AA ratio			
Febuxostat	0.46 ± 0.37	0.52 ± 0.42*	0.51 ± 0.42
Allopurinol	0.43 ± 0.19	0.36 ± 0.19	0.37 ± 0.18

AA, arachidonic acid; EPA, eicosapentaenoic acid; LDL, low-density lipoprotein.
* $p < 0.05$ febuxostat vs. allopurinol.

with allopurinol reduces s-Cr and inhibits the development of renal dysfunction in CKD patients [15]. In this study, febuxostat alleviated the negative effect on the kidneys by lowering serum UA more potently than allopurinol, and it was considered to be safer for CKD patients in view of its route of elimination.

Moreover, the changes of O-LDL and the EPA/AA ratio in this study indicated that febuxostat showed anti-oxidant and anti-atherogenic effects.

Like allopurinol, febuxostat reduces uric acid production by inhibiting xanthine oxidase. However, allopurinol has a similar molecular structure to xanthine, a substrate of xanthine oxidase with a similar molecular structure to xanthine. In contrast, febuxostat has a different molecular structure from xanthine and is a selective xanthine oxidase inhibitor that does not inhibit other nucleic-acid metabolizing enzymes. Uric acid is produced as the terminal metabolite of purine metabolism via xanthine oxidase. Xanthine oxidase is involved in the production of reactive oxygen species, and it has been reported that production of reactive oxygen by endothelial-bound xanthine oxidase is more potently inhibited by febuxostat than by allopurinol [16]. There have been reports that allopurinol lowers the level of O-LDL or reduces vascular oxidative stress, although a high dose of 600 mg/day was used in both studies [17,18].

Tausche et al. administered febuxostat for 1 year and reported that it prevented an increase of arterial stiffness because serum UA was lower in the febuxostat group, while the carotid-femoral pulse wave velocity was increased in the allopurinol group and unchanged in the febuxostat group [19]. Tsuda et al. administered febuxostat in an animal model of renal ischemia–reperfusion (I/R) injury, and they not only found improvement in serum UA and s-Cr, but also reduction in oxidative stress and alleviation of renal tubular injury and interstitial fibrosis [20]. These reports provide evidence that febuxostat has various effects, including alleviation of oxidative stress. Based on such actions, febuxostat has the potential to decrease the incidence of cardiovascular events. New information on its renoprotective effect may be obtained by a multicenter randomized trial in patients with stage 3 CKD that is currently being conducted in Japan [21].

Conclusion

In this study, we analyzed CKD patients from the NU-FLASH trial. We found that febuxostat had a stronger UA-lowering effect, renoprotective effect, anti-oxidant effect, and anti-atherogenic effect than allopurinol. The present findings demonstrated that treatment with febuxostat could possibly improve the long-term prognosis. However, observation was only continued up to 6 months of administration in this study, so further investigations over a longer term are needed in the future.

Limitations

This study was a sub-analysis of the NU-FLASH trial, and definite conclusions could not be drawn because of the small number of subjects. Accordingly, the present findings need to be confirmed by future studies in a larger number of subjects.

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Disclosures

We received lecture fees from Daiichi Sankyo Company (Tokyo, Japan).

Clinical trial registration information

UMIN (http://www.umin.ac.jp/), Study ID: UMIN00000 5964.

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