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ORIGINAL ARTICLE

Safety, efficacy and renal effect of febuxostat in patients with moderate-to-severe kidney dysfunction

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Hyperuricemia (HU) is common in patients with chronic kidney disease (CKD), and accumulating evidence suggests it has a pathogenic role in the progression of the disease. However, a major challenge in treating patients with HU is the adverse effects caused by urate-lowering drugs used to treat CKD. Because of these untoward effects, doses need to be reduced, which leads to suboptimal efficacy. Febuxostat has been shown to be highly efficacious in reducing serum uric acid (sUA) and is well tolerated in patients with mild kidney dysfunction. However, its safety and efficacy have not been well studied in more advanced cases of CKD. We studied the safety and efficacy of escalating doses of febuxostat over a 24-week period in 70 patients with CKD stages 3b, 4 and 5, and we also observed the changes in blood pressure, estimated glomerular filtration rate (eGFR) and proteinuria following the reduction of sUA. Drug-related adverse events (AEs) occurred in only 5 out of 70 patients. All but one of the events were mild, and all five patients fully recovered. By 24 weeks, the reduction of sUA levels was $>40\%$ in CKD stage 3b and $>50\%$ in CKD stages 4 and 5. More than 70% of patients achieved target sUA levels of 6 mg dl^{-1} or less. Multivariate analysis showed that a greater reduction in sUA with febuxostat was associated with an increase in eGFR and a tendency toward decreased proteinuria. Febuxostat was safe and efficacious in the treatment of CKD stages 3b–5.
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Keywords: chronic kidney disease; febuxostat; safety

INTRODUCTION

Hyperuricemia (HU) is a common medical problem in Japan as well as worldwide and is well known to be even more prevalent in patients with chronic kidney disease (CKD).[1,2] Recently, evidence has accumulated showing that HU has a role in the pathogenesis of hypertension, metabolic syndrome, cardiovascular disease and the progression of CKD, indicating the necessity for treatment even in the absence of symptoms of gouty arthritis.[1–4]

However, a major challenge in treating patients with HU is the occurrence of drug-related adverse effects that are often augmented in the presence of kidney dysfunction.[5] Allopurinol is primarily excreted in the urine as the metabolite oxypurinol, which can accumulate and cause toxicity in patients with kidney dysfunction. Furthermore, probenecid, which is the alternative to allopurinol, is relatively contraindicated in CKD because of concerns surrounding urolithiasis, as well as its low efficacy in the presence of kidney dysfunction.[6]

Febuxostat, a novel and potent nonpurine selective xanthine oxidoreductase inhibitor, has been shown to be highly efficacious in reducing serum uric acid (sUA) levels. Because it is mainly metabolized by the liver, it is well tolerated in patients with mild-to-moderate kidney dysfunction.[7,8] However, its safety and efficacy have not been well studied in patients with more advanced CKD.

We studied the safety, tolerability and efficacy of escalating doses of febuxostat over a 24-week period in 70 patients with CKD stages 3b, 4 and 5. We also observed the changes in blood pressure, estimated glomerular filtration rate (eGFR) and proteinuria after the reduction of sUA associated with febuxostat and studied the relationship between the level of reduction in sUA and changes in these renal parameters.

METHODS

This study is a 24-week prospective, open-label, noncontrolled study to evaluate the safety, efficacy and renal effect of febuxostat in Japanese patients with HU and advanced CKD.

This study complied with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies by the Ministry of Health, Labour and Welfare, Japan. The study began after approval was granted by each institutional review board at St Marianna University Hospital (IRB No. 1981) and Jikei University Hospital (IRB No. 23-188 6649). All patients gave written informed consent before participating in the study.

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Subjects

We screened and tried to obtain consent from all outpatients or in-patients who were aged 20 years or over with a diagnosis of HU (serum urate of 8.0 mg dl^{-1} or more) and advanced CKD (eGFR of <45 ml min^{-1} per 1.73 m^2 that was estimated using a formula modified by the Japanese Society of Nephrology).[9] Subjects were enrolled who had not received urate-lowering medication within 1 month before the start of the study. Patients were excluded from the study if they met one of the following conditions: concurrent or recent (within 2 weeks) gouty attack; liver dysfunction (aspartate aminotransferase and/or alanine aminotransferase more than two times the upper normal limit); acute kidney injury or dialysis dependence; history of intolerance to febuxostat; pregnant or breastfeeding women or those who were anticipating pregnancy; and current use of azathioprine or mercaptopurine. Causes of CKD were clinically diagnosed with or without biopsy. The diagnosis of immunoglobulin A nephropathy was made by renal biopsy. Biopsy-proven glomerulonephritis other than immunoglobulin A nephropathy or clinically suspected glomerulonephritis, including immunoglobulin A nephropathy but without biopsy, was diagnosed as chronic glomerulonephritis. Diabetic kidney disease was diagnosed in patients with diabetes only if they had evidence of diabetic retinopathy, significant proteinuria or a long history of diabetes.

Study treatment

Patients who were eligible and agreed to participate in the study by written consent were registered and prescribed febuxostat at an initial dose of 10 mg once daily. Subsequently, febuxostat was titrated after 4 weeks to 20 mg per day and then to the maintenance dose of 40 mg per day at week 8 (or 60 mg per day in 12 weeks, if necessary) and continued until week 24, even if the target sUA level ($\leqslant$6.0 mg dl^{-1}) was achieved with a lower dose. In some patients, the dose was maintained below 40 mg per day if the caring physician considered it appropriate. We evaluated safety and tolerability throughout the study period. Other urate-lowering drugs were not allowed both during the study period and 1 month before the start of the study. All other medications, including those that may affect urate metabolism (such as diuretics and aspirin), were continued throughout the study without changing their dosage. Physicians were careful to observe and check for the occurrence of any AEs throughout the study period. Vital signs (blood pressure, pulse rate) and laboratory tests (red blood cell counts, white blood cell counts, platelet count, hemoglobin, hematocrit, albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, γ-glutamyl transpeptidase, creatine kinase, creatinine, blood urea nitrogen and serum urate) were measured at baseline and at weeks 4, 8, 12, 16 and 24. Urinary protein/creatinine ratio (urinary protein divided by urinary creatinine) was measured using a spot urine sample at baseline and at week 24.

End points and statistical analysis

The primary end points were the safety and tolerability of febuxostat. Any suspected relationship between adverse event (AEs) and the study drug were reported by the primary nephrologist and evaluated based on the clinical course (timing of the event, reversal of event by cessation of the medication, etc). 'Possibly' indicated that, although a relationship between the AE and the study drug could not be excluded, the probability that they were connected was considered to be fairly low (less than a 50% chance). 'Probably' indicated that the probability that AE and the study drug were related was considered to be relatively high (more than a 50% chance).

The other end points included relative (%) change from baseline sUA, the achievement rate of the target sUA ($\leqslant$6.0 mg dl^{-1}) according to the guidelines of the Japanese Society of Gout and Nucleic Acid Metabolism[10] and relative (%) changes in eGFR and urinary protein from their baseline levels.

The distribution of continuous variables was presented as the mean ± s.d., and those of categorical variables were presented as an absolute number (%). To evaluate the association between the change in sUA level or sUA at week 24 and the change in eGFR or urinary protein levels, a multivariate regression analysis was performed using stepwise variable selection methods. A *P*-value <0.05 was considered statistically significant in all analyses. All analyses were performed using the SAS statistical software (version 9.3, SAS Institute, Cary, NC, USA).

RESULTS

After giving written consent, a total of 70 patients were enrolled in the study from December 2011 to November 2012. All patients received febuxostat. Baseline patient characteristics are shown in Table 1. The number of patients with CKD stages G3b, G4 and G5 were 19, 32 and 19, respectively. The average age was 66 ± 12 years old. There were far fewer female than male patients, the former accounting for 23% of all patients. Causes of CKD were diagnosed clinically, with hypertensive nephrosclerosis (30%) and diabetic kidney disease (16%) being predominant. Common comorbidities were hypertension (94%) and diabetes mellitus (34%); cardiovascular disease (13%) and cerebrovascular disease (11%) were not as prevalent. Baseline sUA, urinary protein and blood pressure were 10.2 ± 1.8 mg dl^{-1}, 1.7 ± 1.8 g g^{-1} creatinine and 133/74 mm Hg, respectively.

Safety and tolerability

Fourteen participants (20%) withdrew from the study. However, only 5.7% (4 patients) withdrew owing to the occurrence of an AE. These events included numbness, skin rash, palpitation/chest pain and

Table 1 Baseline patient characteristics

		Baseline eGFR (ml min^{-1} per 1.73 m^2)[a]		
Characters	*All patients (n = 70)*	*< 45 [G3b] (n = 19)*	*< 30 [G4] (n = 32)*	*< 15 [G5] (n = 19)*
Age (years)	66 ± 12	67 ± 11	65 ± 13	67 ± 11
Gender, female	16 (23%)	2 (11%)	10 (31%)	4 (21%)
Cause of CKD				
Hypertensive nephrosclerosis	21 (30%)	6 (32%)	7 (22%)	8 (42%)
Diabetic kidney disease	11 (16%)	3 (16%)	3 (9%)	5 (26%)
IgA nephropathy	4 (6%)	0 (0%)	4 (13%)	0 (0%)
Chronic glomerular nephritis	3 (4%)	1 (5%)	2 (6%)	0 (0%)
Other	31 (44%)	9 (47%)	16 (50%)	6 (32%)
Past illness/comorbidity				
Hypertension	66 (94%)	16 (84%)	31 (97%)	19 (100%)
Diabetes mellitus	24 (34%)	4 (21%)	14 (44%)	6 (32%)
Cardiovascular disease	8 (11%)	1 (5%)	4 (13%)	3 (16%)
Cerebrovascular disease	9 (13%)	2 (11%)	3 (9%)	4 (21%)
Serum urate (mg dl^{-1})	10.2 ± 1.8	9.9 ± 1.5	10.6 ± 2.1	9.8 ± 1.3
eGFR (ml min^{-1} per 1.73 m^2)[a]	23.3 ± 9.8	35.5 ± 3.3	23.1 ± 5.1	11.5 ± 2.1
SBP (mm Hg)	133 ± 18	129 ± 19	133 ± 19	136 ± 17
DBP (mm Hg)	74 ± 10	73 ± 8	75 ± 9	73 ± 13
Urinary protein (g g^{-1} creatinine)	1.7 ± 1.8	1.3 ± 1.8	1.7 ± 1.8	2.1 ± 1.7

Abbreviations: CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A; SBP, systolic blood pressure.
Mean ± s.d.; [ ]: eGFR stages defined in CKD guideline 2012 of Japan Society of Nephrology. G3b: CKD stage G3b ($30\leqslant$eGFR<45), G4: CKD stage G4 ($15\leqslant$eGFR<40), G5: CKD stage G5 (eGFR<15).
[a]eGFR (ml min^{-1} per 1.73 m^2) = 194 × serum creatinine (mg dl^{-1})$^{-0.1094}$ × age (years)$^{-0.287}$ (× 0.739, if female).

Table 2 Adverse events during the study period

	No. of patients (%)	*No. of events*
Any adverse events	6 (8.6%)	8
Any adverse drug reactions[a]	5 (7.1%)	7

[Details of adverse events]

Case no.	*Event*	*Severity*	*Relation to study drug*[b]	*Outcome*	*Onset (day)*[c]	*Dose*[d] *(mg per day)*	*Serum urate*[e] *(mg dl*$^{-1}$*)*	*eGFR stage*[f]	*Discontinuation*
1	Numbness	Mode rate	Possibly	Recovered	12	10	[8.1]	G4	Yes
2	Gouty attack	Mild	Probably	Recovered	106	40	6.1	G3b	No
3	Skin rash	Mild	Possibly	Recovered	55	20	5.3	G5	Yes
4	Palpitation	Mild	Possibly	Recovered	1	10	[11.5]	G4	Yes
	Chest pain	Mild	Possibly	Recovered	1				
5	Edema	Mild	Not related	Not recovered[g]	13	10	[9.0]	G5	No
6	Constipation	Mild	Probably	Recovered	29	10	6.6	G4	Yes
	Neuropathic pain	Mild	Probably	Recovered	29				

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
[a]Events related to the study drug among all adverse events.
[b]'Possibly' indicates the relation between the events and the study drug cannot be excluded but not highly suspected (chance is less than half). 'Probably' indicates the relation between the events and the study drug is highly suspected (chance is more than half).
[c]Days of study treatment.
[d]Dose of study drug when the event occurred.
[e]The latest serum urate before the event occurred, [ ]: baseline data were shown owing to no available data after the start of study treatment.
[f]Defined in CKD guideline 2012 of Japan Society of Nephrology.
[g]Edema accompanied by renal failure as primary disease continued.

constipation/neuropathic pain (Table 2). Other causes for withdrawal included: (1) the patient's circumstances in four cases (5.7%), of which three involved housing moves and one declined to continue the study); (2) exacerbation of comorbidities or physician's judgment in six cases (8.6%), of which one involved worsening of pre-existing hypertension and edema requiring a change in the dose of diuretics and antihypertensives, two had worsening of osteoarthritis requiring nonsteroidal anti-inflammatory drugss and in three cases there was non-adherence to the protocol).

Eight AEs occurred in six patients (8.6%): one patient had one AE unrelated to the study drug leaving 5 out of 70 patients (7.1%) with drug-related AEs. One AE occurred in a patient with CKD stage G3b (5.3%), five AEs occurred in three patients with G4 (9.4%) and two AEs involved two patients with G5 (10.5%), suggesting that AEs were not related to the level of kidney dysfunction. Most AEs were mild without permanent sequelae (Table 2). No clinically significant changes in laboratory data including liver enzymes or blood counts were observed (data not shown).

Serum urate-lowering effect

Febuxostat lowered serum urate levels significantly and steadily by $>40\%$ on average as early as week 12 and by $>50\%$ in CKD stage 4 or 5 at week 24 (Figure 1a). More than 70% of all patients and more than 80% of CKD stage 5 patients reached below the sUA target level of 6.0 mg dl^{-1} as early as week 12 (Figure 1b).

Changes in blood pressure, eGFR and urinary protein

Average systolic and diastolic blood pressure and pulse rate did not change significantly throughout the study period (data not shown). Estimated GFR significantly increased by 7.4% from baseline in CKD stage G3b at week 24, whereas eGFR decreased in G4 and G5 (Figure 2a). Urinary protein levels decreased, although not significantly in CKD stages G3b and G4, at week 24 (Figure 2b).

Because there was no control group in this study (subjects not taking febuxostat), we could not conclude that the changes in eGFR or proteinuria were entirely due to febuxostat. Therefore, to evaluate if these change in eGFR or proteinuria were associated with the degree of reduction of sUA, we conducted a multivariate regression analysis to investigate the association between the change in sUA or sUA at week 24, and the change in eGFR or proteinuria. The analysis showed that all of three parameters of sUA: the relative (%) reduction of sUA (Model 1), the absolute reduction of sUA (Model 2) and sUA at week 24 (Model 3) were selected as a significant independent variables for the increase in eGFR (Table 3). In G4 and G5 patients whose average eGFR did decline from baseline, the absolute reduction of sUA (Model 2) was still selected as a significant independent variable for the smaller decline in eGFR (Table 3). Multivariate regression analysis also suggested that the percent reduction of sUA was associated with the decrease in urinary protein (Table 4).

Because this is an observational study, we are unable to prove a cause and effect relationship between the reduction of sUA and the change in eGFR/proteinuria. It is possible that it was not the decrease in sUA that was responsible for the slower decline in eGFR and the decrease in proteinuria, but *vice versa*. To investigate this possibility, we conducted a logistic regression analysis using eGFR or the level of proteinuria (at baseline or at 24 weeks) as explanatory variables, and the degree of reduction of sUA ($\leqslant$6 mg dl^{-1} at 24 weeks or not, or $\geqslant$30% reduction at 24 weeks from the baseline) as outcome variables. Every analysis yielded nonsignificant results (P = NS).

DISCUSSION

The novel findings in this study are twofold. First, we demonstrated for the first time that febuxostat was efficacious in reducing sUA levels in patients with moderate-to-severe kidney dysfunction (eGFR $<$45 ml min^{-1} per 1.73 m^2) and that it was also safe and tolerable at the efficacious dose. Second, we made the intriguing observation that a greater reduction in sUA was associated with an increase in

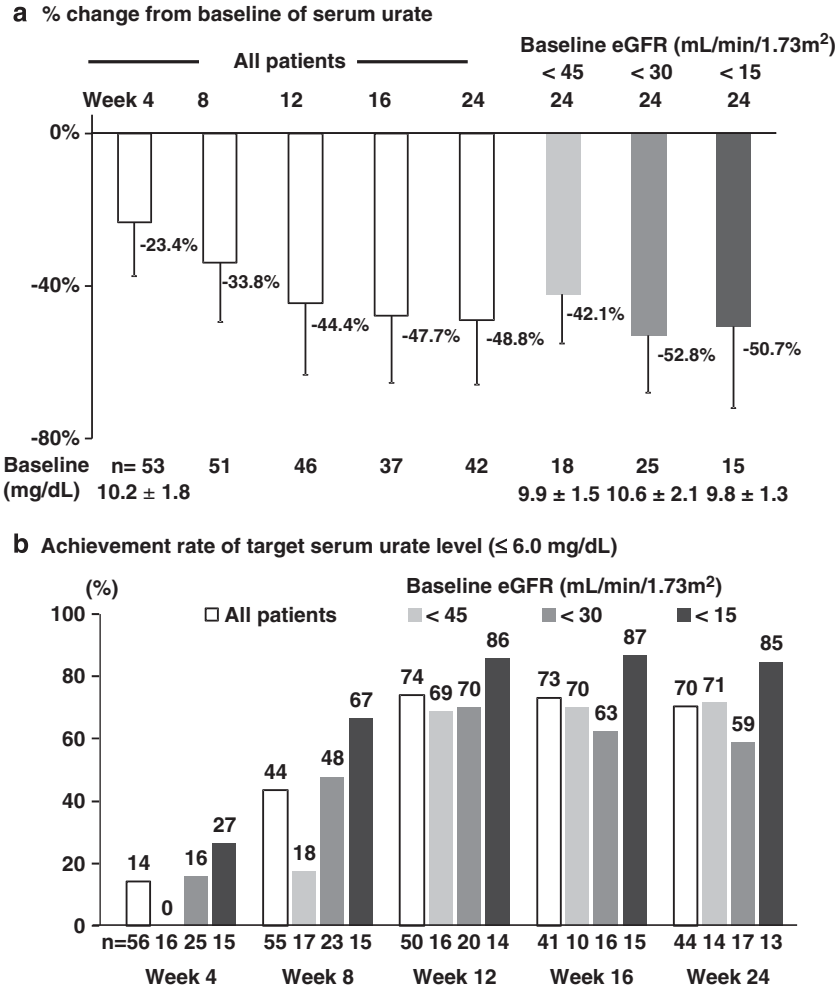

Figure 1 Serum urate-lowering effect of febuxostat in patients with advanced chronic kidney disease (CKD). (**a** and **b**) Mean ± s.d.; serum urate significantly decreased from baseline (paired *t*-test: $P<0.001$ for all time points and all estimated glomerular filtration rate (eGFR) stages).

eGFR and a decrease in proteinuria, even in the absence of any significant change in blood pressure.

Febuxostat was found to be safe and tolerable even in patients with advanced kidney dysfunction. In our study, seven drug-related AEs occurred in only 5 (7%) of 70 patients, and although four out of these five patients discontinued febuxostat, all but one of the events were mild. Further, every patient recovered completely from these AEs. Only one patient experienced a moderate degree of numbness, which resulted in discontinuation of febuxostat and was followed by a complete recovery shortly thereafter. Another patient who suffered from gouty attacks continued to take febuxostat and experienced complete resolution of the arthritis without permanent sequelae. There was no evidence of liver dysfunction or hematologic abnormalities, although there is one report in the literature of acute neutropenia associated with febuxostat in a case of CKD.[11] There are several reasons why febuxostat is safer than other urate-lowering drugs such as allopurinol or probenecid in patients with CKD. Febuxostat is (1) primarily metabolized in the liver, (2) excreted in both the urine and feces, (3) highly selective in its mechanism of action and (4) not uricosuric (less likely to cause urolithiasis).[12] We recently reported the results of a pharmacokinetic and pharmacodynamic study of febuxostat in patients with mild-to-moderate kidney dysfunction (eGFR $>30\,\mathrm{ml\,min^{-1}}$ per $1.73\,\mathrm{m^2}$).[8] Although impaired renal function caused an increase in systemic exposure to unchanged febuxostat, the increase was slight in the presence of mild-to-moderate renal impairment. In addition, there were no AEs, and unchanged febuxostat or its metabolites did not accumulate after repeated exposure.[8] In that study, we also showed that drug-related AEs did not increase as renal dysfunction worsened (AEs occurred in 1 out of 19 CKD stage 3b, 4 out of 32 stage 4, 1 out of 19 stage 5), indicating that the level of kidney dysfunction is not related to vulnerability to AEs. Thus, although we do not have pharmacokinetic/pharmacodynamic data in this present study, we are confident that febuxostat is safe and tolerable even in patients with advanced kidney dysfunction (eGFR $<45\,\mathrm{ml\,min^{-1}}$ per $1.73\,\mathrm{m^2}$).

Questions may arise about the safety profile of febuxostat compared with other urate-lowering drugs, especially allopurinol. Paisansinsup *et al.*[13] reported that the rate of AEs (possible or definite) with the use of allopurinol in CKD ranged from 10.5 to 13.9% according to the level of kidney function and the dose of allopurinol. These statistics are much worse than the safety profile of febuxostat reported in our study. Two important concerns with allopurinol in CKD should be emphasized. First, it is clear that the active metabolite oxypurinol, which is associated with adverse effects, is increased in patients with CKD. Second and more importantly, there have been several reports of a severe allopurinol hypersensitivity

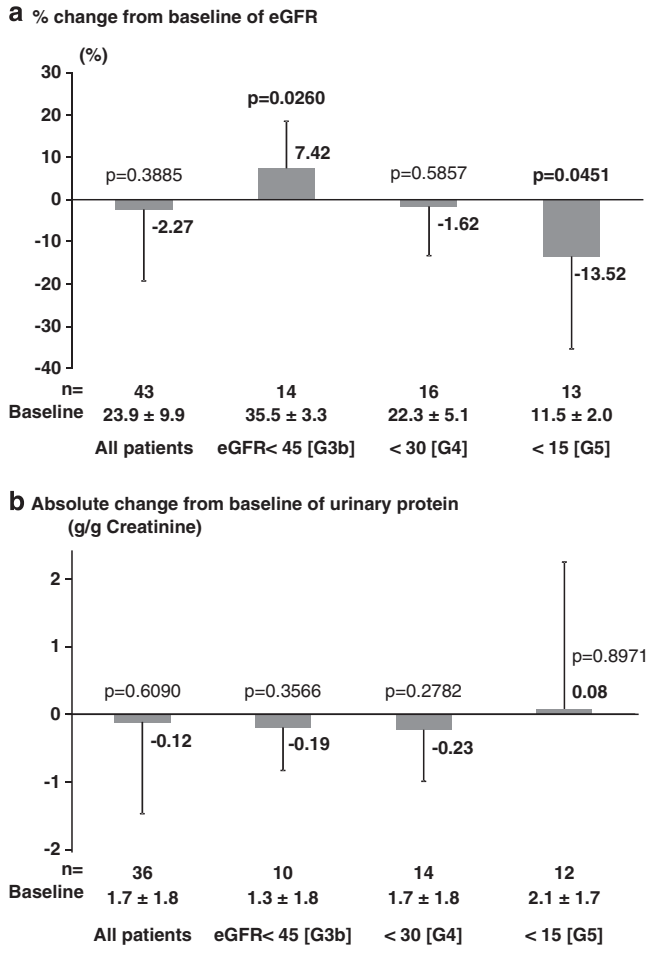

Figure 2 Change in estimated glomerular filtration rate (eGFR) and urinary protein from baseline by febuxostat in patients with advanced chronic kidney disease (CKD). (**a** and **b**) Mean ± s.d., paired *t*-test to assess the change from baseline. [ ]: eGFR stages defined in the CKD guideline 2012 of Japan Society of Nephrology.

syndrome in patients with CKD that could be fatal. This syndrome has not been reported to occur with febuxostat, making it a more attractive drug to use in CKD.

Our study also demonstrated that febuxostat was very efficacious in reducing sUA levels even in patients with moderate-to-severe renal dysfunction. By week 24, the sUA levels were reduced by $>40\%$ in CKD stage 3b and by $>50\%$ in CKD stages 4 and 5. The percentage of patients who achieved target sUA levels of $6\,mg\,dl^{-1}$ or less was as high as 71%, 59% and 85% in CKD stages 3b, 4 and 5, respectively.

Very few studies have addressed febuxostat efficacy in patients with moderate-to-severe renal dysfunction. Schumacher *et al.*[14] demonstrated that febuxostat reduced sUA levels to $<6\,mg\,dl^{-1}$ in 44%, 46% and 60% of patients with mild renal dysfunction (serum creatinine of 1.5–2 $mg\,dl^{-1}$) who were taking 80, 120, and 240 mg per day of febuxostat, respectively.[14] Becker *et al.*[7] reported that patients with CKD stage 3 who took 40 and 80 mg per day of febuxostat achieved sUA levels $<6\,mg\,dl^{-1}$ in 43.1% and 71.3% of cases, respectively.[7] In comparison with these studies, we found that febuxostat was as efficacious if not more in patients with advanced renal dysfunction. We previously found in the pharmacokinetic study that blood levels of febuxostat were slightly, although significantly, increased in patients with mild-to-moderate CKD and impaired kidney function (although there was no accumulation or escalation). This could, in part, be explained by the greater urate-lowering effect of febuxostat in CKD. Before febuxostat became available, allopurinol was the only effective urate-lowering drug, but the dose needed to be reduced to a level that was commensurate with the kidneys' ability to excrete its metabolites. In addition, allopurinol's efficacy is much less than that of febuxostat, especially with the reduced doses that must be used in patients with kidney dysfunction.[7] In fact, Japanese nephrologists tend to limit the dose of allopurinol to only 100 mg per day in CKD stages 4 and 5,[15] which is likely to be ineffective in lowering sUA levels to $<6\,mg\,dl^{-1}$ in most of the cases. With the advent of febuxostat, nephrologists are now able to use a potent urate-lowering drug to achieve targeted sUA levels without safety concerns.

Finally, it is an intriguing finding of our study that the greater reduction in sUA levels with febuxostat was associated with an increase in eGFR and a probable decrease in proteinuria at the 24-week observation point, although it did not significantly change blood pressure. The estimated GFR increased after sUA reduction with febuxostat in patients with CKD stage 3b, but eGFR decreased in patients with CKD stages 4 and 5. However, because of the lack of a control group, it is unclear whether this change in eGFR is due to the reduction in serum urate or to febuxostat itself. Consequently, we further analyzed the association between the degree of sUA reduction and the change in eGFR. The multivariate analysis consistently showed that the greater reduction in sUA levels was associated with less of a decrease in eGFR. Proteinuria did not significantly change during the study period, but the multivariate analysis revealed that the greater reduction of sUA levels was associated with a greater reduction in proteinuria. Because this was an observational study however, we are unable to prove a cause–effect relationship for this association. The reverse may also have been a possibility in that proteinuria might have resulted in a lower amount of protein-bound drug circulating in the blood reducing its capacity to lower uric acid levels. To investigate the possibility of this reverse relationship, we conducted a logistic regression analysis with eGFR or proteinuria as explanatory variables and the degree of reduction in sUA levels as an outcome variable. The results of this analysis did not support the possibility of a reverse relationship.

HU has been well known to be associated with the progression of CKD.[16,17] Iseki *et al.*[1] have also shown that both the absolute value and the change in sUA levels are associated with a change in eGFR.[1] There have been several studies showing a renoprotective effect of lowering sUA levels in patients with CKD, but most of these studies used allopurinol as the urate-lowering agent.[18] Whelton *et al.*[19] found that in patients with either mild or no evidence of renal dysfunction (eGFR of 65.8 ± 13, range 36–106) taking 40–120 mg of febuxostat daily for 5 years improved eGFR by $1\,ml\,min^{-1}$ from baseline for every $1\,mg\,dl^{-1}$ decrease in sUA. Sezai *et al.*[20] also demonstrated that febuxostat preserved or even improved kidney function compared with allopurinol in patients with moderate kidney dysfunction (eGFR of $47.5 \pm 17.3\,ml\,min^{-1}$). Our prospective study is the first to demonstrate that, even in more advanced cases of kidney dysfunction, a greater reduction of sUA levels is associated with a smaller decline in eGFR and less of an increase in proteinuria. Although Feig *et al.*[21] reported that a reduction of sUA reduced blood pressure in the short term, we were not able to reproduce this finding. The different effect on blood pressure between the two studies may reflect differences in the age of the cohort; in the study by Feig, subjects were in adolescence, whereas in our study, participants ranged from middle age to the elderly.

Table 3 Factors associated with % change in eGFR

Variables	*Regression coefficient*	*S.e.*	P-*value*	*Standardized regression coefficient*
All patients				
Model 1				
Diabetes mellitus	−0.087	0.043	0.0494	−0.234
Baseline serum urate (mg dl^{-1})	0.025	0.012	0.0454	0.241
% Change from baseline to eeek 24 of serum urate (per 10%)	−0.032	0.012	0.0112	−0.312
Baseline eGFR (ml min^{-1} per 1.73 m^2)	0.010	0.002	<0.0001	0.585
Model 2				
Change from baseline to week 24 of serum urate (per 1 mg dl^{-1})	−0.035	0.013	0.0087	−0.383
Baseline eGFR (ml min^{-1} per 1.73 m^2)	0.010	0.002	<0.0001	0.586
Model 3				
Baseline serum urate (mg dl^{-1})	0.039	0.013	0.0048	0.383
Serum urate at week 24, ⩾5 mg dl^{-1}	−0.098	0.046	0.0382	−0.283
Baseline eGFR (ml min^{-1} per 1.73 m^2)	0.011	0.002	<0.0001	0.632
G4 and G5 patients				
Model 1				
Baseline eGFR (ml min^{-1} per 1.73 m^2)	0.010	0.005	0.0480	0.370
Model 2				
Change from baseline to week 24 of serum urate (per 1 mg dl^{-1})	−0.039	0.016	0.0209	−0.406
Baseline eGFR (ml min^{-1} per 1.73 m^2)	0.013	0.005	0.0088	0.491
Model 3				
Baseline eGFR (ml min^{-1} per 1.73 m^2)	0.013	0.005	0.0088	0.491

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate.
Multivariate regression analysis in each model including the following explanatory variables using stepwise variable selection with $P<0.15$.
Model 1: % Change from baseline to week 24 of serum urate + basal variables.
Model 2: Absolute change from baseline to week 24 of serum urate (mg dl^{-1}) + basal variables.
Model 3: Serum urate (⩾5 or <5 mg dl^{-1}) at week 24 + basal variables.
Basal variables: Gender, age (years, continuous), hypertension, diabetes mellitus, BMI (continuous), baseline serum urate (mg dl^{-1}, continuous) and baseline eGFR (ml min^{-1} per 1.73 m^2, continuous).

Table 4 Factors associated with absolute change in urinary protein

Variables	*Regression coefficient*	*S.e.*	P-*value*	*Standardized regression coefficient*
All patients				
Model 1				
Baseline BMI	−0.105	0.063	0.1086	−0.272
% Change from baseline to Week 24 of serum urate (per 10%)	0.310	0.139	0.0331	0.367
Model 2				
Change from baseline to week 24 of serum urate (per 1 mg dl^{-1})	0.248	0.123	0.0528	0.330
Model 3				
Baseline urinary protein (g g^{-1} creatinine)	−0.194	0.124	0.1254	−0.260

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate.
Multivariate regression analysis in each model including the following explanatory variables using stepwise variable selection with $P<0.15$.
Model 1: % Change from baseline to week 24 of serum urate + basal variables.
Model 2: Absolute change from baseline to week 24 of serum urate (mg dl^{-1}) + basal variables.
Model 3: Serum urate (⩾5 or <5 mg dl^{-1}) at week 24 + basal variables.
Basal variables: gender, age (years, continuous), hypertension, diabetes mellitus, BMI (continuous), baseline serum urate (mg dl^{-1}, continuous) and % change of eGFR (continuous).

How a reduction in sUA levels with febuxostat can be renoprotective is not well understood, although several reports have suggested a number of potential mechanisms.[22,23] Johnson *et al.*[24] suggested in their beautiful review that urate-lowering therapy blocks the renin–angiotensin system, leading to a decrease in glomerular hypertension, which in turn reduces proteinuria and preserves GFR. However, he also mentioned that HU is tightly associated with cyclosporine nephrotoxicity, which is a non-proteinuric CKD, indicating that a hemodynamic change alone cannot fully explain the drug's renoprotective effect. According to Johnson, urate-lowering drugs may also confer a renoprotective effect by suppressing uric acid's oxidative effect on the endothelium.

Two limitations of our study are the absence of a control group and the relatively small number of participants. However, because our main purpose was to investigate the safety and efficacy of febuxostat in moderate-to-severe kidney dysfunction, we believe that it was not essential to compare febuxostat to other drugs or to enroll more participants. Second, because of restrictions dictated by Japanese health insurance policies, we were unable to measure albuminuria because this test can only be ordered in patients with diabetic nephropathy. However, the average proteinuria in our population exceeded 1 g g^{-1} per creatinine. As, with the exception for rare cases of paraproteinuria, albumin is the main content of urinary protein, we believe that the reduction in proteinuria served as a good indicator of a reduction in albuminuria.

In conclusion, febuxostat is safe, tolerable and efficacious in patients with moderate-to-severe kidney dysfunction. In addition, the greater reduction in sUA levels with febuxostat treatment is associated with a slower progression of CKD, although a causal relationship cannot be confirmed in this study.

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