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Research Article

Therapeutic Potency of Febuxostat for Hyperuricemia in Patients with Chronic Kidney Disease

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Keywords

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Abstract

Febuxostat is a non-purine xanthine oxidase inhibitor for which the metabolic pathway extensively differs from that for allopurinol. Since little information is available about the use of this agent in patients with chronic kidney disease (CKD), we investigated the effects of oral febuxostat for 2 months in patients with CKD, stage G3b–G5, and asymptomatic hyperuricemia. We found that the degree of serum uric acid decrease (ΔUA) after febuxostat administration was significantly larger in patients who had not been previously administered allopurinol or angiotensin receptor blockers. Furthermore, we found a significant positive correlation between ΔUA and baseline UA concentration. Finally, we found a weak negative correlation between ΔUA and baseline estimated glomerular filtration rate, suggesting that febuxostat could efficiently decrease UA levels in patients with severe renal dysfunction. These results suggest that we can prescribe febuxostat more safely and efficiently than allopurinol, for which the dosage has to be carefully reduced in patients with relatively advanced CKD.

ABBREVIATIONS

Chronic Kidney Disease; XO: Xanthine Oxidase; UA: Uric Acid; ARB: Angiotensin II Receptor Blocker; eGFR: Estimated Glomerular Filtration Rate

INTRODUCTION

Although hyperuricemia is a relatively common complication in patients with chronic kidney disease (CKD), a large body of evidence suggests that it has a pathogenic role in the progression of CKD itself [1-3]. A major obstacle when treating patients with CKD with hyperuricemia is the adverse effects caused by allopurinol, including severe dermatological diseases such as Stevens-Johnson syndrome or toxic epidermal necrosis. Therefore, it is necessary to reduce the dose of allopurinol, but this can sometimes lead to inadequate suppression of serum uric acid (UA) levels [4-6]. According to previous reports, febuxostat is highly efficacious in reducing serum UA levels in patients with CKD [7]. However, only a few reports have studied its efficacy and safety in more advanced cases of CKD [8,9].

Febuxostat, a non-purine xanthine oxidase (XO) inhibitor which recently received marketing approval, has been focused on as an alternative for the treatment of hyperuricemia in patients with CKD because it undergoes hepatic metabolism and may require less dose adjustment in association with renal function[10, 11]. However, information regarding the experience with this therapeutic agent among patients with advanced CKD is limited. In this regard, the current study investigated the effects of febuxostat in patients with relatively advanced CKD, i.e., greater than stage G3b, and hyperuricemia in terms of reduction of serum UA levels.

MATERIALS AND METHODS

Forty-nine- patients with CKD who had been prescribed allopurinol, or who had serum UA levels above 8.0 mg/dL and were not receiving anti-hyperuricemic agents, participated in the study. Estimated glomerular filtration rate (eGFR: mL/min/1.73 m^2) was calculated using the formula of the Japanese Society of Nephrology [12]. Eighty-four percent of patients (41/49) were classified in CKD stage 4 or 5 (Table 1). The subjects had to be

in a stable condition, had no history of active liver diseases or any other significant medical status, and no change in diuretics or steroid therapy within one month of study enrolment. The usual medications, such as anti-hypertensive agents, erythropoiesis-stimulating agents and phosphate binders, were continued during the study period. The exclusion criteria were as follows: age of < 20 years or > 90 years, type I diabetes mellitus or type II diabetes mellitus with poor glucose control (glycosylated hemoglobin> 9% at the start of the observation period), treatment with immunosuppressant agents, pregnancy, and any medical or surgical condition that made patients unsuitable for this study as judged by the attending physician. All patients were assigned to oral febuxostat and entered the 2-month treatment period during which the initial dose of febuxostat was 10- 20 mg orally once daily in the morning. The initial dose of febuxostat was principally determined by the attending physician. Twenty-six and 23 patients received febuxostat doses of 10, and 20 mg, respectively. In the group of allopurinol-treated patients, anti-hyperuricemic medication was changed to febuxostat according to the following guideline: If the dose of previously administered allopurinol was 50 mg/day or higher, then the dose of febuxostat was 10 mg/day or 20 mg/day, respectively.

Blood samples were obtained at the beginning and the end of febuxostat treatment. Serum levels of UA, creatinine (Cr), sodium (Na), chloride (Cl), potassium (K), calcium (Ca), inorganic phosphate (Pi), were measured. This study was performed in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of Dokkyo Medical University. All patients included in the present study provided their informed consent.

The data were expressed either as the number of participants or as the percentage (%) of the study population. The remaining data were expressed as means ±standard error (SE). An analysis of variance combined with Fisher's protected least significant difference test for normal distributions, and the Kruskal–Wallis test with Dunn's method for skewed distributions were used to compare the two time points, when appropriate. To evaluate the associations between the degree of UA suppression and the baseline serum UA concentration, the previously used allopurinol dose, and prescription of angiotensin II receptor blocker (ARB), a multivariate regression analysis was performed using stepwise variable selection methods. Values of $p < 0.05$ were considered to be statistically significant. All statistical procedures including multiple regression analyses were performed using the JMP software program for Windows (SAS Institute, Cary, NC) unless otherwise stated.

RESULTS AND DISCUSSION

Current urate-lowering strategies include reducing UA production with XO inhibitors and accelerating the urinary excretion of UA by using uricosuric agents. Uricosuric agents, such as probenicid and benzbromarone, may have limited effectiveness in patients with reduced renal function [13, 14]. The purine analogue XO inhibitor, allopurinol, is widely prescribed for the treatment of hyperuricemia, but requires dose adjustment in subjects with renal impairment [4-6]. Therefore, we used febuxostat in this study, which can be used safely and efficaciously without dose adjustment, even in patients with CKD [8,9].

The demographic profiles of the 49patients included in the present study are summarized in (Table 1). The number of patients at each stage of CKD is also shown in (Table 1).The causes of advanced CKD included diabetic nephropathy, chronic glomerulonephritis, hypertensive nephrosclerosis, and polycystic kidney disease. All subjects were receiving the optimum tolerated medical management. Febuxostat lowered serum UA levels (Total: 8.4 ± 1.6 mg/dL, male: 8.3±1.5, and women: 8.6±1.7 mg/dL at baseline) significantly from 2 months after the initiation of treatment (Table 2A). When we divided the study population according to the underlying cause of CKD, the baseline and 2-month serum UA levels were as follows, respectively: diabetic nephropathy, 8.09 ± 1.85, 6.55 ± 1.24 ($p < 0.005$); chronic glomerulonephritis, 8.67 ± 1.49, 6.60 ± 1.66 ($p < 0.005$); and hypertensive nephrosclerosis, 7.97 ± 1.29, 6.40 ± 1.08 ($p = 0.22$) (Table 2B). Febuxostat was well tolerated by the patients with no withdrawals due to side effects or allergic reactions. Serum levels of sodium, potassium, chloride, calcium, inorganic phosphate, and creatinine did not change during the observation period (Table 2A). No patients experienced symptoms of gouty arthritis, including joint pain, swelling or redness, during the observation period.

The KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease [15] states that there is insufficient evidence to support the use of anti-hyperuricemic agents for lowering serum UA in patients with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay the progression of CKD. Therefore, the appropriate dose of febuxostat among asymptomatic hyperuricemia subjects with advanced CKD has not yet been established. The current findings suggest that even relatively low doses of febuxostat, 10 mg or 20 mg, might effectively reduce serum UA levels in CKD patients to 6.5 ± 1.4 mg/dl after only 2 months of febuxostat administration.

Table 1: Demographic profiles of the patients at the start of the study.

DEMOGRAPHIC CHARACTERISTICS	
Age	57.7±16.7
Sex (male/female)	32/17
CKD STAGE	
IIIb	8
IV	22
V	19
UNDERLYING CAUSES OF CKD, N (%)	
Diabetic nephropathy	15(31)
Chronic glomerulonephritis	26(53)
Hypertensive nephrosclerosis	6 (12)
Polycystic kidney disease	2(4)
MEDICATION, N (%)	
Calcium channel antagonist(s)	35(71)
Angiotensin-converting-enzyme inhibitor	1(2)
Angiotensin receptor blocker(s)	40(81)
Thiazide-like diuretic(s)	5 (10)
Loop diuretic(s)	20(41)

Table 2A. Changes in clinical parameters between the beginning and the end of the observation period

	Total (n= 49)		Male (n= 32)		Female (n= 17)	
	BASELINE	2 MONTHS	BASELINE	2 MONTHS	BASELINE	2 MONTHS
UA(mg/dL)	8.4±1.6	6.5±1.4*	8.3±1.5	6.7±1.1*	8.6±1.7	6.2±1.9*
Na(mEq/L)	139.9±2.8	140.1±4.1	139.8±3.3	140.5±3.3	140.3±1.8	139.9±5.4
K(mEq/L)	4.7±0.7	4.7±0.6	4.7±0.7	4.7±0.6	4.7±0.6	4.7±0.6
Cl(mEq/L)	106.3±5.5	105.8±4.4	106.9±3.8	106.6±3.5	104.9±7.8	104.3±5.6
Ca(mg/dL)	9.3±0.5	9.3±0.5	9.2±0.5	9.2±0.6	9.5±0.5	9.4±0.4
IP(mg/dL)	4.1±1.3	3.9±0.9	3.9±1.3	3.7±0.9	4.3±1.1	4.1±0.9
Cre(mg/dL)	3.3±2.3	3.2±2.0	3.5±2.7	3.4±2.3	2.9±1.1	2.7±1.2
eGFR (mL/min/1.73m^2)	20.1±10.5	20.7±10.2	21.6±11.2	21.9±11.9	18.9±8.0	16.5±6.1

*: $p < 0.001$

Table 2B: Changes in clinical parameters between the beginning and end of the observation period according to the cause of chronic kidney disease.

	BASELINE	2 MONTHS
Diabetic nephropathy	8.09 ± 1.85	6.55 ± 1.24
Chronic glomerulonephritis	8.67 ±1.49	6.60 ±1.66
Hypertensive nephrosclerosis	7.97 ±1.29	6.40 ±1.08

*: $p < 0.005$, #: $p = 0.22$

In the patients who had received allopurinol as an anti-hyperuricemic agent before this study started, ΔUA was significantly smaller than that in the patients who did not previously receive allopurinol ($p < 0.001$, Figure 2A). This is in accordance with the findings of several previous studies showing the superiority of febuxostat over allopurinol with regard to decreasing of serum UA level in CKD patients [7,16]. When we plotted the dose of previously administrated allopurinol and ΔUA, we found a statistically significant negative correlation between them ($p= 0.0020$, Figure 2B). Furthermore, there was a significant positive correlation between ΔUA and baseline UA concentrations ($p< 0.0001$, Figure 3). Finally, we compared ΔUA in the patients with and without ARB administration. ΔUA was significantly larger in the patients not taking ARBs than in those taking ARBs ($p < 0.005$, Figure 4). It is not surprising that the magnitude of febuxostat-induced UA reduction was augmented when it was used in patients with higher serum UA. However, it was unexpected that serum UA would be suppressed more efficiently in patients not taking ARBs than in ARB-treated patients. Because there have been no previous reports investigating the efficacy of febuxostat in ARB-treated patients, its efficacy will need further confirmation in a larger number of patients.

When we focused on the relationship between ΔUA and baseline eGFR, there was a weak negative correlation but this was statistically insignificant (Figure 5). This suggests at least in part that serum concentrations of UA could be efficiently suppressed by febuxostat in patients with severe renal dysfunction.

Therefore, to evaluate whether these changes in ΔUA were independently associated with the baseline serum UA concentrations, ARB prescription, and previously used allopurinol dose, we conducted a multivariate regression analysis. The analysis showed that two parameters, the baseline serum UA concentrations and ARB prescription, were significant independent variables for the change in eGFR (Table 3), but the previously used allopurinol dose was not.

We have to consider the fact that some types of reactive oxygen species (ROS) are produced as byproducts of UA synthesis through XO [17,18]. The pharmacological nature of febuxostat is characterized by a higher bioavailability and a more potent blockade of XO activity than that achieved with allopurinol [4, 19]. Furthermore, febuxostat has been reported to have a more potent inhibitory activity than that of allopurinol against reactive oxygen synthesis [20,21]. Since serum UA levels could be used as a surrogate indicator of XO activity, the lower levels of UA attainable with febuxostat might inhibit cardiovascular events more effectively through strong ROS suppression. We recently reported that not only the serum levels of UA, but also those of 8-hydroxydeoxyguanosine, an oxidative stress marker, were significantly reduced after six months of febuxostat treatment, without adverse events [9]. Therefore we have to continue to investigate the clinical impact of lowering serum UA levels with febuxostat in patients with advanced CKD in terms of concomitantly reducing oxidative stress via the blockade of XO.

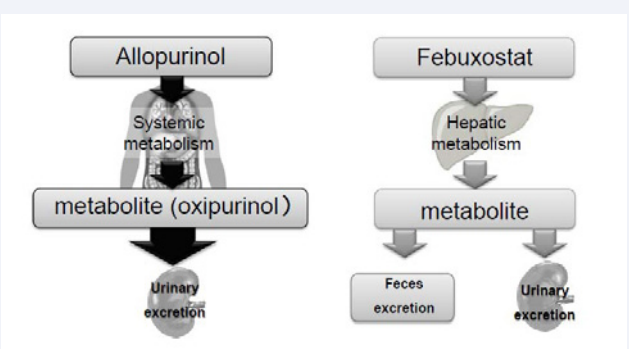

Figure 1 Allopurinol is converted to the active metabolite, oxipurinol, after systemic metabolism. Oxipurinol is mainly excreted in the urine and its serum concentration increases in patients with CKD. It is necessary to adjust the dose depending on the patients' renal function. However, febuxostat is metabolized in the liver and its inactive metabolite is excreted in feces and urine. It is not necessary to adjust the oral dose of febuxostat according to the patients' renal function.

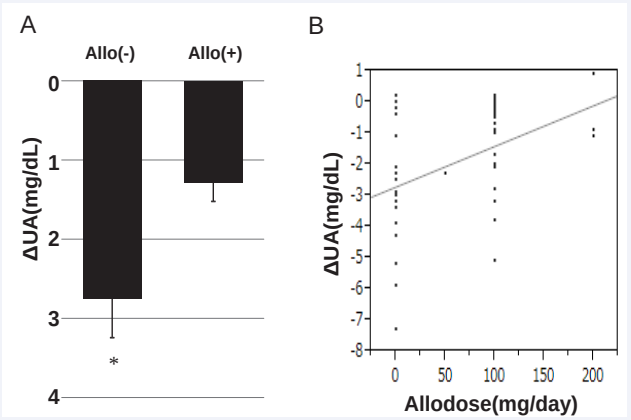

Figure 2 **A.** Compared to patients without prior allopurinol use, patients who received allopurinol before the beginning of this study showed a significantly smaller degree of decrease in serum UA concentration. Allo: allopurinol , *p < 0.001 versus Allo(+)
B. When we plot the dose of allopurinol and the degree of serum uric acid (UA) decrease, we observe a significant correlation between these two values (p< 0.005). The grey line in the graph is the regression line. ΔUA = -2.72 + 0.0130 x Allo dose.

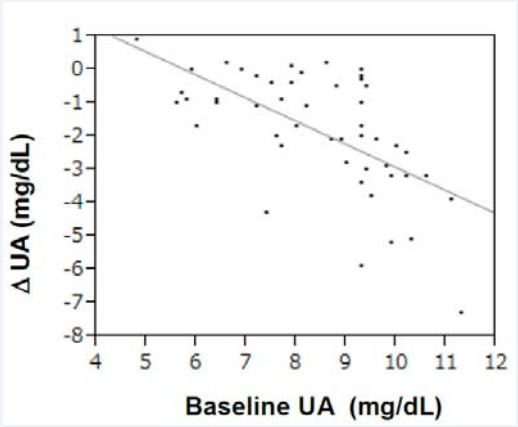

Figure 3 The higher baseline serum urci acid (UA) concentration, the larger the degree of serum UA decrease after febuxostat administration. This positive correlation was statistically significant (p < 0.0001).
The grey line in the graph is the regression line. ΔUA = 3.99 - 0.692 x Baseline UA.

Finally, the number of patients included in the present series was relatively small, and thus this study may be statistically underpowered or the clinical parameters may have been overestimated. Another limitation is the lack of data concerning the duration of allopurinol prescription. As such, our findings should be interpreted with caution. Nevertheless, our results encourage us to pursue further investigations regarding the clinical impact of lowering serum UA level with a low dose of febuxostat in patients with CKD. Obviously, more detailed studies with a larger number of subjects, and assessment of the effects of multiple factors affecting hyperuricemia, such as age, sex, and dietary habits, would shed light on the therapeutic challenges of treating asymptomatic hyperuricemia in patients with various stages of CKD.

CONCLUSION

Febuxostat is more efficacious in CKD patients with a high baseline serum UA concentration; however, its efficiency is blunted in allopurinol- or ARB-treated patients. Febuxostat was well tolerated by all patients with no withdrawals due to side effects. Febuxostat could be used efficaciously and safely even in cases of relatively advanced CKD including stages G4 and G5.

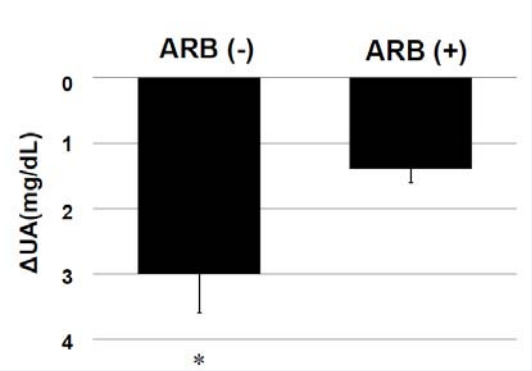

Figure 4 The degree of serum uric acid (UA) decrease after febuxostat administration was significantly larger in the patients without administration of angiotensin II receptor blocker (ARB) than in those who received ARBs. *p < 0.005versus ARB(+).

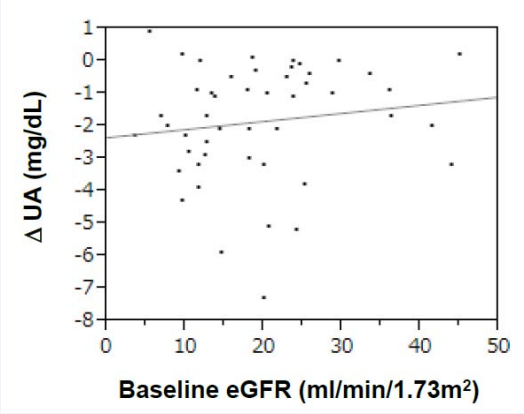

Figure 5 Baseline estimated glomerular filtration rate (eGFR) and the degree of serum uric acid (UA) decrease had a weak negative correlation but this was not statistically significant (p = 0.101). The grey line in the graph is the regression line. ΔUA = -2.48 + 0.0288 x Baseline eGFR.

Table 3: According to the result of multiple-regression analysis, the previously used allopurinol dose, baseline uric acid (UA) level, and angiotensin II receptor blocker (ARB) administration were independent variables to predict the degree of UA decrease.

	Regression coefficient	F statistic	P value
Baseline UA	-0.6	4.03	0.0000275
ARB	1.56	11.5	0.00143
Allo dose	0.00358	1.05	0.31

R^2: 0.543

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