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Comparisons of Therapeutic Effects of Allopurinol and Febuxostat in Chronic Hemodialysis Patients

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SUMMARY

More than few patients on maintenance hemodialysis present with hyperuricemia, and the control of serum uric acid level is an important issue in the long-term management. In addition to allopurinol, febuxostat can be used as a xanthine oxidase inhibitor in hemodialysis patients. In this study, the clinical effects of febuxostat were compared with allopurinol in chronic hemodialysis patients. Eligible hemodialysis patients taking allopurinol were randomly assigned to take 100 mg allopurinol (n = 26) or 20 mg febuxostat (n = 23) for 12 weeks. Serum uric acid was markedly lowered in the febuxostat group (0-week 6.7 mg/dL, 12-week 4.3 mg/dL, $p < 0.001$) as compared with the allopurinol group (0-week 6.0 mg/dL, 12-week 5.8 mg/dL) and systolic blood pressure was lowered by 5 mmHg ($p = 0.036$) at 4-week in the febuxostat group while blood pressure was not significantly changed in the allopurinol group throughout the study period. In addition, the dose of erythropoiesis stimulating agent was reduced (0-week 22.2 μg/wk, 12-week, 17.1 μg/wk, $p = 0.012$) and serum phosphate level was lowered (0-week 5.9 mg/dL, 12-week 5.1 mg/dL, $p = 0.027$) in the febuxostat group but not in the allopurinol group. It is concluded that febuxostat is more effective in lowering serum uric acid than allopurinol in hemodialysis patients. In addition, it is suggested that febuxostat has an advantage in the management of renal anemia and hyperphosphatemia as well as hyperuricemia.

Key words : uric acid, hyperuricemia, hemodialysis, xanthine oxidase inhibitor, febuxostat

INTRODUCTION

Adequate control of circulating substances such as potassium, phosphate and uric acid is one of the important concerns in the long-term management of hemodialysis patients, because these substances are not sufficiently removed during the dialysis session in a considerable number of patients. Actually, it has been observed that majority of hemodialysis patients suffer from hyperuricemia[1]. Although the incidence of gout in hemodialysis patients is not necessarily increased[2], the incidence of gout has been reported to be associated with an increased risk of cardiovascular and all-cause mortality in hemodialysis patients[3]. As to the treatment of hyperuricemia in hemodialysis patients, the effectiveness of diet therapy is limited and uricosuric agents do not work in nature, therefore, a xanthine oxidase inhibitor (XOI) has to be used in most cases in order to reduce serum uric acid

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effectively. For many years, allopurinol had been the only XOI available in medical practice, however, the use of allopurinol is limited in renal failure patients because oxypurinol, the metabolite of allopurinol, is to be excreted in the kidney and the risk of severe dermatological side effects such as Stevens-Johnson syndrome and toxic epidermal necrosis is increased[4,5]. Thereafter, XOIs such as febuxostat and topiroxostat, which are excreted through the liver as well as through the kidneys, have become available[6~8]. These new XOIs can be used in patients with reduced renal function including hemodialysis patients, however, the characteristics of their clinical effects do not seem to be fully clarified in detail and the benefits and the disadvantages have to be carefully examined not only as to the hypouricemic effect but also other side effects beneficial or detrimental to the patients.

In the present study, we compared the therapeutic effects of allopurinol and febuxostat in chronic hemodialysis patients complicated by hyperuricemia and evaluated the usefulness of febuxostat in the long-term management of hemodialysis patients.

METHODS

This study enrolled a total of 50 end-stage renal disease patients undergoing stable maintenance hemodialysis as an outpatient for more than six months and given allopurinol 100 mg once daily for hyperuricemia for more than three months. After the evaluation of basic characteristics and laboratory examination described below, they were randomly divided into two groups. In 26 patients, one dose of allopurinol 100 mg daily in the morning was continued. In other 24 patients, allopurinol was switched to one dose of febuxostat 20 mg daily in the morning. And the administration of allopurinol or febuxostat was continued for 12 weeks. Other medications such as antihypertensive drugs, anti-platelet drugs, vitamin D, phosphate binders and potassium binders were not changed during this 12-week study period.

Physical and laboratory examinations were performed at 0-, 4-, 8- and 12-week of the study. Blood pressure (BP) was measured before each dialysis session in the patients at a supine position after resting more than 10 minutes and the average value during one week was used for evaluation at each time point[9,10]. Body weight gains between dialysis sessions were also averaged for one week. Peripheral blood samples from arterio-venous fistula for hematological tests and blood chemistry were obtained before starting the dialysis session and chest roentgenogram was taken at 0-, 4-, 8- and 12-week.

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects (Fortaleza version, 2013) and was approved by the institutional review board. Informed consent was obtained from all subjects after explaining the study objective and design.

Clinical data were expressed as means ± standard deviations (SD) except for the dose of darbepoetin alfa as erythropoiesis stimulating agent (ESA) where standard errors (SE) were used in drawing the graph. Values between the two groups were compared by *t*-test, however, Wilcoxon test was applied for the data with skewed distribution and the categorical data were compared using chi-square test. The time-course changes in variables during the study periods were analyzed using two-way ANOVA for repeated measures followed by Tukey's method for post-hoc multiple comparisons. A p value less than 0.05 was considered to indicate statistical significance.

RESULTS

Among the 50 patients who were in the study a 72-year-old woman, undergoing dialysis from chronic glomerulonephritis, experienced eruptions in her body trunk two days after starting febuxostat and the administration of febuxostat was stopped. Remaining 49 patients showed good adherence to the therapy and fulfilled the whole study periods. Table 1 shows the background characteristics of these 49 patients. Age, gender and duration of hemodialysis were not significantly different between the group continuing allopurinol and the group changed to febuxostat. Diabetic nephropathy and chronic glomerulonephritis were the frequent causes of renal failure in either group. Physical parameters such as BP, heart rate and body mass index did not significantly differ between the two groups. The complication frequencies of cerebrovascular, cardiovascular and other organ diseases were also comparable in the two groups.

Table 1 Baseline characteristics of the study subjects given allopurinol or febuxostat

	Total n = 49	Allopurinol n = 26	Febuxostat n = 23	*P value*
Gender, male/female	31/18	17/9	14/9	*0.743*
Age, year	66.6 ± 12.9	66.5 ± 14.9	66.8 ± 10.1	*0.923*
Cause of renal failure				
Diabetic nephropathy	23 (47%)	13 (50%)	10 (43%)	*0.648*
Chronic glomerulonephritis	20 (41%)	9 (35%)	11 (48%)	*0.347*
Nephrosclerosis	6 (12%)	4 (15%)	2 (9%)	*0.475*
Duration of hemodialysis, year	9.0 ± 9.4	9.4 ± 9.6	8.5 ± 9.11	*0.733*
Body mass index, kg/m^2	20.4 ± 2.4	20.8 ± 2.5	19.8 ± 2.2	*0.168*
Systolic BP, mmHg	140.8 ± 16.8	139.9 ± 18.2	141.8 ± 15.0	*0.698*
Diastolic BP, mmHg	74.4 ± 10.0	75.0 ± 10.9	73.8 ± 8.7	*0.675*
Heart rate, bpm	73.4 ± 8.5	73.9 ± 9.0	72.8 ± 8.0	*0.686*
Complications				
Cerebrovascular disease	11 (22%)	7 (27%)	4 (17%)	*0.424*
Coronary artery disease	5 (10%)	3 (12%)	2 (9%)	*0.742*
Valvular heart disease	4 (8%)	1 (4%)	3 (13%)	*0.240*
Peripheral artery disease	6 (12%)	4 (15%)	2 (9%)	*0.475*
Chronic liver disease	5 (10%)	2 (8%)	3 (13%)	*0.536*
Chronic lung disease	*3 (6%)*	*1 (4%)*	*2 (9%)*	*0.479*

Data are the mean ± SD. BP, blood pressure.

Table 2 Medications concurrently given with allopurinol or febuxostat in study subjects

	Allopurinol, n = 26	Febuxostat, n = 23
Diuretic	15 (58%)	8 (35%)
Adrenergic inhibitor	5 (19%)	4 (17%)
Calcium channel blocker	11 (42%)	12 (52%)
Renin-angiotensin system inhibitor	12 (46%)	10 (43%)
Antianginal drug	3 (12%)	5 (22%)
Antiplatelet drug	13 (50%)	16 (70%)
Antiarrhythmic drug	2 (8%)	1 (4%)
Anticoagulant	1 (4%)	1 (4%)
Antidiabetic drug	7 (27%)	3 (13%)
Lipid-lowering drug	4 (15%)	5 (22%)
Potassium binder	7 (27%)	2 (9%)
Phosphate binder	21 (81%)	17 (74%)
Vitamin D	11 (42%)	10 (43%)
Calcium mimetic	6 (23%)	6 (26%)
Drug for osteoporosis	4 (15%)	1 (4%)
Iron	5 (19%)	3 (13%)
erythropoiesis stimulating agent	20 (77%)	18 (78%)

Table 2 lists the medications given to the subjects concurrently with allopurinol or febuxostat. The majority of patients were taking antihypertensive drugs, 73.1% in the allopurinol group and 78.3% in the febuxostat group. Calcium channel blockers and angiotensin II receptor blockers were the frequently used class of antihypertensive agents. In addition, most patients were taking phosphate binders and nearly half of the patients were taking active vitamin D as is the case with chronic hemodialysis patients. Antiplatelet drugs were also given to a more than half of the patients for the prevention of arteriovenous

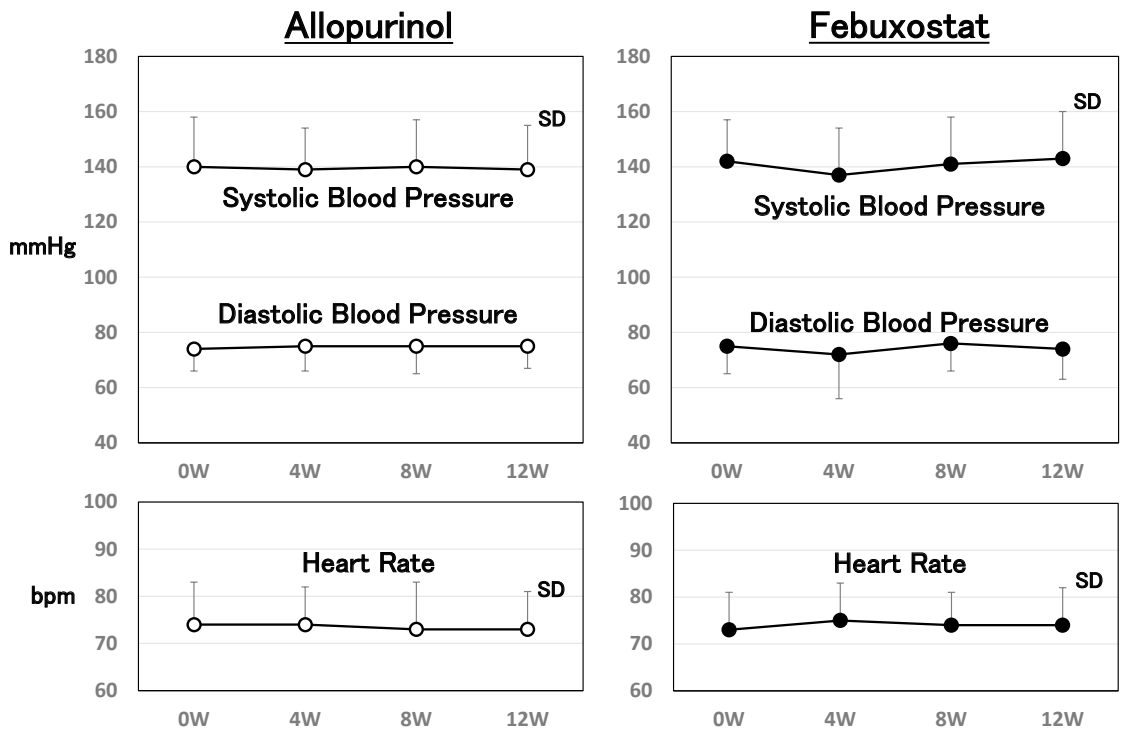

Figure 1

Time-course changes of blood pressure (BP) and heart rate during the 12-week study in chronic hemodialysis patients given allopurinol or febuxostat. *$p<0.05$ versus 0-week.

fistula thrombosis and cardiovascular diseases such as stroke and coronary artery disease. The doses of these drugs were not changed throughout the 12 weeks of study. However, the dose of erythropoiesis stimulating agent (ESA) was modified so that the blood hemoglobin concentration was maintained between 10-12 g/dL according to the guideline of Japanese Society of Dialysis Therapy[11].

Figure 1 depicts the changes in pre-dialysis BP and heart rate during the 12 weeks of study in patients given allopurinol or febuxostat. Both systolic and diastolic BPs were not significantly lowered in the allopurinol group during the study period. In the febuxostat group, systolic BP was significantly reduced by 5 mmHg at 4-week as compared with 0-week, while the systolic BPs at 8- and 12-week were not significantly different from 0-week and the diastolic BP did not significantly changed during 12 weeks. The heart rate did not significantly alter either in the allopurinol or the febuxostat group throughout the study periods.

The changes in parameters of body fluid volume were depicted in Figure 2. Either the dry weight setting or the cardiothoracic ratio on chest roentgenogram did not significantly varied during the study, either in the allopurinol or the febuxostat groups. Neither did the body weight change between the dialysis sessions throughout the study in either group.

Table 3 shows the changes in hematological data and dose of ESA in the allopurinol and the febuxostat groups during the study period. These hematological parameters including blood hemoglobin and hematocrit did not significantly changed during the 12 weeks in either group. Darbepoetin alfa was the only ESA used in this study and the dose was significantly reduced at 8-week and 12-week as compared to 0-week in the febuxostat group, while the dose was not changed in the allopurinol group (Figure 3).

The changes in blood chemistry data during the study period were shown in Table 4. Serum proteins, liver enzymes and electrolytes such as Na, K and Ca were not significantly changed during 12 weeks in the allopurinol or the febuxostat group. Neither serum creatinine nor urea nitrogen significantly varied during the study period. In contrast, serum uric acid was

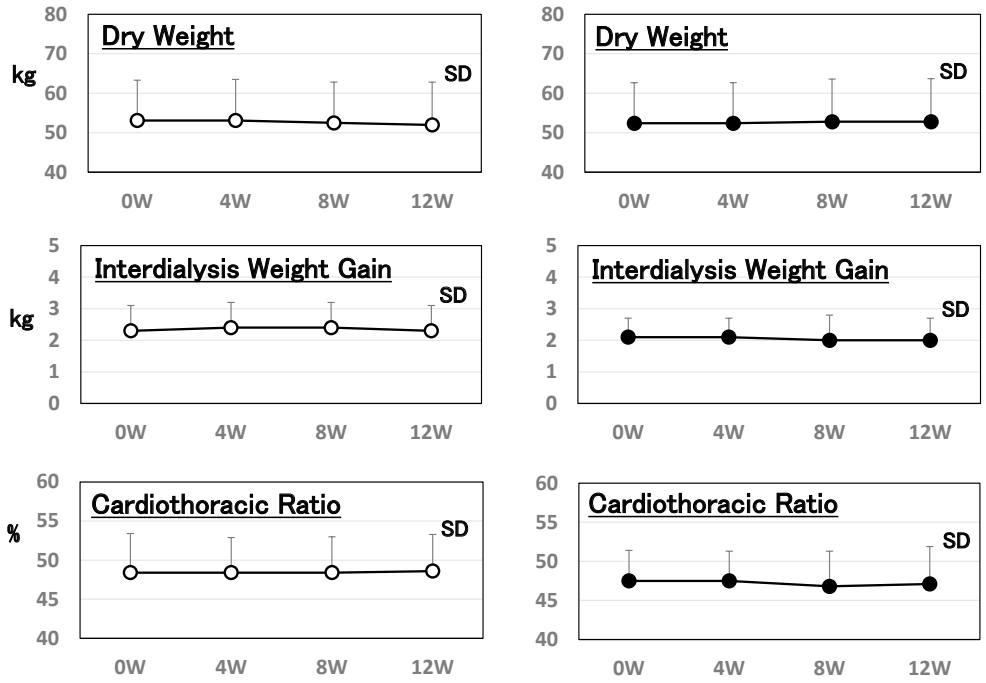

Figure 2

Time-course changes of dry weight, interdialysis weight gain and cardiothoracic ratio on chest roentgengram during the 12-week study in chronic hemodialysis patients given allopurinol or febuxostat.

Table 3 Time-course changes in blood cell counts and erythropoietin dose during the study period in chronic hemodialysis patients given allopurinol or febuxostat

	Allopurinol, n = 29				Febuxostat, n = 23			
	0-week	4-week	8-week	12-week	0-week	4-week	8-week	12-week
White blood cell, $\times 10^3/mm^3$	5.58 ± 1.41	5.33 ± 1.33	5.72 ± 1.45	5.94 ± 1.74	6.35 ± 2.60	6.19 ± 2.03	6.09 ± 1.92	6.25 ± 1.92
Red blood cells, $\times 10^6/mm^3$	349 ± 50	349 ± 46	358 ± 46	349 ± 44	358 ± 60	358 ± 54	361 ± 49	354 ± 50
Blood hemoglobin, g/dL	10.8 ± 1.3	10.9 ± 1.2	11.0 ± 1.1	10.8 ± 1.0	11.4 ± 1.4	11.4 ± 1.1	11.3 ± 1.0	11.1 ± 1.0
Hematocrit, %	33.2 ± 4.0	33.5 ± 3.7	34.4 ± 3.5	33.4 ± 3.1	34.9 ± 4.7	34.9 ± 3.9	34.6 ± 3.3	33.7 ± 3.2
Platelet, $\times 10^3/mm^3$	19.5 ± 5.6	18.1 ± 4.9	19.1 ± 5.6	19.7 ± 7.0	16.3 ± 5.4	16.5 ± 5.3	17.5 ± 5.5	16.5 ± 4.4
Dose of ESA, mg/wk	25.0 ± 20.8	28.8 ± 22.7	26.8 ± 23.1	29.6 ± 23.4	22.2 ± 22.2	20.4 ± 23.8	16.7 ± 17.5*	17.1 ± 18.5*

Data are the mean ± SD. ESA, erythropoiesis stimulating agent ; darbepoetin alpha was used as ESA ; *$p<0.05$ versus 0-week.

markedly reduced in the group given 20 mg febuxostat, while the value was not significantly changed in the group given 100 mg allopurinol at 4-, 8- and 12-week as compared with 0-week (Figure 4, left panel). In addition, serum phosphate was significantly reduced in the febuxostat group at 8-week and 12-week, while the value was not significantly changed in the allopurinol group during the study period (Figure 4, right panel).

DISCUSSION

Hyperuricemia is generally recognized as a risk factor for cardiovascular diseases such as hypertension, stroke and coronary artery diseases[12~16] and has also shown to be associated with the progression of renal dysfunction in patients with chronic kidney diseases (CKD)[12,17~19]. Because the urinary excretion of uric acid is impaired in patients with decreased renal function, serum uric acid level is naturally increased in

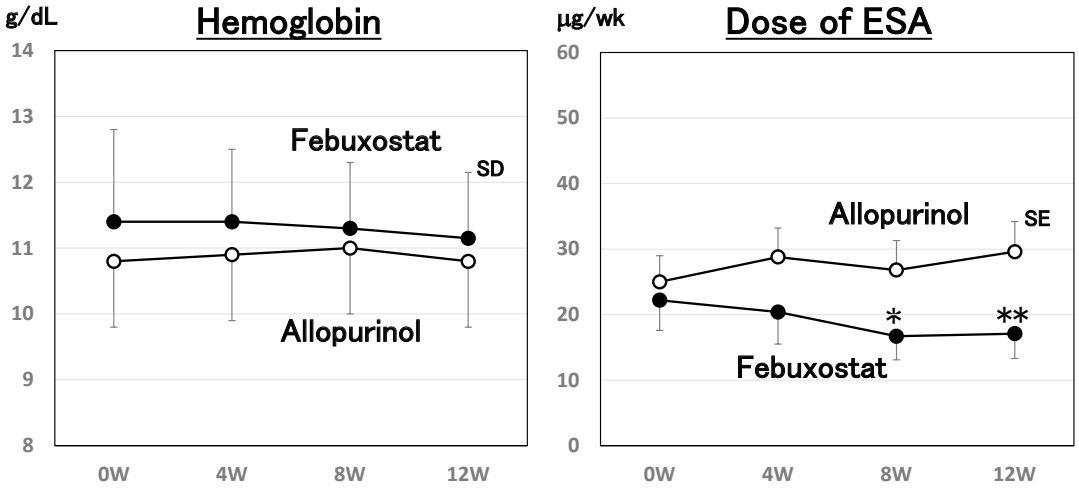

Figure 3

Time-course changes of blood hemoglobin concentration and the dose of erythropoiesis stimulating agent (ESA) during the 12-week study in chronic hemodialysis patients given allopurinol or febuxostat. Darbepoetin alpha was used as ESA.
*p<0.05, **p<0.01 versus 0-week.

Table 4 Time-course changes in blood chemistry data during the study period in chronic hemodialysis patients given allopurinol or febuxostat

	Allopurinol, n=29				Febuxostat, n=23			
	0-week	4-week	8-week	12-week	0-week	4-week	8-week	12-week
Total protein, g/dL	6.5±0.4	6.3±0.4	6.5±0.5	6.5±0.4	6.3±0.5	6.3±0.5	6.5±0.3	6.6±0.4
Albumin, g/dL	3.6±0.4	3.9±0.5	3.9±0.3	3.9±0.6	3.5±0.4	3.6±0.3	3.7±0.3	3.8±0.2
AST, U/L	13±5	13±6	13±6	14±10	13±5	14±8	12±3	12±4
ALT, U/L	10±5	11±6	11±5	12±10	9±4	11±7	9±3	10±5
Urea nitrogen, mg/dL	64±19	66±16	67±15	71±20	68±12	67±12	64±13	62±15
Creatinine, mg/dL	11.2±3.3	11.0±2.8	11.3±2.5	11.1±2.7	10.2±2.8	10.0±2.8	10.0±2.9	10.1±2.9
Uric acid, mg/dL	6.0±1.0	6.1±1.0	5.8±1.1	5.8±1.5	6.7±0.9	4.3±1.6†	4.3±1.7†	4.3±1.8†
Na, mEq/L	139±3	139±3	138±3	137±3	141±2	139±3	140±3	140±3
K, mEq/L	4.7±0.7	4.6±0.7	4.5±0.7	4.6±0.6	4.8±0.6	4.8±0.6	4.6±0.6	4.7±0.7
Ca, mg/dL	9.4±0.7	9.3±0.7	9.6±0.6	9.6±0.7	9.3±0.7	9.3±0.8	9.4±0.9	9.3±0.7
Phosphate, mg/dL	5.9±1.9	5.7±1.8	5.8±1.5	5.8±1.3	5.9±1.4	5.6±1.2	5.2±1.2**	5.1±1.1*

Data are the mean±SD. AST, aspartate aminotransferase ; ALT, alanine aminotransferase. *p<0.05, **p<0.01, † p<0.001 versus 0-week.

these patients. Therefore, hyperuricemia may be caused by reduced renal function and it seems unclear if hyperuricemia contributes to the pathogenesis of renal injuries[17,20]. However, it has been reported that the incidence of CKD was increased with increasing serum uric acid level even in subjects with estimated glomerular filtration rate (eGFR) higher than 60 mL/min/1.73 m^2 at baseline during the following 10 years[21]. In addition, the pharmacological treatment of hyperuricemia with allopurinol has been shown to reduce the incidence of cardiovascular events and delay further deterioration of renal function in CKD patients[22,23]. Therefore, it is speculated that the increase in circulating levels of uric acid plays a role in the progression of renal and cardiovascular organ injuries.

As mentioned above, serum uric acid level is increased in large part of hemodialysis patients, how-

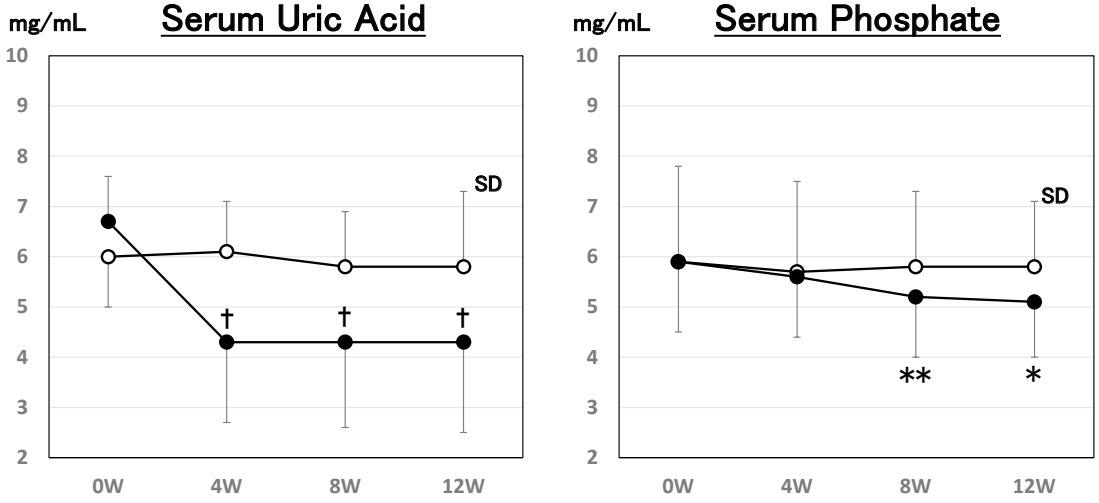

Figure 4

Time-course changes of serum uric acid and phosphate during the 12-week study in chronic hemodialysis patients given allopurinol or febuxostat.
*p<0.05, **p<0.01, †p<0.001 versus 0-week.

ever, it seems controversial whether the pharmacological treatment for hyperuricemia benefits in terms of improving the prognosis of patients[24]. A J-shaped relationship has been observed between serum uric acid levels and mortality in the epidemiological studies of hemodialysis patients[25,26]. It has been suggested that the low serum uric acid level is caused by malnutrition which is associated with poor survival[27]. However, hyperuricemia has been assumed to promote the development and progression of atherosclerosis in hemodialysis patients[28] and acidosis caused by renal failure is supposed to facilitate precipitation and deposition of uric acid in the cardiovascular tissue which certainly seems detrimental to the cardiovascular organs. Furthermore, it has been indicated that dialysis patients experiencing gout, showed increased mortality and high serum uric acid combined with low superoxide dismutase activity was associated with increased cardiovascular and all-cause mortality[29,30]. Therefore, the adequate control of serum uric acid seems desirable in order to reduce cardiovascular risk and mortality even in hemodialysis patients and availability of XOI excreted not only by the kidneys but also by the liver is appreciated to lower serum uric acid in renal failure patients.

It is assumed that atherosclerosis and arteriosclerotic lesions are initiated by functional disorder of the vascular endothelium. This causes the reduced capacity to generate nitric oxide (NO) in response to various stimuli resulting in impaired endothelium-dependent vasorelaxation. The development of endothelial dysfunction is contributed by aging, smoking and lifestyle-related diseases such as diabetes, hypertension and dyslipidemia. In addition to these classical risk factors of atherosclerosis, novel factors such as oxidative stress and inflammation are thought to participate in the etiology and pathogenesis of endothelial dysfunction[31]. It is recognized that the endothelial dysfunction takes place from the early stage of CKD and is deeply involved in the development of cardiovascular disorders[32,33]. Thus, endothelial protection is recommended as a therapeutic target in the management of CKD patients[34].

In order to attain maximum protection and prevention against the development of arterial lesions, care should be considered not only to reduce classical risk factors but also to reduce vascular oxidative stress and vascular inflammation as well. In this context, although uric acid itself has antioxidative activity in nature, reactive oxygen species are generated as byproducts during the process of uric acid synthesis by xanthine oxidase[35~39] and atihyperuricemic therapy with allopurinol has been shown to alleviate oxidative stress and improve endothelial function in patients with CKD[40~42]. As described earlier, allopurinol has been also shown to ameliorate the progression

of renal impairment and reduced the incidence of cardiovascular events in CKD patiets[22,23]. Febuxostat is a selective non-purine XOI characterized by higher bioavailability and more potent blockade of XO activity than allopurinol[6~8,42]. Consequently, it has been indicated that febuxostat is more effective in lowering serum uric acid[6,43~45], which was confirmed by this study in hemodialysis patients. Febuxostat has been shown to be more potent in reducing the markers of oxidative stress and inflammation[46,47]. Furthermore, the renoprotective effect of febuxostat is thought to be stronger than allopurinol considering that the increase in eGFR was observed after changing allopurinol into febuxostat in patients with CKD[43,48].

As to the indices of arterial injuries, Tsuruta et al have demonstrated that the 4-week treatment with febuxostat improved the marker of oxidative stress and endothelial function in hemodialysis patients[49]. In addition, Tausche et al have observed superior effects on oxidative stress and pulse wave velocity by febuxostat as compared with allopurinol after the one-year treatment in patients including CKD[50]. In the present study, systolic BP was significantly reduced at 4-week period in the febuxostat group and it is speculated that the effects of febuxostat on endothelial function and arterial stiffness may have participated, although the hypotensive effects were not observed at 8-week and 12-week. The short-term treatment with allopurinol has been also reported to lower BP in young subjects by reducing peripheral vascular resistance[51,52]. If these vascular effects of XOI were mediated by inhibition of oxidative stress and inflammation, the effects are supposedly stronger in febuxostat than in allopurinol considering febuxostat has been shown to inhibit oxidative stress and inflammation more potently than allopurinol[46,47].

In the present study, the dose of ESA was reduced at 8-week and 12-week in the febuxostat group, while blood hemoglobin was not significantly changed in either group. Because the ESA dose was modified, so that the blood hemoglobin was maintained between 10-12 g/dL during the study, febuxostat may have improved the responsiveness to ESA in hemodialysis patients. It is known that oxidative stress and chronic inflammation are involved in the development of erythropoietin resistance in patients with renal anemia[53~55]. Therefore, it is speculated that more potent inhibitory effects of febuxostat on oxidative stress and inflammation than allopurinol may have contributed to the increase in responsiveness to ESA.

It seems hard to speculate plausible explanation on the mechanism by which febxostat reduced serum phosphate level in hemodialysis patients in this study. Considering that febuxostat has been shown to restore the hampered activation of vitamin D in hyperuricemic rat[56], febuxostat may have decreased serum phosphate reciprocally to the increase in calcium. However, serum calcium levels were not significantly changed in this study and further comprehensive evaluation of mineral bone metabolism including PTH, active vitamin D and markers of osteogenesis and osteolysis to clarify the relationship between uric acid and phosphate.

In conclusion, this study demonstrated that 20 mg febuxostat is more effective in lowering serum uric acid than 100 mg allopurinol in chronic hemodialysis patients. Febuxostat also lowered BP temporally, improved responsiveness to ESA and reduced serum phosphate. These properties of febuxostat are expected to benefit in the long-term management of hemodialysis patients in terms of preventing cardiovascular events and mortality.

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