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Febuxostat for the treatment of hyperuricemia in elderly patients with chronic kidney disease: A retrospective study

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ABSTRACT

Achieving the recommended serum uric acid (sUA) concentration of <6.0 mg/dl is difficult in elderly patients (65 years of age or older) with chronic kidney disease. The xanthine oxidase inhibitor febuxostat has been used for treatment of this patient group, but its efficacy and safety remain unclear. In this retrospective cohort study, we recorded changes in sUA, rates of target sUA achievement (<6.0 mg/dl), changes in estimated glomerular filtration rate (eGFR), and adverse events in 123 elderly patients (mean age 76.6 ± 7.2 years, 84 males and 39 females) with hyperuricemia and severe CKD (eGFR< 30 ml/min/1.73 m^2) treated using febuxostat at Kaohsiung Medical University Hospital from January 2015 to December 2015. Febuxostat significantly lowered mean sUA from 9.5 ± 1.9 versus 5.4 ± 2.1 mg/dl after 12 weeks of treatment (P<0.001), and 60.2% achieved the target sUA of <6 mg/dl. There were no significant changes in eGFR (19.1 ± 6.9 versus 19.6 ± 8.4, P=0.233) or indices of liver dysfunction. Only two patients exhibited adverse events, suspected febuxostat allergy (skin rash and itching) and epigastric pain in one patient each. Febuxostat effectively lowers sUA levels in elderly patients with CKD without severe adverse events.

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INTRODUCTION

Hyperuricemia can cause gout, a common form of inflammatory arthritis in people aged 65 years and older (Stamp and Chapman, 2014). Worldwide incidence of gout has been increasing since 1980 (Arromdee et al., 2002; Chuang et al., 2011), in part due to aging populations. According to a US database, the incidence of gout in the elderly population aged 70–79 years is around 8% compared with only 1.7% at age 50 years (Lawrence et al., 2008). Thus, incidence is expected to increase further with continued gains in life expectancy.

Chronic kidney disease (CKD) is associated with hyperuricemia and is a risk factor for gout. One study reported 39% CKD prevalence in patients with gout (Fuldeore et al., 2011). In 2012, the American College of Rheumatology (ACR) recommended a target serum uric acid (sUA) concentration of <6 mg/dl for all patients with gout (Li et al., 2016). However, elderly patients with gout often have other comorbidities, such as kidney dysfunction, heart disease, and age-related physiological changes, which influence the choice and dose of drugs used, including drugs that reduce sUA (Jackson et al., 2012). Therefore, it is frequently difficult for elderly patients with hyperuricemia and comorbid CKD to achieve the therapeutic goal of sUA <6.0 mg/dl (Mizuno et al., 2014).

Allopurinol is among the most frequently prescribed medications for treatment of gout. However, its active metabolite, the xanthine oxidase inhibitor oxypurinol, may accumulate to toxic levels in patients with renal insufficiency, necessitating dose reduction. The efficacy of allopurinol is dose dependent, so decreasing the dose may increase gout risk (Hira et al., 2015; Dalbeth et al.,

2006). Another clinical study which suggests that increasing the dose of allopurinol above the proposed creatinine clearance-based dose is safe so long as the dose is increased slowly (Stamp et al., 2011).

Moreover, allopurinol may cause a rare but serious hypersensitivity reaction termed allopurinol hypersensitivity syndrome (AHS) (Stamp and Chapman, 2014). Multiple studies have recently shown the risk factors of allopurinol hypersensitivity include the presence of the HLA-B5801 allele, accumulation of oxypurinol metabolites, chronic kidney disease, use of thiazide diuretics (Chohan, 2011). Therefore, allopurinol has several potentially serious disadvantages for treatment of elderly patients with comorbid hyperuricemia and renal insufficiency.

Febuxostat is a noncompetitive inhibitor of xanthine oxidase recommended for reducing sUA in patients with CKD. Although febuxostat has been shown to be effective for elderly patients, its safety and therapeutic efficacy in elderly patients with CKD is still uncertain. We conducted this retrospective study to investigate the efficacy and safety of febuxostat in elderly patients with severe (stage 4/5) CKD and hyperuricemia.

METHODOLOGY

Patients

This is a retrospective study of elderly patients (65 years of age or older) with hyperuricemia and CKD (eGFR rate < 30 ml/min/1.73 m^2)who were treated with febuxostat at the Kaohsiung Medical University Hospital from January 2015 to December 2015. The definition of the different stages of severe CKD, CKD stage 4 is eGFR rate < 30 and ≧15 ml/min/1.73 m^2, CKD stage 5 is eGFR rate < 15 ml/min/1.73 m^2.

Inclusion criteria were age >65 years, eGFR< 30 ml/min/1.73 m^2, and use of febuxostat for at least 14 days. Exclusion criteria were sUA < 6 mg/dl before treatment, missing sUA values before or after treatment, acute gout attack within 2 weeks, acute kidney failure (drastic changes in renal function) within 2 weeks, abnormal liver function before treatment (serum alanine aminotransferase two times higher than the normal value) (normal range is ≦40 IU/L), kidney transplant, and concurrent anti-cancer or immunosuppressive treatment.

Patient data were collected using the electronic medical record system of the hospital, which includes demographic data (age and sex), medical history (mainly focused on cardiovascular and liver diseases), history of gout, and previous medications used for gout treatment (types of drugs and dosages). To evaluate the efficacy of febuxostat and patient renal function, changes in plasma creatinine levels (eGFR) and sUA from baseline were calculated. eGFR is estimated GFR calculated by the modification of diet in renal disease (MDRD) equation : 186 × (creatinine/88.4)-1.154 × (age)-0.203 × (0.742 if female) × (1.210 if black). Adverse reactions to febuxostat were recorded during outpatient follow-up.

The primary treatment goal was sUA< 6 mg/dl within 12 weeks after initiation of febuxostat treatment. Changes in sUA from pretreatment baseline were recorded, and the overall ratio of patients who achieved the treatment goal as well as the association between dose and efficacy was analyzed. Changes in serum creatinine from baseline were monitored during treatment to evaluate effects on renal function. Serum alanine aminotransferase (ALT) level more than twice the normal value was considered indicative of liver damage.

Adverse drug reaction symptoms were evaluated for causality using the Naranjo score as “probable,” “possible,” or “possibility cannot be ruled out but the relative probability is low.” The Naranjo scale is a questionnaire designed by Naranjo et al. (1981) for determining the likelihood of whether an adverse drug reaction (ADR) is actually due to the drug rather than the result of other factors. Scoring is ≥ 9 = definite ADR, 5-8 = probable ADR, 1-4 = possible ADR, 0 = doubtful ADR.

Statistical analysis

Quantitative variables are expressed as mean ± SD (standard deviation) and qualitative variables as percentages. Paired *t*-tests were used to compare changes in serum UA, creatinine, and ALT from baseline following 12 weeks’ of febuxostat treatment. Independent sample *t*-tests were used to compare continuous variables between groups. Chi-square tests were used to analyze the associations of age and medical history with achievement of target sUA. For any analytic subgroup with fewer than five individuals, Fisher test was used instead. A P< 0.05 was considered statistically significant for one-tailed.

RESULTS

Patient characteristics

A total of 123 comorbid patients with hyperuricemia/CKD prescribed febuxostat were enrolled in this study and grouped according to sex (84 males and 39 females) (Table 1) or attainment of target sUA (Table 2). The proportions of patients with hypertension, diabetes, and hyperlipidemia were all over 50% in both sexes and did not differ between sexes. There were also 12 patients with a history of liver disease, mostly chronic hepatitis, including one with hepatitis B and two with hepatitis C. None of these patients had an acute attack within 2 weeks prior to febuxostat treatment and total patients

Table 1. Patient characteristics.

	Total (N=123)	Men (N=84)	Women (N=39)	Men/Women
Age, years, mean±SD	76.6 ± 7.2	76.5 ± 7.4	76.7 ± 6.9	P = 0.88
Comorbidities/Drug				
Hypertension	95 (77.2%)	65 (77.4%)	30 (76.9%)	P = 0.955
Diabetes mellitus	66 (53.7%)	44 (52.4%)	22 (56.4%)	P = 0.677
Dyslipidemia	62 (50.4%)	40 (47.6%)	22 (56.4%)	P = 0.364
Liver disease	12 (9.8%)	9 (10.7%)	3 (7.7%)	P = 0.751
Loop or thiazide diuretic	51 (41.5%)	40 (47.6%)	11 (28.2%)	P = 0.042*
Febuxostat dose				
Initial dose, mean, mg/day	39.5 ± 7.0	39.5 ± 8.2	39.5 ± 3.2	P = 0.979
Final dose, mean, mg/day	37.2 ± 6.9	37.9 ± 6.2	35.9 ± 8.2	P = 0.189
Baseline serum data				
eGFR, mean ± SD, ml/min/ 1.73m^2	19.1 ± 6.9	19.0 ± 6.9	19.2 ± 7.0	P = 0.857
sUA, mean ± SD, mg/dL	9.5 ± 1.9	9.4 ± 1.7	9.5 ± 2.1	P = 0.761
ALT, mean ± SD, IU/L	21.5 ± 9.4	21.9 ± 8.9	20.6 ± 10.4	P = 0.509
Final serum data				
eGFR, mean ± SD, ml/ min/1.73 m^2	19.6 ± 8.4	19.9 ± 8.5	19.2 ± 8.2	P = 0.669
sUA, mean ± SD, mg/dL	5.4 ± 2.1	5.6 ± 2.0	5.1 ± 2.2	P = 0.277
ALT, mean ± SD, IU/L	22.3 ± 12.8	20.9 ± 8.7	25.4 ± 18.8	P = 0.209
Before febuxostat intervention				
No medication	56 (45.5%)	35 (41.7%)	21 (53.8%)	P = 0.207
Only colchicine	14 (11.4%)	9 (10.7%)	5 (12.8%)	P = 0.885
Only colchicine prn	5 (4.1%)	2 (2.4%)	3 (7.7%)	P = 0.325
Colchicine + allopurinol	5 (4.1%)	3 (3.6%)	2 (5.1%)	P = 0.325
Colchicine prn + allopurinol	5 (4.1%)	4 (4.7%)	1 (2.6%)	P = 0.999
Colchicine + benzbromarone	5 (4.1%)	4 (4.7%)	1 (2.6%)	P = 0.999
Colchicine + allopurinol + benzbromarone	1 (0.8%)	1 (1.2%)	0	P = 0.999
Only allopurinol	20 (16.2%)	20 (23.8%)	0	P = 0.001*
Only benzbromarone	12 (9.7%)	6 (7.2%)	6 (15.4%)	P = 0.193
After febuxostat intervention				
Only febuxostat	70 (57.0%)	48 (57.1%)	22 (56.4%)	P = 0.939
Febuxostat + colchicines	32 (26.0%)	23 (27.4%)	9 (23.1%)	P = 0.613
Febuxostat + colchicine prn	16 (13.0%)	11 (13.1%)	5 (12.8%)	P = 0.966
Febuxostat + benzbromarone	2 (1.6%)	1 (1.2%)	1 (2.6%)	P = 0.535
Febuxostat + colchicine + benzbromarone	3 (2.4%)	1 (1.2%)	2 (5.1%)	P = 0.236

*, P-value <0.05 were considered statistically significant; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2); sUA, serum uric acid.

Table 2. Difference of patient characteristics and febuxostat treatment for achieving sUA target.

	Last sUA> 6 mg/dL(n=49)	Last sUA< 6 mg/dL(n=74)	P-value
Men	35 (71.4.%)	49 (66.2%)	0.543
Age, years, mean ± SD	76.4 ± 7.7	76.7 ± 7.0	0.783
Baseline eGFR	18.2 ± 6.8	19.6 ± 7.0	0.277
Baseline sUA	9.9 ± 1.8	9.2 ± 1.9	0.070*
Comorbidities/ Drug			
Hypertension	39 (79.6%)	56 (75.7%)	0.612
Diabetes mellitus	29 (59.2%)	37 (50.0%)	0.317
Dyslipidemia	27 (55.1%)	35 (47.3%)	0.397
Liver disease	3 (6.1%)	9 (12.2%)	0.359

Table 2. Contd.

Loop or thiazide diuretic	24 (49.0%)	27 (36.5%)	0.169
Febuxostat dose, mg/day (inital)	38.0 ± 6.1	40.5 ± 7.4	0.045*
Febuxostat dose, mg/day (final)	38.0 ± 6.1	36.8 ± 7.4	0.348

*, P-value <0.05 were considered statistically significant; sUA, serum uric acid; SD, standard deviation; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2).

average ALT was 21.5 ± 9.4 IU/L, within the normal range (~10−40 IU/L).

Among these patients, 85 had stage 4 CKD and 38 had stage 5 CKD. During the treatment period, a total of 10 patients started HD (hemodialysis) due to changes in disease condition. Among these patients, nine stopped taking febuxostat while one continued treatment. During the study period, no patient underwent PD (peritoneal dialysis) due to changes in condition.

Before febuxostat treatment, the mean sUA was 9.5 ± 1.9 mg/dl (range, 6.1–15.3 mg/dl). The details of drug combinations used prior to febuxostat treatment are summarized in Table 1. Before taking febuxostat, most patients (23patients, 74.2%) using allopurinol received 100 mg daily. Most patients were given a starting febuxostat dose of 40 mg (114 patients, 92.7%).

Efficacy

The mean sUA after febuxostat treatment was 5.4 ± 2.1 mg/dl (range, 1.7–9.9 mg/dl). A total of 74 patients achieved the treatment goal of sUA<6 mg/dl within 12 weeks (60.2%), and 55 patients achieved a sUA lower than 5 mg/dl (44.7%). The mean post-treatment sUA was significantly lower than baseline for the entire group (Figure 1). Patients were divided into two groups based on whether the treatment goal was achieved. Table 2 showed the febuxostat dose used in the lower efficacy group (final sUA> 6 mg/dl) was slightly lower (38.0 ± 6.1 vs. 40.5 ± 7.4 mg, P=0.045), and mean pre-treatment sUA level (9.9 ± 1.8 vs. 9.2 ± 1.9 mg/dL, P=0.070) were higher.

Safety

Mean eGFR value after treatment was 19.6 ± 8.4 ml/min/1.73 m^2 (range, 4.4–49.4 ml/min/1.73 m^2), and the change from pretreatment baseline (0.6 ± 5.3 ml/min/1.73 m^2) was not significant (Figure 2). Similarly, mean final serum ALT was 22.3 ± 12.8 IU/L (range, 8–82 IU/L), and the change from pretreatment baseline was not significant, suggesting no substantial change in liver function. During treatment, two patients experienced adverse reactions. One exhibited hypersensitivity symptoms, including skin rash and swelling, and the other reported abdominal pain. Symptoms in both patients started within 1 week of febuxostat administration. After evaluation by the attending physician, both patients stopped using febuxostat. After termination, the symptoms improved, and no attempts were made to restart febuxostat treatment.

DISCUSSION

The prevalence of hyperuricemia is gradually increasing in parallel with population aging and the accompanying rise in frequency of diseases such as hypertension and CKD (Becker et al., 2011). A case–control study by Hanly et al. (2009) found that elderly people with gout have significantly higher rates of hospitalization and usage of hyperuricemia-inducing drugs (diuretics and insulin) than age- and sex-matched controls. Thus, concurrent use of drugs for diseases of aging may further increase hyperuricemia incidence and complicate treatment. Here we demonstrate the efficacy and safety of febuxostat for elderly hyperuricemic patients with CKD. Of enrolled patients, almost 60% achieved target sUA with 12 weeks, while <2% experienced adverse reactions, suggesting that short-term febuxostat treatment is safe and effective for elderly hyperuricemic patients with CKD.

Febuxostat is a new-generation selective xanthine oxidase inhibitor approved by the Food and Drug Administration (FDA)in 2009 for the treatment of gout caused by hyperuricemia. Khosravan et al. (2008) found that age and sex had no significant effects on the plasma or urine pharmacokinetic and pharmacodynamic parameters of febuxostat, suggesting that no dose adjustment is required based on sex or age alone. However, in a real-world, its safety and therapeutic efficacy in elderly patients with CKD is still uncertain.

Efficacy

This study enrolled 123 elderly patients with chronic kidney failure accompanied with hyperuricemia. The mean treatment dose used was 39.5 ± 7.0 mg. In the post-hoc analysis of the CONFIRMS study (the urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial) by Jackson et al. (2012), the efficacy and safety of

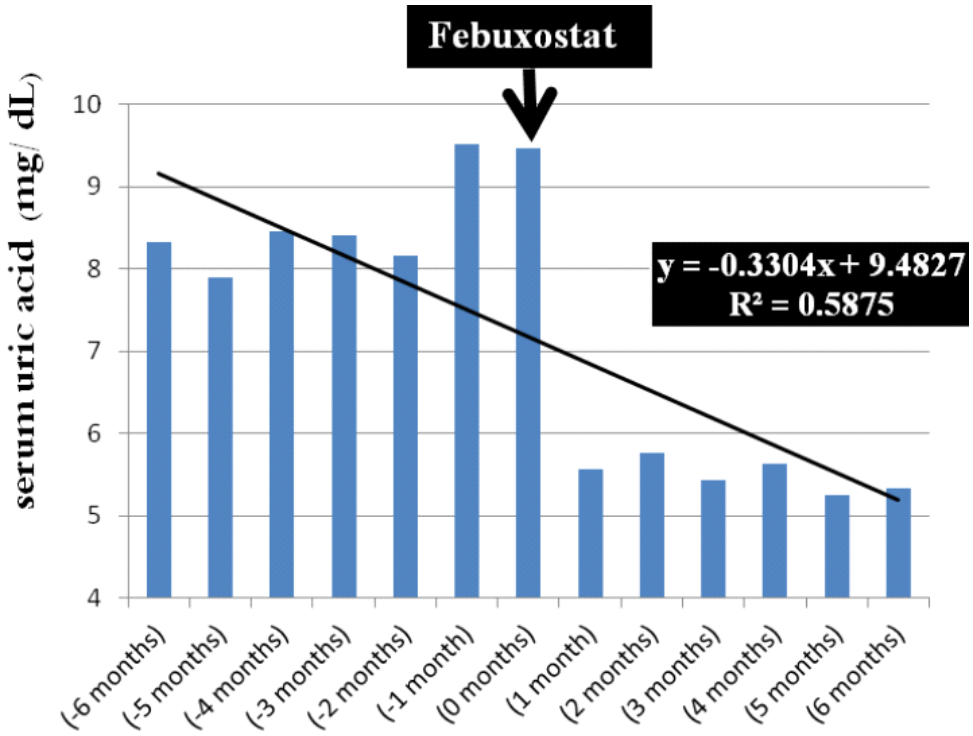

Figure 1. Changes in serum uric acid slope, P < 0.001 were considered statistically significant.

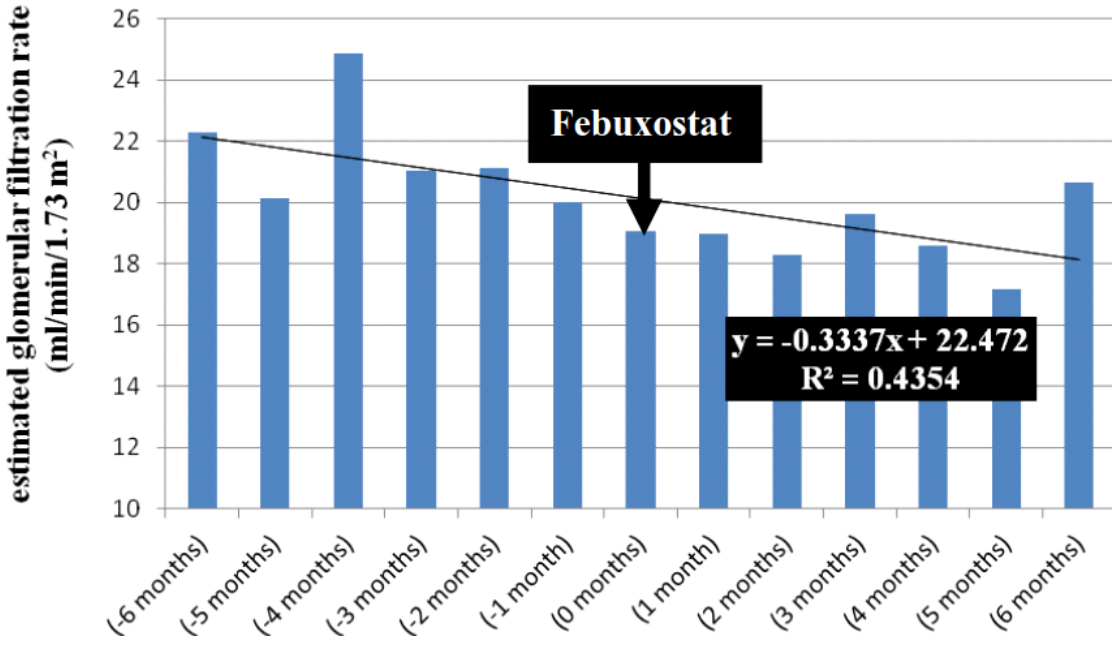

Figure 2. Change in estimated glomerular filtration rate slope, P > 0.05 were no significant different.

febuxostat (40 or 80 mg) and allopurinol (200 or 300 mg, dose adjustment based on renal function) in gout patients aged 65 years or older were studied. The results showed that febuxostat in any doses had better efficacy than allopurinol in elderly people with renal impairment, and both drugs showed good tolerability. According to the

study results, it is recommended that elderly gout patients with renal failure be treated with febuxostat because it has better therapeutic efficacy and fewer side effects (Jackson et al., 2012).

Our study divided patients into two groups according to whether they achieved the treatment goal (sUA< 6 mg/dL) for comparison (Table 2). This may be associated with patients' individuality, responses to drug, and disease severity. With regards to the concurrent usage of drugs that can affect uric acid levels, our study only investigated the effects of loop or thiazide diuretics, which did not show significant differences. Diuretic decreases the excretion of uric acid by directly and indirectly increasing the reabsorption of urates and decreasing the secretion of urates. Its effects are dose-dependent. No significant effects were observed in this study; this may be related to the therapeutic dose.

Becker et al.(2011) divided patients enrolled in the CONFIRMS study according to age and renal function, and compared the drug efficacy. They found that the efficacy of using febuxostat 80 mg/day in elderly patients with moderate kidney dysfunction was significantly better than that using febuxostat 40 mg/day. Considering differences in race and renal function and according to the study results, it is recommended that elderly patients with chronic kidney failure with comorbid hyperuricemia be given short-term febuxostat 40 mg/day, which can effectively decrease uric acid levels. During the treatment process, changes in uric acid levels should be monitored, and doses should be adjusted to increase drug efficacy.

Safety

During the treatment process of this study, there were no serious adverse reactions, which was identical to the results of other studies where febuxostat was used in elderly and CKD patients. This demonstrates the safety of febuxostat. According to a large-scale Phase III clinical trial, adverse reactions often associated with febuxostat are diarrhea, nausea, and liver function abnormalities. In this study, there were no significant differences in liver function before and after treatment (P = 0.683), and this may be associated with the enrollment criteria (patients with liver function index two times greater than the normal value were excluded).

During the study period, the adverse reactions that occurred were skin hypersensitivity symptoms and upper abdominal pain. When Naranjo score was used to evaluate the adverse reaction, the result was possible. Although the possibility cannot be excluded, the relative probability is low. Chohan (2011) divided safety and efficacy of febuxostat treatment in gout and severe allopurinol adverse reactions. The study showed patients with previously documented severe allopurinol adverse reactions, febuxostat treatment was safe. And suggest with careful dose escalation, and close monitoring is considered. The symptoms in both patients improved after drug usage was discontinued. Because they were not re-challenged with the drug, the causal relationship cannot be confirmed.

The incidence of hyperuricemia and cardiovascular disease was significantly correlated with overall mortality. According to cohort study reports, hyperuricemia is an independent risk factor for all-cause mortality and cardiovascular disease mortality (Chen et al., 2009). The CONFIRMS study published by Becker et al.(2011) showed that the incidence of cardiovascular adverse reactions was significantly higher in elderly people than in young people. Prospective blinded adjudication evaluation showed that the adverse reactions were not correlated with uric acid lowering treatment. Nevertheless, long-term safety data of febuxostat is limited. In drug safety communication released on November 15, 2017 by the FDA (USA), the incidences of heart-related events of febuxostat were reported to be higher than those with allopurinol. Clinical trial results showed that the overall treatment does not increase the risk of comorbidities but increases the risk of heart-related death. The clinical study by White et al. (2018) suggests that there is a higher risk of total and cardiovascular mortality with Febuxostat than with Allopurinol. But in the intention-to-treat analysis is only almost 10% patients. Due to a limited follow-up period, our study did not find any such relation. Nonetheless monitoring of related risk factors is needed to increase the safety of the drug treatment.

Study limitations

Because the design of this study lacks a comparator (such as allopurinol), only descriptive data were reported. Although the efficacy of the dose used can be confirmed, comparison data were lacking. In addition, this study is conducted in one country and lacks data from different races. With regards to safety, although relevant test data are available, standardized monitoring cannot be performed because this is a retrospective study. Because the subjects enrolled were outpatients, mild adverse reactions may be overlooked or the incidence may be underestimated due to differences in patients' tolerability of symptoms. Due to the limitation of follow-up time, we were unable to perform long-term efficacy and safety monitoring. In the future, large-scale, multicenter, prospective, controlled studies are needed to provide more supporting data.

Conclusion

This study shows the therapeutic efficacy and safety of

short-term febuxostat used in elderly CKD patients with comorbid hyperuricemia. Febuxostat does not require dose adjustment based on sex or age, but differences in renal function must be considered. Majority of the CKD patients who used febuxostat, which can effectively decrease serum uric acid levels, achieved the treatment goal. The study did not find any drug-related serious adverse reactions, and most patients had good tolerability toward the drug. The drug safety communication released by FDA must be consulted for patients under long-term treatment. Close attention should be paid to heart-related adverse reactions to increase the drug safety.

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Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by the authors. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-E (I)-20170001).

Conflict of Interest

Ai-Yu Yang declares that they have no conflict of interest.

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