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ORIGINAL RESEARCH

Efficacy and safety of febuxostat in elderly female patients

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Background: Maintenance of low serum urate levels is important for the management of gout. Achieving the recommended serum urate levels of less than 6.0 mg/dL is difficult in elderly (65 years of age or older) patients with renal impairment. Xanthine oxidase inhibitors allopurinol and febuxostat are used for this purpose. Although febuxostat had been shown to be efficacious in elderly patients, its safety and efficacy in elderly female patients with hyperuricemia remain unclear.

Objective: The aim of this study was to assess the efficacy and safety of febuxostat in elderly female patients.

Methods: We studied a retrospective cohort study. The study included elderly Japanese patients (65 years of age or older) who were treated with febuxostat at Fujita Health University Hospital from January 2012 to December 2013. The treatment goal was defined as achievement of serum urate levels of 6.0 mg/dL or lower within 16 weeks; this was the primary endpoint in the present study. Adverse events of febuxostat were defined as more than twofold increases in Common Terminology Criteria for adverse events scores from baseline.

Results: We evaluated 82 patients treated with febuxostat during the observation period and classified them into male (n=53) and female (n=29) groups. The mean time to achievement of the treatment goal was significantly shorter in the female group (53 days) than in the male group (71 days). There were no significant differences in adverse events between the 2 groups.

Conclusion: Our findings suggest that the efficacy of febuxostat in elderly female patients is superior to that in elderly male patients and that the safety is equivalent.

Keywords: febuxostat, elderly female patients, hyperuricemia

Introduction

Maintenance of low serum urate (sUA) levels is important for the management of gout.[1] Achieving the recommended sUA levels of less than 6.0 mg/dL[2,3] is difficult in elderly (65 years of age and older) patients with renal impairment. The xanthine oxidase inhibitors allopurinol and febuxostat have been widely used for this purpose.

Allopurinol has been used as a first-line drug for the treatment of hyperuricemia.[3] Adverse reactions such as hepatic disorder, hypersensitivity vasculitis, and bone marrow depression have been reported.[4–8] Moreover, the dose of allopurinol requires reduction according to the degree of renal impairment.[9,10]

Febuxostat is a nonpurine selective inhibitor of xanthine oxidase that forms a very stable interaction with both the oxidized and reduced forms of the enzyme.[11] Becker et al reported superior efficacy of febuxostat compared with that of allopurinol in diabetic gout patients.[12] However, the efficacy of febuxostat was not superior to that of allopurinol in the Febuxostat versus Allopurinol Controlled Trial,[6] and there was no significant difference between the two drugs with respect to the rate of adverse events (AEs).[6,13,14]

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Febuxostat has been shown to be efficacious in elderly patients;[13] however, the efficacy and safety of febuxostat in elderly female patients with hyperuricemia remain unclear. To promote proper use of febuxostat, we investigated the efficacy and safety of febuxostat in elderly female patients.

Methods

Subjects

Elderly Japanese patients (65 years of age or older) who were treated with febuxostat at Fujita Health University Hospital from January 2012 to December 2013 were included in the study. Patients treated with hemodialysis or peritoneal dialysis, those treated with anticancer or immunosuppressive therapies, those with baseline sUA levels of less than 7.0 mg/dL, and those for whom sUA levels were not measured within 16 weeks after starting febuxostat therapy were excluded. The patients were divided into two groups: males and females.

Investigations

This retrospective cohort study used information from the electronic medical records of Fujita Health University Hospital. Renal function in patients was evaluated using estimated glomerular filtration rate values. These values were calculated using the modified isotope dilution mass spectrometry-traceable Modification of Diet in Renal Disease Study equation.[15] The treatment goal was defined as achievement of sUA levels of 6.0 mg/dL or less[16] within 16 weeks; this was the primary end point in the present study. AEs of febuxostat were defined as more than twofold increases in Common Terminology Criteria for Adverse Events scores compared with baseline. We focused on AEs commonly observed at high frequency when using xanthine oxidase inhibitors.[6–8,17] Among them, leukopenia hepatic disorder, thrombocytopenia, and anemia were selected for use as secondary end points in the present study. This study was approved by the Ethics Board of Fujita Health University Hospital.

Statistical analysis

Continuous data are presented as the mean (range), and nominal data are presented as percentages. Continuous and nominal data were analyzed with Student's *t*-test and chi-square test, respectively. The mean time to achievement of the treatment goal was measured from the initiation of febuxostat treatment until the first observation of sUA levels of 6.0 mg/dL or less. Time-to-event curves were plotted using the Kaplan–Meier method, and comparisons among groups were performed with the log-rank test. In these tests, a two-sided *P*-value of less than 0.05 was considered significant. SPSS version 22.0 software (IBM Corporation, Armonk, NY, USA) was used for statistical analysis.

Results

We evaluated 82 patients treated with febuxostat during the observation period and classified them into male (n=53) and female (n=29) groups. Their baseline characteristics and comorbidities are listed in Table 1. The mean body weight and body surface area of the female group were significantly lower than those of the male group. Baseline renal function was lower in the female group, whereas liver function and sUA levels were similar between the 2 groups. Morbidity rates for hypertension and diabetes mellitus were not significantly different between the 2 groups. The incidence of a history of cardiovascular events was also similar in the groups.

The results of mean time to achievement of the treatment goal are presented in Figure 1. The mean time in the female group (53 days; 95% confidence interval, 39–68 days) was significantly shorter than that in the male group (71 days; 95% confidence interval: 60–83 days).

AEs after treatment with febuxostat are indicated in Table 2, and the grades of AEs are shown in Table 3. There were no significant differences in all terms between the 2 groups.

Discussion

The dose of febuxostat commonly prescribed in Japan (10–20 mg/day) is lower than that prescribed in other countries, and there was a time lag preceding the drug's introduction in Japan. Moreover, the majority of patients with hyperuricemia are male. Thus, clinical evidence of the suitability of febuxostat for elderly female patients in Japan is less than that accumulated in many other countries. To increase the usefulness of febuxostat, we evaluated the efficacy and safety of febuxostat in elderly female patients in Japan. Although achievement of the treatment goal was difficult in patients with renal impairment, more than 70% of the female patients achieved sUA levels of 6.0 mg/dL or less within 16 weeks. Furthermore, the mean time to achievement of the treatment goal was shorter in female patients than in male patients. These results suggest that the efficacy of febuxostat is superior in elderly female patients.

Khosravan et al concluded that neither age nor sex has a clinically significant effect on the pharmacokinetics,

Table 1 Baseline characteristics and comorbidities

Characteristics and comorbidities	Male (n=53)	Female (n=29)	*P*-value
Age (range), years	75 (65–89)	78 (65–92)	0.160
Body weight (range), kg	58 (38–79)	46 (32–72)	<0.001
Body surface area (range), m^2	1.6 (1.2–2.0)	1.4 (1.1–1.8)	<0.001
Febuxostat dose (range), mg/day	13 (10–20)	13 (10–20)	0.827
10 mg/day (%)	36 (68)	19 (66)	
20 mg/day (%)	17 (32)	10 (35)	0.824
Serum creatinine (range)	2.7 (0.8–7.5)	2.5 (0.8–7.0)	0.531
eGFR (range), mL/min	25 (6.0–69)	18 (4.0–35)	0.014
ALT (range), IU/L	18 (3.0–75)	16 (4.0–100)	0.629
AST (range), IU/L	23 (8.0–73)	26 (12–100)	0.468
BUN (range), mg/dL	40.1 (11.1–84.0)	40.9 (10.8–101.7)	0.842
Serum urate (range), mg/dL	9.4 (7.3–15.3)	9.5 (7.1–14.7)	0.783
<9.0 (%)	22 (42)	10 (34)	0.588
9.0 to <10.0 (%)	18 (34)	9 (31)	
10.0 to <11.0 (%)	8 (15)	8 (28)	
≥11.0 (%)	5 (9)	2 (7)	
Hematocrit (range), %	32.4 (19.6–46.7)	31.9 (22.5–41.0)	0.677
Hemoglobin (range), g/dL	10.8 (6.8–15.5)	10.4 (7.5–13.5)	0.450
Erythrocyte (range), $\times 10^3$	3.5 (2.1–5.4)	3.4 (2.59–4.36)	0.583
Leukocyte (range), $\times 10^3$	6.2 (1.0–14.7)	6.1 (3.1–10.8)	0.806
Platelet (range), $\times 10^4/\mu L$	18.4 (2.8–39.1)	18.1 (1.86–55.0)	0.886
Hypertension (%)	47 (88.7)	25 (86.2)	0.979
Diabetes mellitus (%)	31 (58.5)	18 (62.1)	0.752
Cardiovascular events (%)	40 (75.5)	22 (75.9)	0.968

Note: To establish *P*-values, the *t*-test or χ^2 test were used.
Abbreviations: eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen.

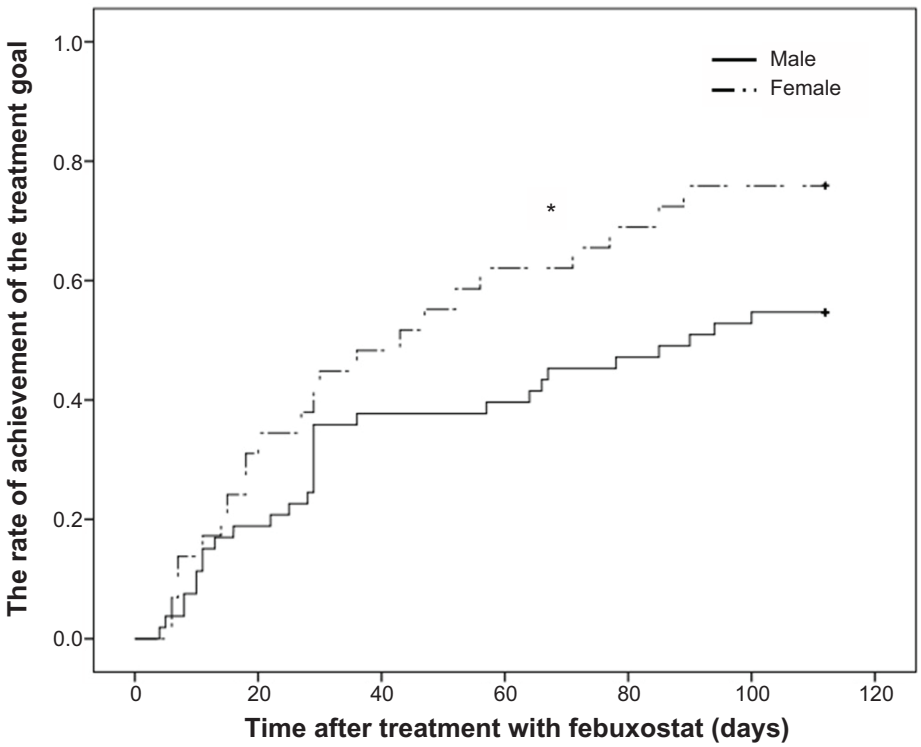

Figure 1 Mean time to achievement of the treatment goal.
Notes: The mean times to achieve serum urate levels of 6.0 mg/dL or less in the male and female groups were 71 days (95% confidence interval, 60–83 days) and 53 days (95% confidence interval, 39–68 days), respectively. *P=0.047, male versus female, log-rank test.

Table 2 Adverse events after treatment of elderly male and female patients with febuxostat

Characteristic	Male (n=53)	Female (n=29)	*P*-value
Number of patients with adverse events (%)	5 (9.4)	5 (17.2)	0.496
Leucopenia (%)	2 (3.8)	1 (3.4)	0.589
Hepatic disorder (%)	2 (3.8)	2 (6.9)	0.530
Thrombocytopenia (%)	1 (1.9)	1 (3.4)	0.756
Anemia (%)	3 (5.7)	1 (3.4)	0.927

pharmacodynamics, or safety of febuxostat.[18] Their results are in conflict with those of the present study. Khosravan et al investigated these parameters in healthy subjects and assessed the parameters after 7 days,[18] whereas the present study focused on elderly patients using low doses of febuxostat and observed the parameters for 16 weeks. Therefore, their subjects, doses, and duration of evaluation were different from those of the present study. Moreover, renal function and body surface area levels in female patients in the present study were low; thus, the blood concentrations of febuxostat are expected to have been higher than those observed in the previous study. Some previous reports have suggested that the efficacy of febuxostat[13,19,20] increases in a dose-dependent manner, whereas its safety in elderly patients is not affected by high doses.[13] Although the blood concentration of febuxostat may be increased in female patients, the incidence of AEs in female patients was similar to that in male patients. Thus, our results are consistent with those of previous reports. These results suggest that a low dose of febuxostat is safe and efficacious in elderly female patients.

Our study has some limitations. This study employed a retrospective design, and the number of subjects was small. Therefore, larger, prospective, multicenter studies (eg, Febuxostat versus Allopurinol Controlled Trial) will be needed to further validate our results. In addition, the blood concentration of febuxostat was not measured. Further studies that focus on the pharmacodynamics of febuxostat in elderly patients will be needed.

Table 3 Grades of adverse events after treatment with febuxostat

Grade classification	Male (n=53)	Female (n=29)	*P*-value
Grade 2 (%)	2 (3.8)	3 (10.3)	0.480
Grade 3 (%)	4 (7.6)	2 (6.9)	0.737
Grade 4 (%)	0 (0)	0 (0)	–

Conclusion

In the present study, we demonstrated that the efficacy of febuxostat in elderly female patients is superior to that in elderly male patients, whereas the safety is equivalent.

Disclosure

The authors report no conflicts of interest in this work.

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