Febuxostat has currently played pivotal role in the treatment of hyperuricemia, but there is little comprehensive information for the determinants of individual difference in efficacy of febuxostat. Therefore, the present study, a retrospective investigation, was carried out to analyze the effects of patient characteristics on the efficacy of febuxostat. A total of 225 patients who were continuously prescribed the same dose of febuxostat for 8–12 weeks from the initial therapy were enrolled in the present study. The data, including patient information and laboratory data, were collected from electronic medical records. Serum urate lowering effects of febuxostat were evaluated by calculating the change in serum urate level at baseline and at 8–12 weeks after starting febuxostat. The multiple regression analysis showed the change in serum urate level was significantly lower in male patients and in those with a lower baseline serum urate level, higher previous dose of allopurinol, lower dose of febuxostat and lower body surface area-unadjusted estimated glomerular filtration rate. Concomitantly administered drugs did not show a significantly influence on the efficacy of febuxostat. In conclusion, it should be noted that the serum urate lowering efficacy of febuxostat may decrease in patients with a higher previous dose of allopurinol, renal impairment or male patients. The basic findings of the present study are believed to contribute to the proper use of febuxostat.

Key words febuxostat; allopurinol; urate; uric acid; gender; renal impairment.

Hyperuricemia is induced by an imbalance between production and excretion of urate, and not only causes urate crystal deposition disease, including gouty arthritis and renal impairment, but also is a risk factor for hypertension and dyslipidemia. For these reasons, improvement of lifestyle and drug therapy are necessary in patients with hyperuricemia. Allopurinol and febuxostat, xanthine oxidase inhibitors, are mainly chosen for drug therapy of hyperuricemia. Allopurinol, a conventional xanthine oxidase inhibitor, can cause serious adverse effects in patients with renal impairment because oxypurinol, an active metabolite of allopurinol, is excreted via the kidneys. Therefore, it is necessary for patients with renal impairment to receive a reduced dose. On the other hand, as febuxostat, a once-a-day non-purine xanthine oxidase inhibitor, is excreted into feces and urine in a well-balanced manner after being metabolized in the liver, febuxostat can be safely used in patients with mild, moderate or severe renal impairment. Therefore, there are many cases of switching from allopurinol to febuxostat in patients who have allopurinol resistance or in whom allopurinol is difficult to use due to renal impairment. Thus, in current drug therapy for hyperuricemia, febuxostat has played a more pivotal role compared with allopurinol.

One of the clinical problems of febuxostat therapy is the large individual difference in the urate-lowering efficacy of febuxostat. Hyperuricemia is a chronic disease, and is apt to needing long-term pharmacotherapy. In addition, although febuxostat has no fatal adverse effects, a sudden drop in the serum urate level is also known to cause gout at the start of pharmacotherapy for hyperuricemia. Therefore, individual adjustment of the initial dose of febuxostat is clinically desired. However, there is little information on individual treatment with febuxostat. Individual differences have been considered to be induced by pharmacological and/or pharmacokinetic variability i.e., lifestyle, genetic factors, physiological factors and concomitantly administered drugs. As the urate lowering efficacy and plasma concentration of febuxostat exhibit dosage linearity ranging from 10mg/d to 120mg/d, the variation of febuxostat plasma concentration is considered to be especially important for the individual difference in urate lowering efficacy. Previous studies have demonstrated that concomitant drugs, such as antacids, as well as physiological factors, including age, gender, liver function and renal function, can affect the febuxostat pharmacokinetics. Therefore, these factors seem to vary the urate lowering efficacy of febuxostat. Patients with hyperuricemia are apt to exhibit complications, including hypertension, dyslipidemia and renal impairment, and are frequently co-prescribed drugs, such as antihypertensive agents, statins and diuretic agents. As some antihypertensive agents and diuretic agents have been reported to vary the serum urate level by affecting the kinetics of urate, the co-administration of these drugs may indirectly affect the urate lowering efficacy of febuxostat. In addition, the decrease of renal function may also indirectly affect the urate lowering efficacy of febuxostat because excretion of urate via the kidneys decreases in patients with renal impairment.

The serum urate level is a useful biomarker in febuxostat therapy. However, it is difficult to predict the serum urate lowering efficacy of febuxostat by serum urate level before start-
ing febuxostat therapy. Clarifying the effects of patient characteristics on the serum urate lowering efficacy of febuxostat is believed to provide a basic knowledge for predicting serum urate lowering efficacy of febuxostat using patient data before starting febuxostat. However, there are few comprehensive analyses of such relationships in clinical practice. The purpose of the present study was to discover the patient characteristics associated with the serum urate lowering efficacy of febuxostat by retrospective investigation.

MATERIALS AND METHODS

Patient and Collection of Patient Data  The present study was a retrospective study approved by the ethics committee of Shiga University of Medical Science Hospital (Ethics Committee approval number: 27-136) and Kyoto Pharmaceutical University (Ethics Committee approval number: 16-02), and performed in accordance with the ethical principles for medical research outlined in the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The patients prescribed febuxostat May 2011 to April 2015 at Shiga University of Medical Science Hospital were included in the present study. Inclusion criteria: patients who were continuously prescribed febuxostat (once a day, 10mg/d or 20mg/d) longer than 2 weeks from initial therapy. Exclusion criteria: 1) patients who were prescribed febuxostat at another hospital in the past, and 2) patients with missing laboratory data, including serum urate level at baseline and after starting febuxostat.

The data, including patient information, such as age (year), gender, body surface area (m²), febuxostat dose (mg/d), previous allopurinol dose (mg/d) and concomitantly administered drugs (aspirin, angiotensin II receptor blockers, beta blockers, calcium blockers, gastric secretion inhibitors, statins and loop/thiazide diuretics), as well as laboratory data, such as serum urate level (mg/dL), alanine transaminase (ALT) level (IU/L) and estimated glomerulus filtration rate (eGFR) level (mL/min/1.73 m²), were collected from electronic medical records. The mean values of laboratory data were calculated 4 weeks before starting febuxostat. Exclusion of the data on serum urate level are listed below: 1) data after discontinuing prescription of febuxostat, 2) data after changing dose of febuxostat, and 3) data after suspected poor compliance because the interval between scheduled visit date and actual visit date was more than 1 week. The serum urate level after starting febuxostat was calculated as the mean value at each defined period until the dose of febuxostat changed. The previous dose of allopurinol was the most recent dose at 4 weeks before starting febuxostat. In addition, concomitantly administered drugs that had been prescribed 4 weeks before starting febuxostat were continuously prescribed for 8–12 weeks after starting febuxostat for all subjects. The concomitantly administered drugs were classified by therapeutic category, but irbesartan and losartan, which have been reported to decrease serum urate,21,24) were distinguished from other angiotensin II receptor blockers.

Data Analysis  Serum urate lowering effects of febuxostat were evaluated by calculating the change in serum urate level (%) with the following formula.

\[
\text{The change in serum urate level } \% = \left( \frac{\text{Serum urate level after the initiation of febuxostat}}{\text{Baseline serum urate level}} - 1 \right) \times 100
\]

The differences in the change of serum urate level between the two groups were analyzed with the Mann–Whitney U test. The relationships among the change in serum urate level and patient characteristics were analyzed by Spearman's rank-correlation analysis. A forced entry multiple regression analysis was performed to correct for confounding factors. The significance level was set at \( p < 0.05 \). Statistical analysis was performed using the statistical software, SPSS II version 23.0. (IBM, Armonk, NY, U.S.A.)

RESULTS

The scheme of patient selection is summarized in Fig. 1. A total of 442 patients met the criteria for this study out of 956

Fig. 1. The Scheme of Patient Selection in the Present Study
patients who were prescribed febuxostat at Shiga University of Medical Science Hospital. The serum urate lowering profile of 442 patients is shown in Fig. 2. Febuxostat markedly decreased the serum urate level and increased the change in serum urate level in an early stage, and the serum urate level and the change in serum urate level were stable at 4 weeks or later.

For statistical analysis, the data of 225 patients who were continuously prescribed the same dose of febuxostat were used in order to exclude the effects of dose change. The 225 patients analyzed in the present study are summarized in Table 1. The numbers of patients receiving febuxostat at a dose of 10 mg/d and 20 mg/d were 156 patients and 69 patients, respectively. The numbers of patients who were treated for hyperuricemia with febuxostat for the first time (previous allopurinol dose was 0 mg/d) and who were already treated with allopurinol (previous allopurinol dose was 25–200 mg/d) were 141 patients and 84 patients, respectively. Medians of the serum urate level for baseline and 8–12 weeks after starting febuxostat were 8.4 (2.8 to 13.6) mg/dL and 6.4 (3.3 to 12.0) mg/dL, respectively, and median of the change in serum urate level was −22.7 (−60.7 to 76.6) %.

The univariate analysis was performed to analyze the effects of patient characteristics on the change in serum urate level. Here, gender ($p=0.012$), body surface area ($r=0.188$, $p=0.005$), previous allopurinol dose ($r=0.381$, $p<0.001$) and baseline serum urate level ($r=−0.504$, $p<0.001$) were significant factors. However, age, ALT, body surface area-adjusted eGFR, body surface area-unadjusted eGFR, febuxostat dose and concomitantly administered drugs were not significant.

The results of the forced entry multiple regression analysis regarding effects of patient characteristics on the change in serum urate level are shown in Table 2. Similar to the results of the univariate analysis, gender ($p=0.022$), previous allopurinol dose ($p<0.001$) and baseline serum urate levels ($p<0.001$) were significant. In addition, body surface area-adjusted eGFR ($p=0.046$) and febuxostat dose ($p=0.015$) were also significant. However, concomitantly administered drugs were not significant. Adjusted R square was 0.429 and multicollinearity did not occur because the variance inflation factor (VIF) among the patient characteristics was less than 2.

**DISCUSSION**

To our knowledge, this study is the first to comprehensively analyze the effects of patient characteristics on the efficacy of febuxostat in clinical practice. Similar to the previous reports, the serum urate lowering efficacy of febuxostat was observed at an early stage, and the serum urate level was stable at 4 weeks or later (Fig. 2). To prevent gouty arthritis, it is very important to maintain a serum urate level below 6.0 mg/dL. Therefore, in several clinical trials, drug efficacy has been evaluated with the percentage of patients achieving...
A serum urate level below 6.0 mg/dL.\(^9\)\(^,\)\(^28\) As well as the therapeutic target level, the change in serum urate level, a continuous variable, has also been used in many studies as a marker of drug efficacy.\(^16\)\(^,\)\(^29\) As this continuous variable is thought to be capable of evaluating the effects of patient characteristics more quantitatively, the change in serum urate level seemed to be a better marker of drug efficacy. Therefore, the change in serum urate level at 8–12 weeks was selected as the primary endpoint of the present study. A negative correlation was observed between the change in serum urate level and renal clearance affects urate excretion.\(^23\) A weak negative correlation was observed between the change in serum urate level and decreases in body surface area-unadjusted eGFR (mL/min/1.73 m\(^2\)). From these observations, as urate excretion may have larger contribution to urate accumulation in male patients than in females because the reabsorption of urate in the renal tubular epithelial cells in females is lower than in males.\(^32\) However, the mean (± standard deviation) baseline serum urate level in male and female patients were 8.3 (±1.6) and 8.6 (±1.8), respectively. This may be attributed to effects from other factors. From these observations, as urate excretion may have larger contribution to urate accumulation in male patients than in female patients, the urate lowering efficacy of febuxostat in male patients is considered to be decreased.

No correlation was observed between the change in serum urate level and body surface area-adjusted eGFR by the univariate analysis. The efficacy of febuxostat in patients with mild, moderate or severe renal impairment has been reported to be equivalent to that in patients with normal renal function,\(^10\)\(^,\)\(^33\)\(^,\)\(^34\) which is consistent with the results of the present study. In the multivariate analysis, the body surface area-adjusted eGFR (mL/min/1.73 m\(^2\)) was added as an explanation factor to better reflect the renal urate excretion because 70% of urate excretion from the body is carried out via the kidneys and renal clearance affects urate excretion.\(^23\) A weak negative correlation was observed between the change in serum urate level and decreases in body surface area-unadjusted eGFR.

### Table 2. Results of Multiple Regression Analysis Using a Forced on Entry Method

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression coefficients</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male: 1/female: 0)</td>
<td>7.81</td>
<td>1.22 to 14.40</td>
<td>0.022</td>
</tr>
<tr>
<td>Body surface area (m(^2))</td>
<td>4.80</td>
<td>−9.85 to 19.45</td>
<td>0.519</td>
</tr>
<tr>
<td>ALT (U/I)</td>
<td>−0.130</td>
<td>−0.316 to 0.057</td>
<td>0.171</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>−0.132</td>
<td>−0.261 to −0.002</td>
<td>0.046</td>
</tr>
<tr>
<td>Febuxostat dose (20 mg: 1/10 mg: 0)</td>
<td>−6.60</td>
<td>−11.92 to −1.27</td>
<td>0.015</td>
</tr>
<tr>
<td>Allopurinol previous dose (mg/d)</td>
<td>0.120</td>
<td>0.068 to 0.172</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline serum urate level (mg/dL)</td>
<td>−7.72</td>
<td>−9.24 to −6.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concomitantly administered drugs (use: 1/no use: 0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>−1.92</td>
<td>−8.03 to 4.20</td>
<td>0.537</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>1.63</td>
<td>−3.70 to 6.96</td>
<td>0.546</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>1.98</td>
<td>−3.70 to 7.65</td>
<td>0.492</td>
</tr>
<tr>
<td>Calcium blockers</td>
<td>−2.10</td>
<td>−7.01 to 2.82</td>
<td>0.401</td>
</tr>
<tr>
<td>Gastric secretion inhibitors</td>
<td>−2.78</td>
<td>−7.67 to 2.12</td>
<td>0.265</td>
</tr>
<tr>
<td>Irbesartan/Losartan</td>
<td>5.54</td>
<td>−2.26 to 13.35</td>
<td>0.163</td>
</tr>
<tr>
<td>Loop/thiazide diuretics</td>
<td>3.35</td>
<td>−1.84 to 8.54</td>
<td>0.205</td>
</tr>
<tr>
<td>Statins</td>
<td>1.08</td>
<td>−3.91 to 6.07</td>
<td>0.670</td>
</tr>
<tr>
<td>Intercept</td>
<td>37.1</td>
<td>12.2 to 62.0</td>
<td>0.004</td>
</tr>
</tbody>
</table>

CI: Confidence interval, Objective variable: Change in serum urate level (%), Adjusted \(R^2=0.429\), \(p<0.001\), Bold font indicates significance at \(p<0.05\).
after correcting for other factors (Table 2). This suggests that the urate lowering efficacy of febuxostat may decrease in patients with renal impairment and this may be because the renal urate excretion may have larger contribution to urate accumulation as renal function decreases. On the other hand, involvement of febuxostat plasma concentration is unlikely because the plasma concentration in patients with renal impairment was equivalent or increased compared with patients with normal function.\(^\text{10,20,33}\)

As influence of concomitant drugs on urate lowering efficacy of febuxostat was not observed in the present study (Table 2), it is suggested that the representative concomitant drugs may not have an influence on the efficacy of febuxostat. For the reason mentioned above, the concomitant drugs are considered not to have an influence on the change in the serum urate level even if they influence the baseline serum urate level by affecting the kinetics of urate. In addition, as gastric secretion inhibitors did not have an influence on the urate lowering efficacy of febuxostat, the suppression of absorption of febuxostat by antacids\(^\text{17}\) may be caused by adsorption with magnesium hydroxide or aluminum hydroxide rather than a rise in intragastric pH, or gastric secretion inhibitors may not have an influence on the change in the serum urate level despite suppression of absorption of febuxostat.

There are some limitations in the present study. 1) Febuxostat dosage was limited to 10 mg/d or 20 mg/d because the study was a retrospective investigation in a single-center. 2) The environmental factors, including lifestyle, and genetic factors which have been reported to affect the serum urate level,\(^\text{15,30}\) were not able to be considered. These environmental factors may contribute to the remaining part of the multiple regression analysis in the present study. In addition, the dosage regimen and the individual effects of the concomitant drugs were not considered because of the limited number of patients. Furthermore, although all the concomitant drugs prescribed in other hospitals were not necessarily described, they were determined as much as possible by referring to documents, such as a letter of reference from another hospital. The present study was based on a retrospective investigation of a limited number of patients, and further studies may be necessary to remove the limitations.

CONCLUSION

In the present study, the serum urate lowering efficacy of febuxostat was significantly lower in patients with a lower baseline serum urate level, higher previous dose of allopurinol, lower dose of febuxostat, lower body surface area-unadjusted eGFR or male patients. In addition, concomitant drugs did not affect the serum urate lowering efficacy. The basic findings of the present study are believed to contribute to the proper use of febuxostat.

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Conflict of Interest  TU received research promotion grants (Shogaku Kifuku) from Teijin Pharma. However, the research topics of this donation grant are not restricted. The other authors declare no conflict of interest.

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