Abstract

Objectives: Febuxostat, a nonpurine xanthine oxidase, is known to be effective and safe, even in patients with chronic kidney disease. However, there are insufficient data about the efficacy and safety of febuxostat in kidney transplant patients.

Materials and Methods: We reviewed medical records of all kidney transplant patients who were prescribed febuxostat between August 2012 and May 2015 at Asan Medical Center in Seoul, Korea. The efficacy and safety results of febuxostat in transplant patients were evaluated. To compare the efficacy of febuxostat, results of kidney transplant patients who were prescribed benzbromarone or allopurinol for more than 1 year during the same period were also reviewed.

Results: Thirty-one patients were included in this study. The initial serum uric acid level of 481.83 ± 143.36 µmol/L decreased to 302.18 ± 150.50 µmol/L after 1 month of febuxostat use. Only 1 patient had altered sense of taste after taking febuxostat, but this symptom quickly improved and he continued treatment. No other adverse events were reported. In addition, at 12 months, mean serum uric acid levels were 280.77 ± 78.52 µmol/L in the febuxostat, 332.52 ± 72.57 µmol/L in the benzbromarone, and 363.45 ± 60.08 µmol/L in the allopurinol group. However, we found no apparent effect on estimated glomerular filtration rate ($P = .344$). The mean doses of febuxostat, benzbromarone, and allopurinol were 52.31 ± 5.33 mg/day, 42.19 ± 1.69 mg/day, and 146.67 ± 16.52 mg/day.

Conclusions: Febuxostat reduced serum uric acid levels effectively in kidney transplant patients without severe adverse events.

Key words: Renal transplantation, Uric acid, Xanthine oxidase inhibitor

Introduction

Febuxostat is a nonpurine xanthine oxidase inhibitor that was approved by the European Medicines Agency in 2008 and by the US Food and Drug Administration in 2009. Febuxostat is selective for the enzyme xanthine oxidase, unlike allopurinol, which inhibits other enzymes involved in purine and pyrimidine metabolism. In addition, febuxostat is excreted by both the urinary and fecal pathways after being metabolized to acyl glucuronide metabolites in the liver. A small portion of the parent compound undergoes oxidative metabolism by cytochrome P450 enzymes. Allopurinol is a xanthine oxidase inhibitor, and both allopurinol and its metabolites are excreted in the urine. Therefore, dose reduction is necessary in patients with renal impairments. Benz bromarone increases the urinary excretion of uric acid and may have limited effects in patients with chronic kidney disease (CKD).

As shown in several previous phase 3 clinical trials, febuxostat doses at 80 and 120 mg/day were found to be significantly more effective than allopurinol at 100 to 300 mg/day in lowering serum uric acid levels in patients with hyperuricemia and gout. Febuxostat was also generally well tolerated, with the most frequent adverse events reported to be abnormal liver function tests and gastrointestinal symptoms. Some trials excluded patients with renal impairment, whereas others included patients with mild to moderate renal dysfunction. In the studies that included patients with renal impairment, febuxostat was reported to be more efficacious than allopurinol and equally safe.

The influence of hyperuricemia on renal function and graft survival in kidney transplant recipients is controversial. Although some studies have found
no association between serum uric acid and graft function,\textsuperscript{12,13} most studies reported an influence of hyperuricemia on graft function and survival.\textsuperscript{14-17} In a recent study at our center that reviewed kidney transplant patients between 1990 and 2009, hyperuricemia was an independent risk factor for graft dysfunction (hazard ratio of 1.454; \( P < .001 \)).\textsuperscript{17}

Several urate-lowering agents for the treatment of hyperuricemia are currently in use. However, there are insufficient data about the efficacy and safety of febuxostat in kidney transplant patients. Therefore, in our present study, we reviewed kidney transplant patients who were prescribed febuxostat and evaluated its efficacy and safety.

**Materials and Methods**

**Patients**

We reviewed medical records of all renal transplant patients who were prescribed febuxostat between August 2012 and May 2015 at Asan Medical Center, an academic hospital, in Seoul, Korea. All patients were followed until June 2015. Patients were included in this study regardless of estimated glomerular filtration rate (eGFR) or previous urate-lowering drugs. Patients who received other organ transplants or who were younger than 18 years were excluded. Patients who were prescribed febuxostat for less than 1 month were also excluded. To identify the efficacy of febuxostat, patients who were prescribed benzbromarone or allopurinol during the same period were also reviewed. The study was approved by the local institutional review board (2015-0806).

**Study design**

This was a retrospective observational study. All patients who used febuxostat for more than 1 month were assessed. Serum uric acid levels and eGFR values were collected. Any adverse events were recorded. In addition, patients who were prescribed febuxostat, benzbromarone, or allopurinol for at least 1 year at the time of enrollment were evaluated to identify the efficacy of febuxostat in transplant patients but not to compare exactly the efficacy of drugs. Changes in uric acid and eGFR were assessed in addition to transplant characteristics. Finally, effects and safety were evaluated in patients who were prescribed febuxostat for more than 18 months. Some patients used febuxostat for over 2 years. Febuxostat was started at a dose of 40-80 mg/day and adjusted according to the serum uric acid levels. Benzbromarone was prescribed at a dose of 25 to 50 mg/day, and allopurinol was started at 100 to 300 mg/day according to renal function. These drugs were also adjusted according to clinical responses. The original drug of febuxostat was prescribed, which was more expensive than other urate-lowering drugs. The cost of 80 mg/day febuxostat was twice the cost of 300 mg/day allopurinol, which was also twice the cost of 50 mg/day benzbromarone.

**Data collection**

Data were obtained from inpatient and outpatient electronic medical records. Transplant-related information, including donor type, donor age, human leukocyte antigen (HLA) mismatch, ABO incompatibility, HLA sensitization, and cause of end-stage renal disease were collected. Medication data were also obtained, not only for urate-lowering agents but also for immunosuppressants or any other medication. Serum uric acid levels and eGFR were checked every 3 months. Adverse events were evaluated by medical records and laboratory data, such as liver function tests and complete blood counts. Estimated glomerular filtration rate was calculated as follows: isotope-dilution mass spectrometry-traceable Modification of Diet in Renal Disease (eGFR [mL/min/1.73 m\(^2\)] = 175 \times \text{serum creatinine}^{1.154} \times \text{age}^{0.203} \times 0.742 \text{ if patient is female or 1.212 if patient is black}).\textsuperscript{18}

**Statistical analyses**

Data are expressed as mean ± standard deviation or as numbers and percentages. For categorical variables, chi-square test and Fisher exact test were used. Continuous variables were compared using the \( t \) test, analysis of variance, or Kruskal-Wallis test, as appropriate. The rates of change in eGFR and serum uric acid levels over the study period were calculated for each patient by linear regression analysis. All reported \( P \) values are 2-sided, and \( P < .05 \) was considered statistically significant. All statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY).

**Results**

**Patients**

Thirty-one patients were included in this study (Figure 1). The mean duration of febuxostat use was 11.90 ± 8.79 months (range, 1-27 mo). Twenty-six
patients (83.9%) were male, and the mean age was 43.45 ± 10.93 years (range, 20-65 y). The most common cause of end-stage renal disease was hypertension (38.7%). Twenty-four patients (77.4%) received kidney transplants from living donors. Most patients were also taking calcineurin inhibitors (71.0% were receiving tacrolimus, 25.8% cyclosporine, and 80.6% mycophenolate). In addition, 6 patients had an eGFR of < 30 mL/min/1.73 m² when they began using febuxostat. Of the 31 study patients who were prescribed febuxostat, 13 used it for more than 1 year. The remaining 18 patients were followed up for less than 1 year or discontinued the drugs within 1 year due to improved hyperuricemia.

During the same time period (August 2012 to May 2015), 48 renal transplant patients were prescribed benzbromarone and 15 were prescribed allopurinol for more than 1 year. There was no significant difference in baseline characteristics among the groups (Table 1). In the febuxostat group, 1 patient used 80 mg and the other 12 patients used 40 mg, although the dose was increased to 80 mg for 3 of them. In the benzbromarone group, 15 patients used 25 mg and 33 patients used 50 mg. In the allopurinol group, 1 patient used 300 mg, 9 patients used 200 mg, and 5 patients used 100 mg according to renal function.

Efficacy of febuxostat and outcomes of other urate-lowering agents
In 31 patients, the initial serum uric acid level of 481.83 ± 143.36 μmol/L decreased to 302.18 ± 150.50 μmol/L after 1 month of febuxostat use. Twenty-one patients (67.7%) achieved serum uric acid levels ≤ 356.88 μmol/L (6 mg/dL). In patients who used urate-lowering agents for more than 1 year, mean serum uric acid levels also decreased in all groups (Figure 2). In the febuxostat and benzbromarone groups, but not the allopurinol group, mean serum

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of the Study Patients Who Used Urate-Lowering Agents for More Than 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febuxostat</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Gout, No. of patients (%)</td>
</tr>
<tr>
<td>Causes of ESRD, No. of patients</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Donor type, No. of patients</td>
</tr>
<tr>
<td>Living donor</td>
</tr>
<tr>
<td>Deceased donor</td>
</tr>
<tr>
<td>Donor age, y</td>
</tr>
<tr>
<td>Delayed graft function, No. of patients</td>
</tr>
<tr>
<td>Rejection, No. of patients</td>
</tr>
<tr>
<td>ABO incompatible, No. of patients</td>
</tr>
<tr>
<td>HLA sensitized, No. of patients</td>
</tr>
<tr>
<td>HLA mismatches ≥ 3, No. of patients (%)</td>
</tr>
<tr>
<td>1st or 2nd kidney transplants, No. of patients</td>
</tr>
<tr>
<td>Immunosuppressant, No. of patients</td>
</tr>
<tr>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Sirolimus</td>
</tr>
<tr>
<td>Mycophenolate</td>
</tr>
<tr>
<td>Azathioprine</td>
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<tr>
<td>RAS blocker, No. of patients</td>
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<tr>
<td>Diuretics, No. of patients</td>
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<tr>
<td>Statin, No. of patients</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index; ESRD, end stage renal disease; HLA, human leukocyte antigen; RAS, renin-angiotensin system

**Figure 1.** Follow-Up Duration and Number of Febuxostat-Treated Patients

**Figure 2.** Serum Uric Acid Levels in Febuxostat, Benzbromarone, and Allopurinol Groups
uric acid levels were ≤ 356.88 μmol/L. At 12 months, significantly more patients in the febuxostat group achieved serum uric acid levels ≤ 356.88 μmol/L than in the allopurinol group (84.6% vs 40.0%; \( \text{P} = .024 \)) (Figure 3). However, there was no significant difference in the rate at which uric acid levels changed between the groups after 6 and 12 months (Table 2). The slope of the eGFR was positive in the febuxostat and allopurinol groups and negative in the benzbromarone group, although there was no statistically significant difference found between the groups. The eGFR measurements during follow-up are shown in Figure 4.

Safety of febuxostat
During the follow-up period, only 1 of 31 patients noted an altered sense of taste after taking febuxostat, but this symptom quickly improved and he continued treatment. No other adverse events were reported. One patient who was given sirolimus for Kaposi sarcoma with febuxostat for 27 months did not experience any adverse events. One patient was inadvertently prescribed febuxostat for 2 months.

Table 2. Rates of Estimated Glomerular Filtration Rate and Serum Uric Acid Level Changes Over 1 Year

<table>
<thead>
<tr>
<th></th>
<th>Febuxostat</th>
<th>Benzbromarone</th>
<th>Allopurinol</th>
<th>( \text{P} ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \text{eGFR}, \text{ mL/min/1.73 m}^2 )</td>
<td>0.286 ± 1.224</td>
<td>-0.419 ± 2.976</td>
<td>0.413 ± 1.538</td>
<td>.344</td>
</tr>
<tr>
<td>( \Delta \text{Uric acid (12 months), \text{ µmol/L}} )</td>
<td>-37.83 ± 33.55</td>
<td>-30.93 ± 22.60</td>
<td>-34.68 ± 37.42</td>
<td>.731</td>
</tr>
<tr>
<td>( \Delta \text{Uric acid (6 months), \text{ µmol/L}} )</td>
<td>-80.78 ± 89.23</td>
<td>-85.48 ± 44.02</td>
<td>-85.48 ± 44.02</td>
<td>.280</td>
</tr>
</tbody>
</table>

Table 3. Efficacy and Safety of Febuxostat in Patients Who Used Febuxostat for More Than 18 Months

<table>
<thead>
<tr>
<th></th>
<th>18 months (n = 10)</th>
<th>21 months (n = 9)</th>
<th>24 months (n = 3)</th>
<th>27 months (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid ≤ 356.88 \text{ µmol/L (6 mg/dL)}, No. of patients (%)</td>
<td>9 (90%)</td>
<td>8 (89%)</td>
<td>3 (100%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Uric acid, \text{ µmol/L}</td>
<td>248.03 ± 108.85</td>
<td>262.90 ± 83.27</td>
<td>259.93 ± 101.12</td>
<td>196.28 ± 168.33</td>
</tr>
<tr>
<td>eGFR, \text{ mL/min/1.73 m}^2</td>
<td>65.43-429.26</td>
<td>130.86-386.62</td>
<td>154.65-356.88</td>
<td>77.32-313.24</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>45.90 ± 16.35</td>
<td>48.44 ± 17.23</td>
<td>46.33 ± 28.04</td>
<td>39.50 ± 31.82</td>
</tr>
<tr>
<td>Range</td>
<td>15.0-72.0</td>
<td>15.0-64.0</td>
<td>17.0-62.0</td>
<td></td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>26.20 ± 12.89</td>
<td>18.56 ± 7.58</td>
<td>17.67 ± 5.86</td>
<td>16.50 ± 0.71</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>19-51</td>
<td>13-26</td>
<td>11-22</td>
<td>16-17</td>
</tr>
<tr>
<td>Range</td>
<td>19-51</td>
<td>13-26</td>
<td>11-22</td>
<td>16-17</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>34.60 ± 58.67</td>
<td>14.00 ± 5.98</td>
<td>13.33 ± 3.06</td>
<td>11.50 ± 2.12</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>8-199</td>
<td>7-28</td>
<td>10-16</td>
<td>10-13</td>
</tr>
<tr>
<td>Range</td>
<td>8-199</td>
<td>7-28</td>
<td>10-16</td>
<td>10-13</td>
</tr>
<tr>
<td>WBCs, \times 10^9/L</td>
<td>8.06 ± 4.53</td>
<td>7.20 ± 3.09</td>
<td>5.97 ± 1.04</td>
<td>6.10 ± 1.56</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.80-19.60</td>
<td>3.50-12.90</td>
<td>4.80-68.00</td>
<td>5.00-7.20</td>
</tr>
<tr>
<td>Range</td>
<td>120 ± 270</td>
<td>125 ± 188</td>
<td>129 ± 172</td>
<td>128 ± 290</td>
</tr>
<tr>
<td>Platelets, \times 10^9/L</td>
<td>183.10 ± 57.89</td>
<td>173.44 ± 59.98</td>
<td>125.00 ± 20.08</td>
<td>101.00 ± 25.46</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>117-279</td>
<td>104-289</td>
<td>104-144</td>
<td>83-119</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; SD, standard deviation; WBC, white blood cell
with azathioprine, which is contraindicated due to the risk of increasing azathioprine level in the blood.\textsuperscript{19} However, no adverse events were reported during these 2 months. In addition, there were 2 patients who used febuxostat for 27 months (Table 3). However, 1 of these patients started dialysis at 26 months and stopped febuxostat after 1 month of dialysis. He had no adverse events after long-term febuxostat use with a very low eGFR. His uric acid level and eGFR at 27 months were influenced by dialysis. The other patient who used febuxostat for 27 months had a uric acid level of 315.27 μmol/L and an eGFR of 62.0 mL/min/1.73 m\textsuperscript{2}. One patient had an abnormal liver function test and anemia after 18 months of febuxostat use. However, aspartate transaminase and alanine transaminase levels were elevated after steroid pulse therapy due to the suspicion of organ rejection in this patient. The anemia was determined to be an adverse effect of trimethoprim/sulfamethoxazole administered for prophylaxis of pneumocystis pneumonia.

**Discussion**

In our present study, febuxostat was safely used in kidney transplant patients. The efficacy of febuxostat in lowering uric acid levels was comparable with other urate-lowering agents in clinical settings, and there was no apparent effect on eGFR. Previous studies have also reported that febuxostat was effective in lowering uric acid levels without severe adverse events in kidney transplant patients.\textsuperscript{4,5} Tojimbara and associates\textsuperscript{5} enrolled 22 renal transplant recipients with hyperuricemia between June 2012 and January 2013 and treated them with febuxostat. Three months after initial febuxostat treatment, 10/22 patients (45%) achieved uric acid levels of ≤ 356.88 μmol/L and 16 patients (73%) maintained uric acid levels of ≤ 356.88 μmol/L up until their last follow-up visit. One patient stopped taking febuxostat due to numbness in the arms. There were no additional adverse events reported in that study. In a study from Sofue and associates,\textsuperscript{4} 26 of 51 kidney transplant recipients with post-transplant hyperuricemia between June 2012 and June 2013 were treated with febuxostat. The febuxostat group showed a significant decrease in serum uric acid and a higher rate of achieving target uric acid levels (50% vs 24%; odds ratio 3.17; 95% confidence interval, 0.96-10.5; \textit{P} = .08) than the control group, which included unmedicated patients and patients on conventional urate-lowering therapy. Changes in the allograft eGFR did not vary between the groups, and there were no severe adverse events. The aforementioned studies had follow-up durations of approximately 1 year.\textsuperscript{4,5} In our present study, 10 patients who used febuxostat for more than 18 months were included, and 3 of these used febuxostat for more than 2 years. Our present study also included a patient with a low eGFR impending dialysis and a patient who was taking sirolimus due to Kaposi sarcoma. In addition, the febuxostat doses (40-80 mg/day) in our current patient series were higher than in previous studies (10-20 mg/day). Only 1 of our study patients had an altered sense of taste, which was quickly resolved without discontinuation of the medication. There were no additional adverse events.

Previous studies have reported that febuxostat reduces uric acid more effectively than allopurinol in patients with CKD.\textsuperscript{2,20-23} In addition, the febuxostat-treated groups showed better renal function than the allopurinol-treated groups in some of these earlier reports.\textsuperscript{21-23} Tanaka and associates\textsuperscript{2} performed a prospective, randomized, open-label, parallel-group trial in hyperuricemic patients with stage 3 CKD. Febuxostat resulted in a significantly greater reduction in serum uric acid than conventional therapy (-130.87 μmol/L vs -17.85 μmol/L; \textit{P} < .001). Serum creatinine levels and eGFR did not significantly change in either group. However, febuxostat treatment for 12 weeks reduced the urinary levels of liver-type fatty acid-binding protein, albumin, and beta-2 microglobulin, suggesting a possible renoprotective effect. Akimoto and associates\textsuperscript{20} also observed that 6 months of febuxostat treatment significantly reduced 8-hydroxydeoxyguanosine, an oxidative stress marker. This could be explained by inhibition of xanthine oxidase, an important source of reactive oxygen species, although further studies are necessary to determine the exact mechanisms. In our present study, changes in eGFR were not different among groups, although the slope of eGFR was positive in the febuxostat and allopurinol groups compared with the negative slope in the benzbromarone group. The negative slope of eGFR in the benzbromarone group could be because the benzbromarone group had the highest number of patients with ABO-incompatible and HLA-sensitized kidney transplants. Transplant patients have more
diverse factors influencing renal function than patients with CKD. In addition, the lack of statistical difference in this study was most likely due to the small number of patients.

Our study had several limitations. First, it was retrospectively performed using electronic medical records. Therefore, we did not have access to some detailed information, including the exact incidence of gout flare. Second, the number of patients was small. However, we collected all patients who were prescribed febuxostat as transplant patients in our center, and we followed these patients up to recently. It is necessary to accumulate data and experiences because data on febuxostat use in transplant recipients are scarce. Third, the doses of 3 urate-lowering agents were not consistent. Therefore, this study could not conclude which agent was better. However, febuxostat showed comparable efficacy with other urate-lowering agents in a real clinical setting. Fourth, there were several transplant-related factors that may have affected our study outcomes.

In conclusion, febuxostat reduced serum uric acid levels effectively in kidney transplant patients without severe adverse events. A well-designed, prospectively randomized study is required to provide more accurate safety and efficacy data for febuxostat in kidney transplant patients.

References