Efficacy and Safety of Febuxostat, a Novel Nonpurine Selective Inhibitor of Xanthine Oxidase for the Treatment of Hyperuricemia in Kidney Transplant Recipients

T. Tojimbara, I. Nakajima, J. Yashima, S. Fuchinoue, and S. Teraoka

ABSTRACT

Background. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol for patients with hyperuricemia. In this study, we evaluated the efficacy and safety of febuxostat for the management of hyperuricemia in renal transplant recipients.

Patients and methods. Between June 2012 and January 2013, a total of 22 renal transplant recipients (56 ± 10 years old) with hyperuricemia were enrolled in this study. All patients underwent de novo kidney transplantation, except for 1 patient, who received a second kidney transplant. Ten patients receiving allopurinol and 3 patients receiving benzbromarone were converted to febuxostat at doses of 10–20 mg/d. In the remaining 9 patients, who did not have a history of other urate-lowering medications, febuxostat was initiated at a dose of 10 mg/d.

Results. Uric acid levels after initiation of febuxostat were significantly lower than before treatment (5.7 ± 0.7 mg/mL vs 8.0 ± 0.8 mg/mL; P < .001). At last follow-up visit, 16 of the 22 patients (73%) achieved uric acid levels of ≤6.0 mg/dL, despite the low dosage of febuxostat. All patients were maintained on febuxostat without serious adverse events, except for 1 patient, who discontinued febuxostat because of numbness in the arms.

Conclusions. Low-dose febuxostat is a promising alternative to allopurinol or benzbromarone for the treatment of hyperuricemia in kidney transplant recipients. The long-term urate-lowering efficacy and safety of febuxostat with regard to renal function in kidney transplant recipients with hyperuricemia requires further investigation.

ORGAN-TRANSPLANT RECIPIENTS who are treated with cyclosporine (CsA) have an increased risk of gout; hyperuricemia is present in approximately 80% of transplant recipients, and gout develops in ≥10% within the first few years after transplantation [1-5]. In addition, tacrolimus (Tac), an alternative calcineurin inhibitor, also causes hyperuricemia [2].

Allopurinol, a xanthine oxidase inhibitor, is the most common urate-lowering medication; however, its adverse effects may be severe or life threatening, and they occur more often in patients with renal insufficiency [4]. Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase, is a potential alternative to allopurinol for patients with hyperuricemia and gout. Febuxostat has minimal effects on other enzymes involved in purine and pyrimidine metabolism, and it is metabolized mainly by glucuronide formation and oxidation in the liver [6]. In a study that included subjects with renal impairment, the serum urate-lowering effect of febuxostat was unaltered and there were no adverse events [7]. Furthermore, long-term treatment with febuxostat prevents renal deterioration and maintains renal function in patients with hyperuricemia [8]. In this

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study, we evaluated the efficacy and safety of febuxostat for the management of hyperuricemia in renal transplant recipients.

PATIENTS AND METHODS

This study was approved by our ethics committee, and was in accordance with the Helsinki Declaration of 1975. Between June 2012 and January 2013, a total of 22 renal transplant recipients with hyperuricemia were enrolled in this study. All patients were out-patients, and all were asymptomatic, except for 1 patient, who had a history of several gout attacks. All patients underwent de novo kidney transplantation, except for 1 patient, who received a second kidney transplant. Six of the 22 transplanted kidneys were from cadavers, and the remaining 16 were from living donors, including 2 ABO-incompatible grafts. Eighteen recipients were men and 4 were women. The mean ages of the recipients and donors were 56 ± 0.89 and 1.00 ± 0.73, respectively. The pretransplant dialysis interval was 48 ± 55 months (range, 0–169). The body weight and body mass index of the recipients were 64 ± 12 years (range, 34–72) and 57 ± 10 (range, 27–73), respectively. Human leukocyte antigen-AB and -DR mismatches were 2.05 ± 0.89 and 1.00 ± 0.73, respectively. The pretransplantation creatinine level was 64 ± 0.9 mg/kg (range, 49–82) and 23.3 ± 3.0 kg/m² (range, 19.8–30.8), respectively. The median size of the recipients was 63 ± 0.7 months (range, 8–346). All patients were maintained with a double- or triple-immunosuppressive regimen that included calcineurin inhibitors (CsA [n = 15] or Tac [n = 7]), mycophenolate mofetil, and methylprednisolone. All patients received mycophenolate mofetil at a dose of 1000–1500 mg/d except for 1, who was maintained with CsA and methylprednisolone. Fourteen of the 22 patients were on a double-drug immunosuppressive regimen that included mycophenolate mofetil and a calcineurin inhibitor without methylprednisolone.

Doses of febuxostat were adjusted on the basis of patient response. Relative changes in peripheral blood cell count, blood chemistry including uric acid level, renal function, and adverse events were assessed. Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease equation modified for a Japanese population [9]. Both CsA and Tac trough levels were determined as whole blood concentrations with a chemiluminescence immunoassay technique. The patients were followed up for an average of 12 ± 2 months. The minimum follow-up was 7 months.

Continuous data are presented as mean values and standard deviations. Statistical analyses were performed by analysis of variance using StatPlus software (AnalystSoft, Alexandria, VA). \( P < .05 \) was considered significant.

RESULTS

The average uric acid level before treatment with febuxostat was 8.0 ± 0.8 mg/dL (range, 5.5–9.8). Ten patients who had been receiving allopurinol (100–200 mg/d) were converted to febuxostat at a dose of 20 mg/d. Three patients who had been receiving benzbromarone (25–50 mg/d) were converted to febuxostat at a dose of 10 or 20 mg/d. In the remaining 9 patients who had not previously received urate-lowering drugs, febuxostat was initiated at a dose of 10 mg/d. Table 1 summarizes uric acid levels, renal function, peripheral blood cell counts, liver function, and trough levels of calcineurin inhibitors before initial treatment with febuxostat, 3 months after the initiation of febuxostat, and at the time of the patients’ last visit to the outpatient clinic. There were significant differences in uric acid levels before and after the initiation of febuxostat, both in patients without previous urate-lowering therapy and in the conversion group (\( P < .001 \) and \( P < .001 \), respectively; Table 1). Three months after the initial treatment with febuxostat, 10 of the 22 patients (45%) achieved uric acid levels of ≤6.0 mg/dL (6.3 ± 0.9). In 16 of the 22 patients (73%), uric acid levels were maintained ≤6.0 mg/dL (5.7 ± 0.7) at the time of the patients’ last visit to the outpatient clinic. The average dosages of febuxostat at 3 months after initiation of febuxostat and at last follow-up visit were 16.0 ± 5.0 mg/d (range, 10–20) and 19.1 ± 8.1 mg/d (range, 10–40), respectively.

There was no difference in serum creatinine levels and estimated glomerular filtration rate before and after the initiation of treatment with febuxostat. White blood cell counts and hemoglobin levels remained stable before and after conversion, as did renal function. In addition, liver enzyme levels and blood concentrations of calcineurin inhibitors were not affected by treatment with febuxostat (Table 1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>3 Months After</th>
<th>Last</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid (mg/dL) in all patients</td>
<td>8.0 ± 0.8</td>
<td>6.3 ± 0.9</td>
<td>5.7 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Uric acid (mg/dL) in patients without previous urate-lowering therapy</td>
<td>8.4 ± 0.2</td>
<td>6.3 ± 0.7</td>
<td>5.6 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Uric acid (mg/dL) in conversion group</td>
<td>7.8 ± 1.1</td>
<td>6.2 ± 1.2</td>
<td>5.8 ± 0.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>1.66 ± 0.7</td>
<td>1.58 ± 0.37</td>
<td>1.63 ± 0.61</td>
<td>.940</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>39.5 ± 14.3</td>
<td>40.3 ± 14.6</td>
<td>39.8 ± 14.5</td>
<td>.983</td>
</tr>
<tr>
<td>WBC (µL)</td>
<td>6,155 ± 1,578</td>
<td>5,859 ± 1,616</td>
<td>6,145 ± 1,845</td>
<td>.804</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>12.1 ± 1.7</td>
<td>12.5 ± 1.5</td>
<td>12.6 ± 1.8</td>
<td>.564</td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>29 ± 19</td>
<td>31 ± 19</td>
<td>39 ± 19</td>
<td>.921</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>18 ± 5</td>
<td>20 ± 6</td>
<td>18 ± 5</td>
<td>.310</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>13 ± 5</td>
<td>15 ± 5</td>
<td>13 ± 4</td>
<td>.322</td>
</tr>
<tr>
<td>Trough level of CsA (ng/mL)</td>
<td>73 ± 25</td>
<td>73 ± 25</td>
<td>67 ± 26</td>
<td>.758</td>
</tr>
<tr>
<td>Trough level of Tac (ng/mL)</td>
<td>5.4 ± 2.1</td>
<td>5.9 ± 2.5</td>
<td>5.7 ± 1.4</td>
<td>.888</td>
</tr>
</tbody>
</table>

Abbreviations: 3 Months After, 3 months after initiation of febuxostat; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Before, before initiation of febuxostat treatment; Cr, creatinine; CsA, cyclosporine; eGFR, estimated glomerular filtration rate; γ-GPT, glutamyltranspeptidase; Hb, hemoglobin; Last, at last follow-up visit; Tac, tacrolimus; WBC, white blood cells.
All patients maintained their use of febuxostat without serious adverse events except for 1 patient. This patient stopped taking febuxostat because of numbness in the arms within 1 month after the initiation of febuxostat treatment.

DISCUSSION

Although the precise mechanisms of hyperuricemia in renal transplant recipients are not fully understood, it is postulated that the intrarenal vasoconstriction and decreased coefficient of glomerular ultrafiltration owing to calcineurin inhibitor nephrotoxicity causes enhanced tubular urate reabsorption, whereas the reduced renal mass associated with chronic CsA (or Tac) nephrotoxicity eventually leads to a reduction in urate secretion [10]. Renal dysfunction, use of diuretics, and obesity are other risk factors for hyperuricemia after renal transplantation [5]. Uric acid induces endothelial cell dysfunction, decreases nitric oxide production, stimulates vascular smooth muscle cell proliferation, activates the renin-angiotensin system, and produces various inflammatory mediators [5,10,11]. A recent systematic review by Huang et al [11] suggested that hyperuricemia may be an independent risk factor for allograft dysfunction.

Although it is well-established that gout attacks should be treated, the impact of urate-lowering therapy in organ transplant patients with asymptomatic hyperuricemia remains controversial, and side effects of the most commonly used medications must be considered. Especially in allopurinol, >5 enzymes in purine and pyrimidine metabolism are affected. In contrast, febuxostat inhibits xanthine oxidase selectively and mainly metabolized in the liver. Therefore, febuxostat may be expected to have fewer adverse events, and mild-to-moderate renal impairment does not impede its effect. No dose adjustment seems to be necessary for patients with renal insufficiency [7]. In this study, administration of febuxostat resulted in a prompt and persistent reduction in the serum urate concentration, despite the fact that the initial dosages of febuxostat were very low. In our study, there were no critical adverse events (eg, rash, hypersensitivity reactions or organ dysfunction) except for in 1 patient, who experienced numbness in his arms. Febuxostat affected neither renal graft function nor bone marrow function.

In conclusion, low-dose febuxostat is a promising alternative to allopurinol or benz bromarone for the treatment of hyperuricemia in kidney transplant recipients. The long-term urate-lowering efficacy and safety with regard to renal function in kidney transplant recipients with hyperuricemia warrants further investigation.

REFERENCES